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THE MANAGEMENT AND POTENTIAL ROLE OF PROBIOTICS IN GASTRIC ULCER: A REVIEW

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ABSTRACT

One of the most common chronic gastrointestinal disorders, gastric ulcers, is characterised by a compromised mucosal barrier. Chronic usage of non-steroidal anti-inflammatory medicines (NSAIDs) and Helicobacter pylori (H. pylori) infections are two of the main causes of ulcer development. Usually, acid-suppressing drugs and antibiotics are used in treatment. Additionally, probiotics are being investigated as a possible therapy and preventative strategy for stomach ulcers, but, as a result of mounting evidence of antibiotic resistance as well as adverse effects from both antibiotics and acid-inhibiting medications in recent decades. Probiotics are now showing promise for use in the treatment of stomach ulcers, according to experimental and clinical investigations. This article offers a summary of the wider health advantages of probiotics on a range of gastrointestinal and systemic illnesses, with a focus on stomach ulcers and the underlying cellular and molecular processes. Probiotics support angiogenesis, improve the balance between cell proliferation and death, boost the synthesis of prostaglandins, mucus, growth factors, and anti-inflammatory cytokines, and help preserve the stomach mucosal barrier. The paper also looks at data that suggests probiotics may be used to eradicate H. pylori.

1. INTRODUCTION

Thin bands of loose connective tissue support the single layer of epithelial cells that line the stomach mucosa that are thinly coated with smooth muscle fibres. In addition to the stomach epithelium's natural acidic and enzymatic secretions, many people also regularly consume alcohol, which is broadly distributed, and duodenal bile.[1] Thus, stomach mucosal damage is quite common in many people and may lead to gastric ulcers. Untreated stomach ulcers may progress to gastric cancer, which has a high fatality and morbidity rate or catastrophic consequences such bleeding and perforation.[2] The most common treatment plans for stomach ulcers today include inhibiting acid production with proton pump inhibitors and using clarithromycin, amoxicillin, and metronidazole to eradicate H. pylori. However, because of the adverse effects of current therapeutic medications, and other factors, efforts are being undertaken to find new treatment approaches, and the high prevalence of stomach ulcer recurrence.[3]

Since probiotics are increasingly being used to prevent and treat a variety of systemic and gastrointestinal problems, many doctors and cell biologists are curious to know more about their effects on H. pylori and stomach ulcers. Even though there aren't many clinical studies looking at how probiotics affect stomach ulcers, a number of laboratory investigations have shown encouraging findings. The purpose of this study is to provide a summary of the current body of research about the possible use of probiotics in the prevention and treatment of stomach ulcers.[4]

2. Gastric ulcer

One of the most prevalent and dangerous long-term illnesses affecting the upper gastrointestinal tract is gastric ulcers. Gastric ulcer prevalence ranges from 2.4% in the Western population to 6.1% in Asia.[5] The recurrence rate is still significant despite improvements in anti-ulcer treatment. A stomach ulcer is a deep, localised necrotic lesion that affects the thickness of the whole mucosa as well as the muscularis mucosa. Most experts agree that these ulcers form as a result of an imbalance between the stomach's luminal surface's protective mucosa and things that might harm it. The main risk factors for the formation of ulcers in developing nations include smoking cigarettes, long-term, regular NSAID usage, and the high frequency of H. pylori.[6]

At the onset of ulcerogenesis, the protective mucous layer that the epithelial cells have produced is disturbed. Parietal and zymogenic cells may secrete more acid and pepsin, which might harm the mucous layer. Smoking increases the proton pump's production, which leads to increased acid secretion and ulcer development.[7] The endothelial cells in the capillaries behind the connective tissue may become visible if the mucous layer is damaged because the surface epithelium may peel off. Insufficient oxygen and nutrients will result from the destruction of capillaries. This will lead to hypoxic necrosis of deep glandular cells, such as parietal also emit pro-inflammatory and vasoactive mediators that exacerbate the mucosal microcirculation. Ulcers ultimately arise as a result of epithelia and connective tissue necrosis.[7]

An organised variety of several systems collaborate to treat a gastric ulcer by restoring the stomach's equilibrium between harmful and protective substances (Fig. 2). Epithelial cells and connective tissue components are used to repair the mucosal defect throughout the healing process, epidermal growth factor, and a number of cytokines all regulate these processes in a coordinated spatial and temporal way.[8] Hypoxia triggers angiogenesis, which includes fibroblast growth factor, vascular endothelial growth factor, and angiopoietins and is necessary for healing. Research found that bone marrow-derived stem and progenitor cells are drawn to the site of damage and help with the regeneration of epithelial and connective tissue components, in addition to local mucosal cells from living tissue at the ulcer border. These stem cells are thought to proliferate before committing to several routes and differentiating into zymogenic cells, mucous neck, surface mucous, and parietal. They create and release trefoil factor 2, which helps mucosal healing by lowering the acid production of parietal cells.[9]

Potential uses for cell therapy in the treatment of stomach ulcers exist. Injecting (locally or intravenously) bone marrow mesenchymal stem cells into rat models of stomach ulcers revealed that they promoted ulcer repair.[10] The underlying processes, however, are unknown, and more research is required on this stem cell injection method. With the growth of all cell lineages or only mucous cells, several research have shown the feasibility of creating artificial stomach tissue from isolated gastric organoids, isolated gastric stem cells, or gastric stem cell lines. These encouraging results need to be examined and tested in gastric ulcer animal models.[11]

3. Probiotics

The use of probiotics for treating stomach ulcers was inspired by a study conducted by Elliott et al. in 1998. In their research using a rat model of acetic acid-induced stomach ulcers, they found that gram-negative bacteria rapidly colonized the ulcer site, which significantly hindered the healing process. In contrast, colonization by gram-positive bacteria appeared to promote ulcer healing. The administration of the exogenous probiotic strain *Lactobacillus* significantly accelerated the healing of these ulcers, highlighting the potential therapeutic benefits of probiotics in this context.[12]

Elie Metchnikoff, a Nobel laureate, first proposed the idea of probiotics in 1900. He found that consuming Yoghurt or fermented milk containing live bacteria (Lactobacillus bulgaricus) improves the gastrointestinal system's biological properties. According to the International Scientific Association for Probiotics and Prebiotics and the Food and Agriculture Organisation (FAO), probiotics are living microorganisms that improve host health when given in adequate amounts.[13]

Numerous studies have shown that certain lactobacilli have Probiotics have many positive benefits, including as lowering the number of dangerous bacteria in the stomach and helping to treat inflammatory, allergic, and cancerous diseases. These health advantages have been shown to be provided by lactobacilli, whether they are taken as separate strains like Lactobacillus rhamnoses GG, Lactobacillus gasser OLL2716, or Lactobacillus acidophilus, or in combination as a probiotic mix like VSL, are very beneficial in accelerating the healing of stomach ulcers in rats.[14] Increased cellular proliferation to apoptosis caused by Particularly in the vicinity of ulcer margins, Lactobacillus rhamnoses GG promotes epithelial cell regeneration. A probiotic blend has been shown in clinical investigations to improve more successfully than a single strain, the traits of indigenous microorganisms. In addition to bacteria, many yeasts have also been studied and have shown potential therapeutic benefits in a rat model of ibuprofen-induced stomach ulcers. Saccharomyces bouvardia is one such yeast. This yeast's neuraminidase activity eliminates sialic acid residues from the gastric epithelial cells' apical membranes. When sialic acid is lost, H. pylori is unable to employ adhesins to adhere to the epithelial cells.[15]

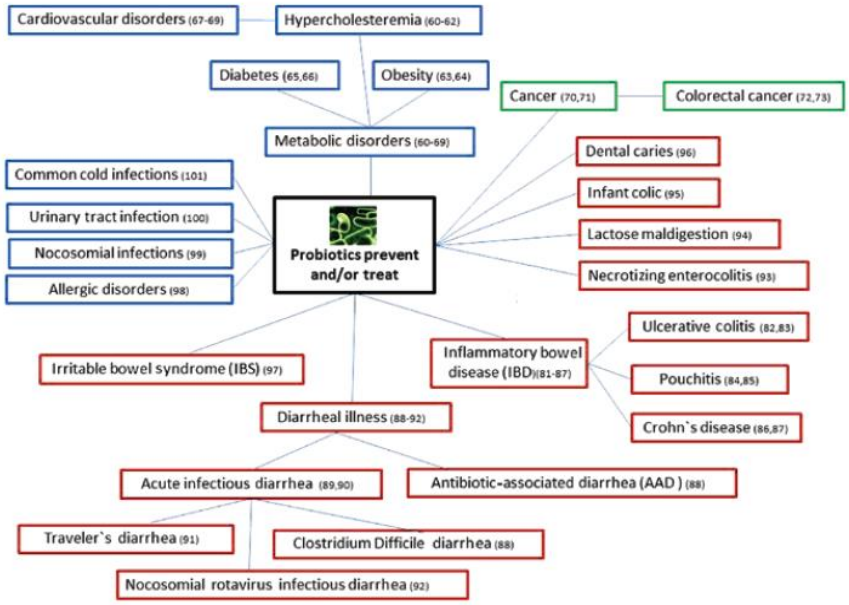

Figure 1: Summary of conditions reported to be helped by probiotics, including gastrointestinal (red), non-gastrointestinal (blue), and neoplastic (green) conditions.

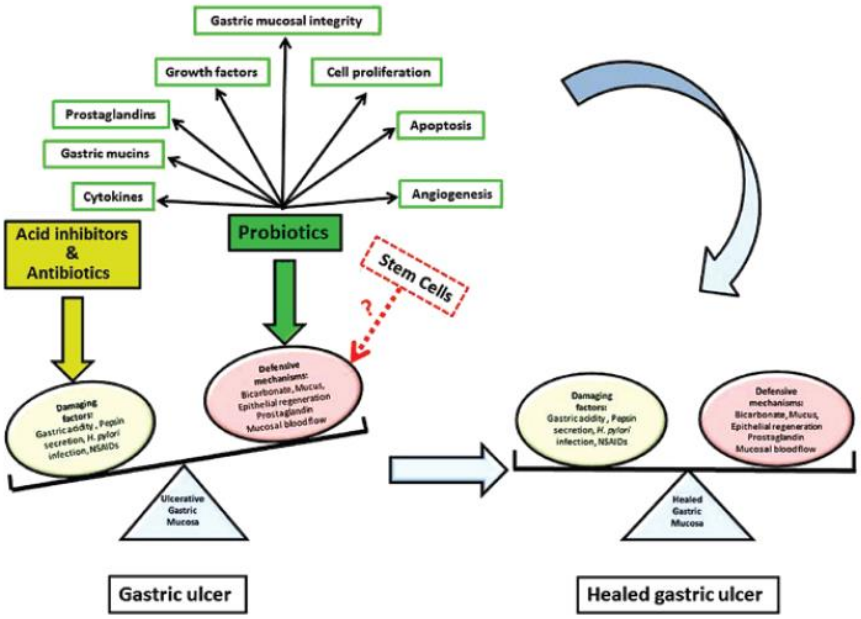

Figure 2: An overview of the causes and available treatments for stomach ulcers.

Probiotics have been the subject of more than 13,438 research publications, 1,422 of which were published in 2015. Several of these papers include insightful findings employing animal models, in vitro tests, and volunteers in good or bad health to demonstrate the influence of probiotics on the gastrointestinal system.[16] Irritable bowel syndrome is the primary digestive condition that probiotic research focuses on. Studies examining probiotics' impact on stomach ulcers, however, are few. It's possible that this is a result of the host's unfavourable physiological circumstances, such as bile acids, digestive enzymes, an acidic environment, and mechanical stress, all of which hinder certain probiotics' ability to survive and grow. A large dosage of many probiotics has been used to treat various disorders, and probiotics packed into an appropriate delivery method have been created.[17]

Probiotics' capacity to survive the stomach's acidic environment, as well as the bile and hydrolytic enzymes found in the stomach and duodenum, is a major factor in how useful they are. Numerous studies have shown that the primary factors influencing their longevity are the probiotic strain, exposure period, and acidity level are found in a variety of pharmaceutical and dairy probiotic products are often employed because they have a high capacity to survive gastrointestinal transit.[18]

Testing several probiotics has shown that Bifidobacterium infants/adolescent is/bifidum and Streptococcus thermophilus do not attach to the stomach mucosa as well as Lactobacillus acidophilus and Bifidobacterium longum do. According to studies, Lactobacillus acidophilus can live at pH 3 for 3 hours while Lactobacillus rhamnoses can survive at pH 2.5 for 4 hours.[19] Moreover, in the pH range of 1.5–3.0, numerous strains of Lactobacillus acidophilus and Bifidobacterium sustained viability for around 3 hours. Whereas a Bifidobacterium strain may tolerate stomach acidity for 3 hours at a pH of 3, and even slowly drops to Streptococcus thermophilus and Lactobacillus Delbruck do not have a pH of 2 or 1 after an hour.[20]

F-type ATPase has been suggested as the cause of certain probiotic strains' ability to survive in the stomach. For defence against acidic environments is in charge of producing a steady gradient between the extracellular and intracellular pH. Hence, the F0F1 ATPase is increased in an acidic environment and produces a proton motive force by proton ejection, which raises the intracellular pH. According to reports, Strong cytoplasmic buffering capabilities of Lactobacillus acidophilus allow for stability in acidic conditions and changes in cytoplasmic pH. Since glycolysis allows proton exclusion by supplying ATP to F0F1 ATPase, glucose helps lactobacilli survive in acidic environments.[21]

Probiotic strains that have been coated or microencapsulated have been created to overcome certain probiotics' poor capacity to survive. Recently, Vilene and colleagues used sodium alginate to make lactobacillus fermentum CECT5716-containing gastro-resistant tablets. Additionally, calcium alginate beads have been used to treat stomach ulcers brought on by cold constraint and have been proposed as a way to protect the intestinal tract's ability to absorb viable probiotic strains.[22]

By using non-living probiotic strains, coating may help address the issue of acid-sensitive probiotic bacteria not surviving in the stomach, microencapsulation, and dietary supplements. Certain live probiotic strains cannot withstand gastric transit, yet their dead versions are nonetheless helpful. Both living and dead probiotics may modify biological responses, according to strong evidence from in vitro and animal research. The term "paraprobiotics" or "ghost probiotics" now refers to nonviable probiotics.[23]

Research has shown that whereas heat-killed bifidobacteria greatly increase the generation of heat-killed interleukin (IL)-6 and tumour necrosis factor (TNF). The gastrointestinal immune system is strengthened against vancomycin-resistant enterococci by the Enterococcus faecalis fraction. Immunodeficient mice may be shielded against Candida albicans by consuming Lactobacillus acidophilus and Lactobacillus casei fractions that have been heat-killed. Further research has shown that probiotic mixes or their DNA, even if they are not alive, may improve the experimental colitis-affected animals' anti-inflammatory response.[24]

4. Effects of probiotics on gastrointestinal and systemic disorders

Fig. 1 summarises the preventative and therapeutic benefits of probiotics in different diseases of the gastrointestinal and non-gastrointestinal systems agents for a number of metabolic diseases, including obesity, diabetes, and hyperlipidaemia or hypercholesterolaemia. Consequently, using probiotics may help lower your chance of developing atherosclerosis and high blood pressure.[25]

Probiotics may be useful in the prevention and treatment of cancer, according to several studies carried out over the last few decades. Data show that the microbial composition of the gut (dysbiosis) is altered in a noticeable way in individuals with colon cancer. Giving rats Lactobacillus salivarius Ren orally may avoid the significant dysbiosis that occurs when they are administered 1,2 dimethylhydrazine to generate colon cancer. This successfully suppresses the process that causes colon cancer.[26] Probiotic treatment Mice that have colon cancer caused by 1,2 dimethylhydrazine are prevented from growing by Bacillus subtilis and Clostridium butyricum. Regarding the possible connection between probiotics and carcinogenesis in relation to stomach cancer, nothing is known. However, a number of in vitro studies have shown that probiotics have very promising anti-proliferative and pro-apoptotic actions on gastric cancer cells. Probiotics may also help cancer patients avoid the harmful side effects of radiation and chemotherapy, according to study.[26]

Given the growing prevalence of antibiotic resistance, there has been discussion on the possible use of probiotics as supplements to or even in substitute of oral antibiotic therapy. When used often and without a prescription, antibiotics may harm the gut flora and lead to resistance. By re-establishing the normal microbiota and fighting off harmful, resistant bacteria, probiotic treatment may aid in the recovery of patients in certain situations.[27]

Through the use of sophisticated methods, a number of genetically altered probiotic strains have been created with specific ability to produce vaccinations, anti-inflammatory cytokines, and anti-pathogenic substances. To provide live mucosal vaccines for different antigens generated from bacteria, viruses, and parasites, Lactococcus lactis strains have been engineered. Additionally, the rotavirus spike protein component VP8, which helps to prevent rotavirus infection, has been produced using recombinant strains of Lactococcus lactis. Probiotics may eventually be used as delivery systems to treat lesions of the gastrointestinal mucosa.

Pharmabiotics are a brand-new, customised drug delivery method based on probiotics.[28]

Lactose intolerance, inflammatory bowel illnesses, travellers' diarrhoea, antibiotic-associated diarrhoea, colic, and acute infectious diarrhoea are among the digestive illnesses for which there is evidence that probiotics may be beneficial. However, there is little information on the possible connection between probiotic supplementation and the prevention and healing of stomach ulcers.[29]

5. Probiotics' preventive and healing benefits on gastric ulcer

Several research have looked at the use of probiotics in the treatment of stomach ulcers during the last 20 years. Studies investigating the probiotics' preventive and therapeutic benefits have shown encouraging findings. The majority of the investigations on the literature contains studies on the impact of probiotics on the healing of stomach ulcers in rats.[30] Probiotic strains such as Bifidobacterium animalis VKL/VKB, Bifidobacterium bifidum/brevis, Escherichia coli Nissle 1917, Lactobacillus acidophilus, Lactobacillus rhamnosus GG, and Lactobacillus gasseri OLL2716 were used in this study with specificity. Probiotics may reduce the development of acute gastric mucosal lesions and hasten the healing of stomach ulcers, according to several research. Probiotics' ability to effectively heal stomach ulcers is attributed to a number of cellular and molecular processes.[31]

Gastric mucosal barrier defence. Three primary barriers maintain the mucosal integrity in a healthy stomach. I The mucus, bicarbonate, and phospholipid layer that makes up the preepithelial barrier is situated between the epithelium and the stomach lumen. ii) The continuous layer of surface epithelial cells that make up the epithelial barrier are joined by tight junctions and secrete a variety of substances, including trefoil factors, heat shock proteins, and prostaglandins.[32] Furthermore, the proliferation of stem/progenitor cells, which is controlled by a number of processes including growth hormones, prostaglandins, gastrin, and the anti-apoptotic protein survivin, results in ongoing cell renewal. Additionally, the continuous synthesis of prostaglandins, nitric oxide, and hydrogen sulphide maintains microcirculation via capillaries, while mucosal sensory innervation is essential for controlling mucosal blood flow. These compounds shield endothelial cells from harm and stop platelets and leukocytes from clumping together. These elements work together to create the subepithelial barrier.[33]

The disruption of the stomach mucosal barrier and the development of a gastric ulcer occur when one or more of the aforementioned defence systems are changed. There are two primary methods by which probiotics may benefit the gastrointestinal mucosa. Examples of antagonistic action include lactic acid or antibiotic compounds that inhibit the growth of hazardous bacteria, or by competing for the same nutrients and growth factors, which inhibits the growth of pathogens or their ability to adhere to stomach epithelial cells. IgA secretion, phagocytosis induction, natural killer cell activation, protective cytokine stimulation, proinflammatory cytokine downregulation, and T cell response modulation (Th1 induction and Th2 attenuation) are all examples of immunomodulatory function.[34]

Three mice models of induced stomach ulcers were recently studied, employing alcohol, pyloric ligation, and cold stress restriction. The probiotic bacterial strain Clostridium butyricum was administered to these animals beforehand, which decreased the histopathological changes, particularly the damage to the stomach mucosa and the infiltration of inflammatory cells. The same research also shown that this bacterium reduced the harm caused by oxidative stress by reducing malondialdehyde levels and inhibiting the action of catalases and superoxide dismutases. These results were consistent with the pretreatment with omeprazole.[35]

Uchida and Karakazu's study found that rats given LG21 yoghurt containing Lactobacillus gasseri OLL2716 as a pretreatment substantially and dose-dependently reduced the development of acetic acid-induced stomach ulcers. This result was mediated by a rise in mucosal prostaglandin E2/I2 synthesis. Significantly, a prostaglandin inhibitor, reduced the gastroprotective action of prostaglandin.[36] Later, by stimulating the formation of prostaglandins, the same investigators showed that giving yoghurt to patients for 10 days greatly expedited the healing of chronic stomach ulcers. Nevertheless, yoghurt containing Lactobacillus gasseri OLL2716 exposed to gamma radiation boosted prostaglandin production without compromising the healing of the stomach ulcers brought on by acetic acid. These results show that the beneficial effects of LG21 yoghurt on ulcer healing are not always explained by an increase in prostaglandin synthesis. Recently, the stable metabolite of prostaglandin I2, 6 ketoprostaglandin F1, was shown to be reduced in mice models of generated stomach ulcers pretreated with the probiotic Clostridium butyricum.[37]

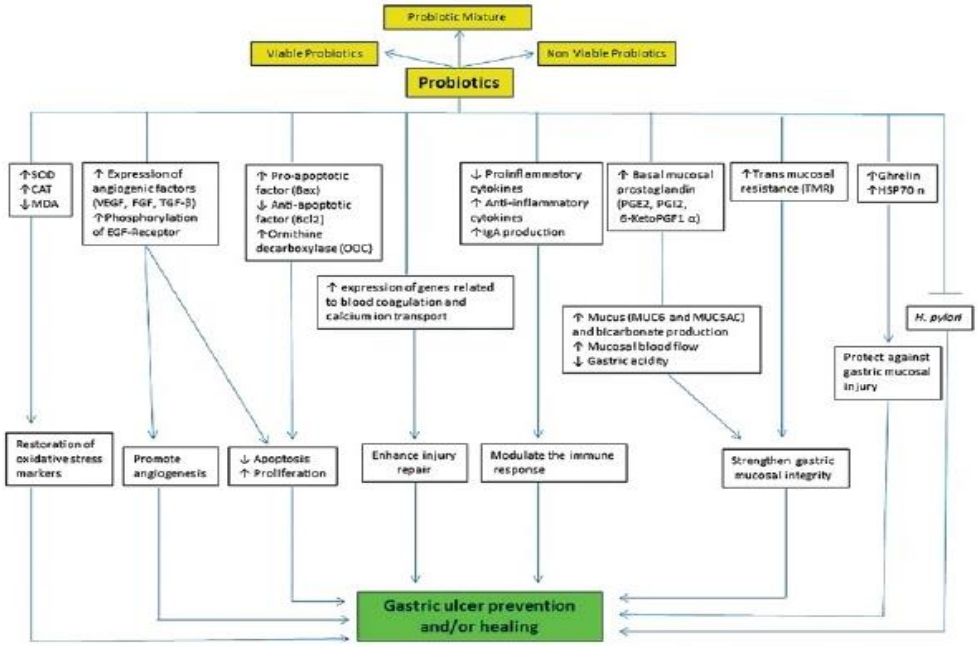

Figure 3: An overview of the key cellular and molecular processes that are thought to be involved in probiotics' impact on stomach ulcers.

5.1 Gastric Mucus

The cohesive material known as gastric mucus is made up of around 95% water and 5% mucin glycoproteins, as well as salts, immunoglobulins, different cellular and serum macromolecules, and trefoil peptides. Mucus produces two separate layers on the luminal surface of the stomach lining: an inner layer that adheres firmly and an outer layer that adheres loosely. The outer layer releases nitric oxide, absorbs nitrite, and binds toxic chemicals in the lumen. The inner layer, on the other hand, is crucial for shielding the stomach lining from acid and digesting enzymes.[38]

By (i) forming a physical barrier, (ii) attaching to bacterial adhesins to stop bacterial attachment, (iii) preserving high levels of secreted IgA and lysozyme on the epithelial surface, (iv) scavenging free radicals, and (v) postponing proton penetration from luminal acid into the gastric surface cells so that secreted bicarbonate can neutralise it, the mucus layer protects the gastric mucosa. In this manner, the stomach mucus promotes the survival and preservation of advantageous microflora in addition to protecting the epithelial cells.[39]

5.2 Proliferation of cells and death

Maintaining the stomach mucosal barrier requires constant cell regeneration. Both humans and rats have had the method and cell types involved in this renewal described. This renewal process is regulated by a number of components and cell types in the stomach's corpus area, including parietal cells and enteroendocrine cells (Karam and Al-Menhali, unpublished data).[40] Studies have also looked at how probiotics affect apoptosis and cell division. In rats with ethanol-induced gastric mucosal lesions, for example, pretreatment with Lactobacillus rhamnosus GG dramatically reduced the number of apoptotic cells. The overexpression of the anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) is responsible for this decrease in apoptosis. Further research revealed that the same Lactobacillus strain stimulates cell proliferation, which is mediated by ornithine decarboxylase, in addition to inhibiting apoptosis in gastric mucosal cells.[41]

Probiotics have angiogenesis-promoting effects on yeast in addition to bacterial strains. For instance, Saccharomyces boulardii has shown promise in the treatment and prevention of stomach ulcers in rats brought on by ibuprofen.[42] Furthermore, thioredoxin from the edible yeast Saccharomyces cerevisiae has been shown in recent DNA microarray tests to protect the stomach mucosa. The therapeutic potential of this yeast-derived protein is highlighted by the way it controls hundreds of genes involved in the repair of ulcerative mucosa in rats that has been produced by stress or exposure to ethanol or HCl.[43]

6 Probiotics' effects on H. pylori

Gastric ulcers were long thought to be caused by stress, poor nutrition, and the use of NSAIDs. Nonetheless, the global gastroenterological practice has evolved with the identification of H. pylori and its link to stomach ulcers.[44]

In the harsh, acidic environment of the stomach, H. pylori may colonise and live for decades, causing progressive inflammatory, ulcerative, and neoplastic alterations. Ten to twenty percent of H. pylori-infected individuals may eventually develop ulcers. The global

elimination of H. pylori is crucial to the recent decline in ulcer incidence.[45]

For gastroenterologists, eliminating H. pylori and treating associated alterations in the stomach mucosa continue to be difficult tasks. The reason for this challenge might be because H. pylori infections often start in early infancy, when the developing stomach glands are full with proliferating stem cells (Karam and Bharwani, unpublished data). Since H. pylori cannot be totally eradicated by antibiotics alone, the internationally recognised gold standard is a triple treatment regimen that includes clarithromycin, amoxicillin, metronidazole, and a proton pump inhibitor. Although no study has shown a 100% success rate, this method has demonstrated an eradication rate of 90%.[46]

Standard triple treatment has been far less successful in several countries due to rising clarithromycin resistance. Alternative regimens, such as quadruple, sequential, concurrent, dual, and rescue therapy, have been created to address this problem. The wider use of these regimens is, however, restricted by poor patient compliance brought on by the growth in antibiotic resistance and the related adverse effects.[47]

Numerous researches have examined the potential of probiotics to improve H. pylori eradication regimens and lessen related adverse effects during the last 10 years. Probiotics have also been shown to lower the chance of developing stomach ulcers in persons with H. pylori who do not exhibit any symptoms. The ability of the probiotic strain Lactobacillus salivarius to stop and eradicate H. pylori colonisation in the stomachs of gnotobiotic BALB/c mice was initially reported by Kabir and associates.[48]

7 CONCLUSIONS

An imbalance between detrimental elements and the stomach mucosa's defence systems results in gastric ulcers. According to research, probiotics may hasten the healing of stomach ulcers via a number of processes that include both protective and harmful elements. Despite the paucity of in vivo research on probiotics' impact on stomach ulcers, certain cellular and molecular data suggests that they may have therapeutic and preventive benefits. Furthermore, a number of investigations have pinpointed certain probiotic strains that support the elimination of H. pylori by both immunological and non-immunological means. Although further study is required, this makes probiotics an intriguing alternative for treating stomach ulcers. A combined clinical and experimental approach might provide useful ways for optimising probiotic usage in health and disease treatment, taking into account variables including probiotic strains, doses, commercial formulations, and patient variety.

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