Journal of Pharmaceutical Research International

33(28A): 137-145, 2021; Article no.JPRI.68085
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Comparative Study of the Efficacy of Prebiotics and Probiotics as Dietary Supplements in Rats with Gastric Ulcer

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i28A31518
Editor(s):
(1) Dr. Giuseppe Murdaca, University of Genoa, Italy.
Reviewers:
(1) Gislaine Barbosa Bezerra, Laboratório de Morfologia e Patologia Experimental ITP, Brazil.
(2) Sonali Nigam, Saint Aloysius College, India.
Complete Peer review History: http://www.sdiarticle4.com/review-history/68085

Original Research Article

Received 22 February 2021
Accepted 29 April 2021
Published 05 May 2021

ABSTRACT

Gastric ulcer is considered as main problem of gastrointestinal disease, presenting one of the most important health issues in all societies. This comparative study designed to explore the anti-ulcerogenic role of probiotics and prebiotics and to evaluate the most potent effect against gastric ulcer. Sixty rats were distributed into 6 groups : G1 Healthy control; G2 gastric ulcer (GU), ulcer was induced by four oral doses of Aspirin 200 mg/kg b.w./week ;G3 Prebiotics (PreB) administered orally group (0.5 g/day); G4 Probiotics (ProB) administered orally group (0.5 mg/day); G5 Prebiotics (Therapeutic): prebiotics was administered orally at dose (0.5g/day) for 30 days after induction of gastric ulcer (GU+PreB); G6 Probiotics (Therapeutic): probiotics was administered orally at dose (0.5mg/day) for 30 days after induction of gastric ulcer (GU+ProB). Oxidative stress parameters and inflammatory markers were measured. Results revealed that: aspirin caused gastric ulcer associated with increased MDA, TNF-α, IL-6, and IL-10 and decreased gastroprotective mediators SOD, GSH, CAT, and PGE2compared with control rats. Treatment with prebiotics or probiotics efficiently reduces gastric injury, oxidative stress and proinflammatory cytokines. Comparing treatment groups showed that, Probiotics as a therapeutic group was the most potent demonstrated a hopeful role against gastric ulcer.

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Keywords: Aspirin; gastric ulcer; gastrointestinal disease; prebiotics; dietary supplement.

1. INTRODUCTION

Gastric ulcer is a usual peptic ulcer**,** the process of healing is very difficult because it involves inflammation and antioxidant, proliferation and migration of gastric mucosal cells, matrix remodeling, angiogenesis and rebalance of gastroprotective, that causes returning of tissue composition [1]. Reduction of gastric offensive supports the process gastric ulcer healing which might be helpful medical system for remediation of peptic ulcers [2].

Etiology of gastric ulcer is multi-factorial. High acid secretion and decreased mucosal barrier contribute to initiation and progression of gastric ulcer. The etiology is ranging from Helicobacter pylori infection to imbalance between aggressive secretions of pepsin, hydrochloric acid, reflux of bile, formation of free radicals, stress, spicy food, lifestyle characteristics, alcohol, 5-hydroxy-tryptamine, platelet activating factor and drugs and cytoprotective factors, including the function of the mucus-bicarbonate barrier, prostaglandins, surface active phospholipids, mucosal blood flow, cell renewal and migration, enzymatic and non-enzymatic antioxidants and some growth factors [3].

Low-dose aspirin can induce mucosal damage in patients through both topical and systemic mechanisms [4]. Aspirin is a potent nonsteroidal anti-inflammatory drug that used for ameliorating pain, fever, and inflammation, also it has anti-platelet characteristics in cardiovascular diseases,thus used in avoidance of cardiovascular related symptoms. Aspirin usage causes gastrointestinal toxicity that leads to severe bleeding, depending upon the treatment duration. Gastro-mucosal injury produced by aspirin resulted from its inhibiting property on cyclooxygenase which decrease prostaglandins [5]. Studies have demonstrated that aspirin is related to high risk of peptic ulcer (Ishikawa et al., 2008).

Although the gastric mucosa was long-considered sterile, owing to its acid milieu, the normal human stomach in fact has a rich microbiota [6]. The microbial load is lower in the stomach compared to other parts of the gastrointestinal tract and the predominant phyla are Actinobacteria (including Bifidobacterium), Bacteroidetes, Firmicutes (including Lactobacillus spp), and Proteobacteria (including Helicobacter spp.) [7].

The most widely quoted definition of a prebiotic is that provided by Gibson and Roberfroid in [8] as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon. Molecules classically regarded as prebiotics include oligosaccharides, inulin, fructo-oligosaccharides, and galacto-oligosaccharides [9].The World Health Organization (WHO) define probiotics as "live microorganisms which when administered in adequate amounts confer a health benefit on the host" [10]. This underscores the potential for the therapeutic use of probiotics to restore the normal gastric microbiota [7]. The most commonly used probiotic bacteria belong to the genera Lactobacillus and Bifidobacterium [11]. This study aims to investigate the effect of prebiotics and probiotics in the treatment of peptic ulcer in male albino rats. Gastric ulceration will be induced by Aspirin administration. Also, we will perform a comparative study between the efficacies of prebiotics and probiotics to evaluate the more potent effect. This will be performed through biochemical and histopathological analysis.

2. MATERIALS AND METHODS

2.1 Probiotic and Prebiotic

Probiotic was obtained as natural product from iHerb as tablets, each tablet contains 0.5 mg (100 million cfu) Lactobacillus acidophilus (LactoBif).California Gold Nutrition Co., USA. Prebiotic was obtained as natural product from iHerb as powder, each serving contains 1.55 g of Xylooligosaccharides (Bifido Boost). PreticX^{TM} Prebiotic Co., USA.

2.2 Experimental Animals

Adult male albino rats weighing 100-120 g will be used in this study. Rats will be supplied from the Animal House Colony of King Fahd Medical Research Center, Jeddah. After the acclimatization period, Rats will be controlled with a 12 h light/dark cycle at King Fahd Medical Research Center Animal Facility Breeding Colony. Rats will be housed with *adlibitum* access of water and standard laboratory diet.

2.3 Experimental Design

Sixty male rats were randomly divided to six groups (10 rats per group). The groups were treated as follows:

Group I (Negative Control): Healthy rats received basal diet.

Group II (GU): Ulcerated rat group, gastric ulcer was induced in rats by oral doses of aspirin (200 mg/kg b.w./week) (Positive control).
Group III (PreB): Rats fed on basal diet and supplemented daily with prebiotic dissolved in saline solution at a concentration of 0.5g/ml by oral gavage.
Group IV (ProB): Rats fed on basal diet and supplemented daily with probiotic dissolved in saline solution at a concentration of 0.5mg/ml (100 million CFU /ml) by oral gavage.
Group V (GU+PreB): Rats fed on basal diet and supplemented daily with prebiotic at a concentration of 0.5g/ml by oral gavage after induction of gastric ulcer.
Group VI (GU+ProB): Rats fed on basal diet and supplemented daily with probiotic at a concentration of 0.5mg/ml (100 million CFU /ml) by oral gavage after induction of gastric ulcer.

2.4 Blood Sample Collection

At the end of the experimental period (4 weeks) , the rats were fasted overnight prior to blood collection and were then sacrificed under ether anesthesia. Blood was collected by retro-orbital puncture and the serum was separated by allowing the blood samples to clot for 30 minutes at temperature of 25°C and centrifuged at 5000 rpm for 20 minutes. The samples were then separated into numerous aliquots and stored at -20°C until analyzed.

2.5 Statistical Analysis

Data were statistically analyzed by comparing the values for different experimental groups with the values of individual normal ones. Results were expressed as mean + S.E. Significant differences among groups were analyzed using analysis of variance ONE-WAY ANOVA coupled with Statistical Package for the Social Science (SPSS) program. ANOVA at $p < 0.001$ was considered significant.

3. RESULTS

3.1 Biochemical Findings

Results in Table 1 showed the effect of different treatments on serum inflammatory biomarkers of all experimental groups. Administration of aspirin resulted in a potent inflammatory response as indicated by a marked significant elevation ($p \leq 0.001$) in serum IL-6, IL-10, and TNF-α with a concomitant decline ($p \leq 0.001$) in PGE2 levels as compared to the control group. Whereas, Prebiotic and probiotic supplementation, significantly ($p \leq 0.001$) improved the inflammatory biomarkers levels. In the same context, results revealed the most significant improvement in IL-6, IL-10, and PGE2 levels were observed in probiotic supplemented group (G6) followed by prebiotic supplemented group (G5) as compared to gastric ulcerative group (G2) .

Data are express as mean +/- standard deviation of means (SD). Significance are made using One Way ANOVA test followed by least significance test (LSD). a: significance versus G1; b: significance versus G2; c: significance versus G3; d: significance versus G4, e: significance versus G5. C; Control, GU; Gastric Ulcer Group, PreB; Prebiotic Group, ProB; Probiotic Group, GU+PreB: Gastric Ulcer Prebiotic Group, GU+ProB; Gastric Ulcer Probiotic Group.

Oxidative stress is a critical pathogenic factor during gastric ulceration. Figs. (1, 2, 3, and 4) represents the effect of different treatments on serum oxidative stress markers. Aspirin induced oxidative stress represented as a significant reduction ($p \leq 0.001$) in gastric SOD, CAT, and GSH enzyme levels, but a significant increase ($p \leq 0.001$) in lipid peroxidation MDA level as compared to control group. In contrast, treatment with prebiotic (G5) and probiotic (G6) significantly improved ($p \leq 0.001$) the level of oxidative stress markers. Comparing results of serum levels of SOD, MDA, CAT and GSH showed no significant differences noticed between prebiotic (G3) and probiotic (G4) groups and control group.

4. DISCUSSION

Induction of gastric ulcer (GU) is a major adverse effect caused by non-steroidal anti-inflammatory drugs (NSAIDs). Therefore, they have been used widely to establish animal models of gastric ulcer [1].The present study demonstrated that aspirin reduced the production of prostaglandin E2 (PGE2) in the ulcerated group as compared to control group.PGE2 protects the gastric mucosa by increasing mucus secretion, maintaining blood flow, and decreasing acid secretion [12]. Abood et al. [13] reported the ability of PGE2 to inhibit TNF-α production, which was confirmed by our findings. Moreover, the gastroprotective mediator NO regulates gastric PH and increases blood flow through its vasodilation effect [14].

Moreover, prostaglandins have been considered as an important gastroprotective agent and suppression of their production has been shown to allow luminal aggressive factors to produce their damaging effect [15].

In the present study results showed that, Aspirin administration increased TNF-α levels. A significant aspirin-induced alteration in cytokines in rat gastric tissue was previously studied [16]. Among the proinflammatory cytokines, TNF-α possesses multiple pathophysiological roles in gastric ulcer including activation of apoptosis and neutrophil infiltration [17]. TNF-α is a key cytokine that has an established role in systemic inflammation where it induces vasodilatation, vascular permeability along with recruitment of inflammatory cells [18].

Table 1. Effect of different treatments on serum levels of inflammatory markers in all studied groups

	IL-6 (pg/ml)	IL-10 (pg/ml)	TNF-α (pg/ml)	PGE2 (pg/ml)
GI (C)	6.27 ± 1.1	11.80 ± 2.2	14.1± 1.6	1.42 ±0.19
GII (GU)	19.17 ± 1.7^{a}	36.11 ± 4.5^{a}	35.5 ± 4.2^{a}	0.54 ± 0.21^{a}
GIII (PreB)	8.59 ± 3.6^{ab}	12.09 ± 2.1^{b}	14.3 ± 2.08^{b}	1.47 ± 0.23^{b}
GIV (ProB)	6.57 ± 0.87^{bc}	12.66 ± 2.0^{b}	13.7 ± 1.4^{b}	1.45 ± 0.16^{b}
GV (GU+PreB)	9.63 ± 0.86^{abcd}	16.16 ± 3.3^{abcd}	19.7 ± 3.1^{abcd}	1.18 ± 0.27^{abcd}
GVI (GU+ProB)	7.76 ± 1.6^{bcde}	14.83 ± 2.5^{abcde}	17.2 ± 5.5^{abcd}	1.33 ± 0.22^{abcde}

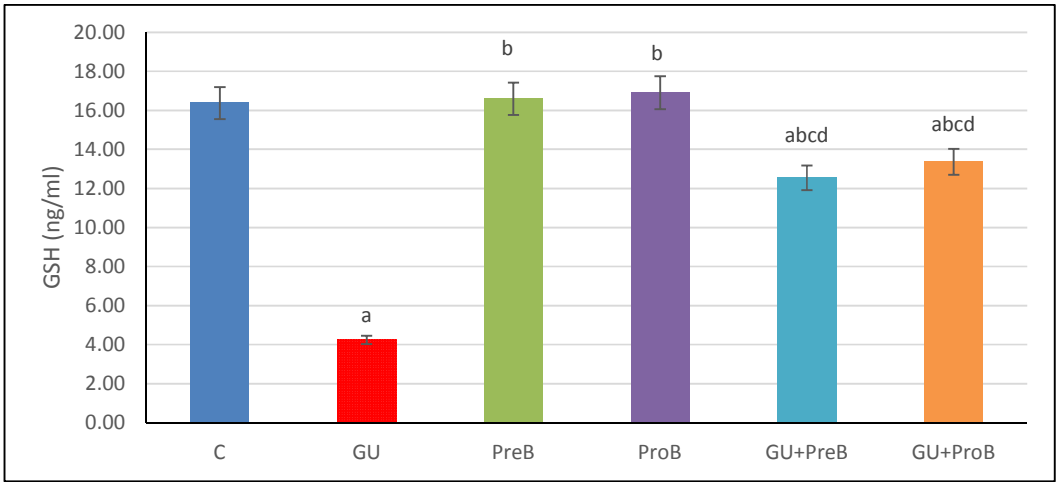

Fig. 1. Comparison of serum levels of GSH (ng/ ml) in different studied groups

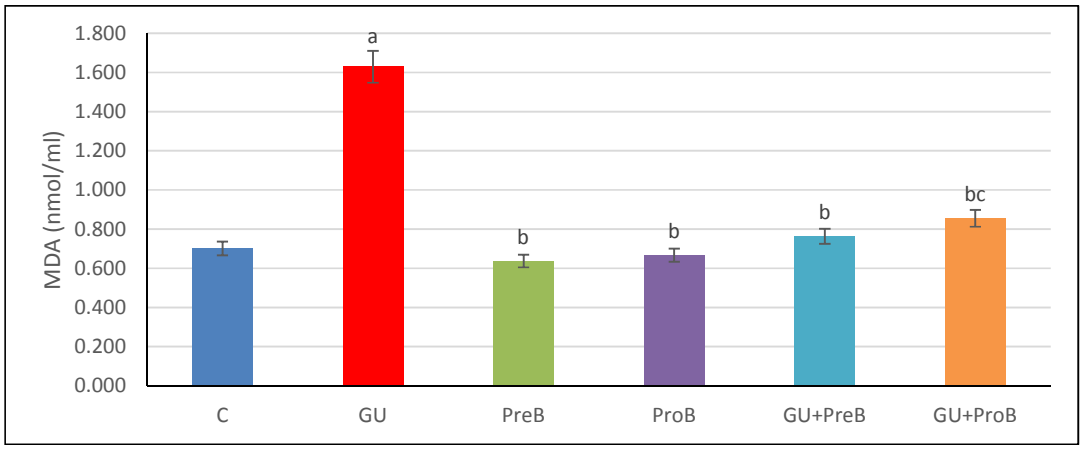

Fig. 2. Comparison of serum levels of MDA (nmol/ ml) in different studied groups

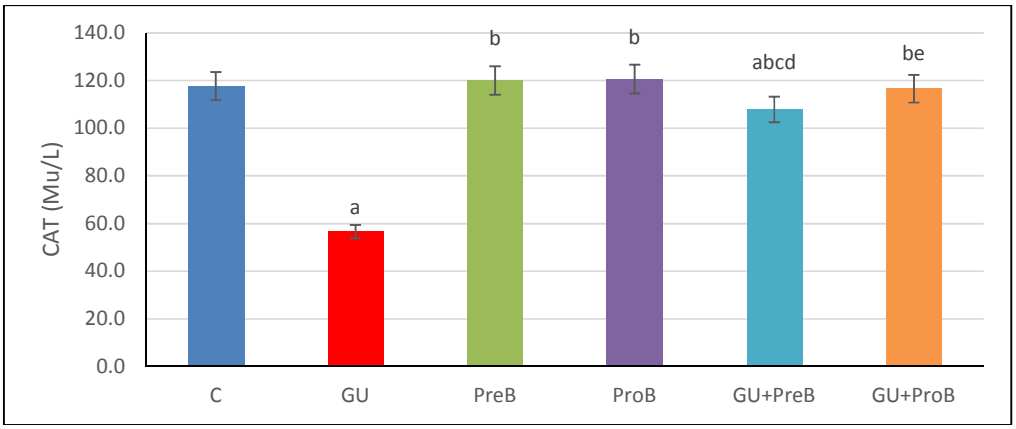

Fig. 3. Comparison of serum levels of CAT (Mu/ L) in different studied groups

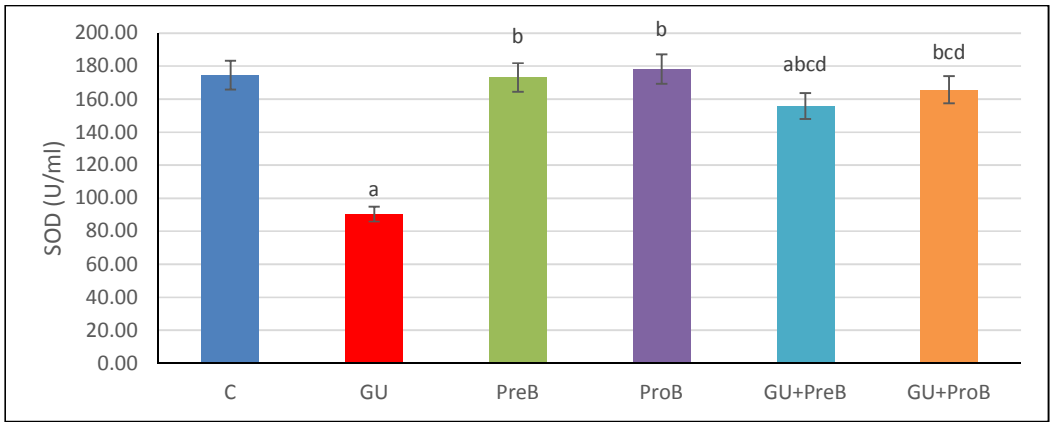

Fig. 4. Comparison of serum levels of SOD (U/ ml) in different studied groups

Prebiotics (PreB) were referred to indigestible food ingredients capable of providing health benefits to the host through selective stimulation of the activity of colonic bacteria. Dietary prebiotics are usually those indigestible fibrous compounds passed through the upper gut to stimulate probiotics growth [19]. The results provide that prebiotics in the form of xylooligosaccharides (XOS) reduced TNF-α, IL-6, and IL-10 productions in gastric ulcer-prebiotics supplemented rats (GU+PreB). These effects may account for the immunomodulatory activities of XOS. The consumption of XOS may be able to improve innate immunity, and to protect against inflammatory diseases.

Prebiotics play important roles in the metabolic processes associated with immunomodulation. Gut barrier dysfunction allows movement of various inflammatory mediators like the bacterial lipopolysaccharide (LPS) from the gut into the blood stream, a process known as metabolic endotoxemia, and shown to be an important factor in the development of obesity and diabetes in mice models [20]. The gut barrier integrity associated with immunity, can be enhanced when prebiotics and subsequent short chain fatty acids (SCFAs) release act. The immunomodulatory effect of prebiotics is influenced by the existing human gut microbiota (HGM) diversity. Anaerobic fermentation of prebiotics produces mainly SCFA's which can modulate the expression of genes responsible for production of anti-inflammatory cytokines in epithelial tissue [21]. The production of SCFA's from prebiotic fermentation by HGM, is the key for the maintaining gut health, intestinal morphology, and function [22].

The present study demonstrated that probiotics (ProB) significantly reduced the secretion of TNFα, IL-10 and IL-6. The effects of probiotics in the form of Lactobacillus Acidophilus (L. Acidophilus) were associated with regulation and

the normalization of epithelial barrier integrity. The administration of L. acidophilus was shown to have a modest and significant improvement in gastric function as compared to the gastric ulcer group, as well as changes in intestinal immune biomarkers such as serum PGE2.

The action mechanisms of probiotics interfere with the gut epithelial and immune cells composition and functions. Probiotics are well known to boost the immunity of humans by protecting against gastrointestinal pathogens, thus the mechanisms of action by which they exert their beneficial effects on the host include secretion of antimicrobial substances, competitive exclusion for adhesion sites and nutritional sources, enhancement of intestinal barrier function, and immunomodulation (Wan et al., 2019).

Probiotics can induce anti-inflammatory cytokines such as IL-10 and TGF-β, by down-regulating the expression of proinflammatory cytokines, such as TNF and IFN-γ to enhance mucosal immune responses [23]. Some studies indicate that the immunoregulatory effects of probiotics may be beneficial in intestinal inflammation treatment as they modulate the intestinal microbiota; improve epithelial barrier function and strengthen the intestinal wall by decreasing its permeability; reduce bacterial translocation and endotoxemia; improve intestinal inflammation; and reduce oxidative and inflammatory liver damage [24].

Free radicals decreased antioxidant enzymes activities and initiate lipid peroxidation which is an important event in the toxicity mechanism of aspirin [25]. Non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin have previously been reported to decrease antioxidant enzymes activity in rat stomach thereby causing gastric ulceration (Durak et al., 2011). This is associated with overpowering of the cellular antioxidant defence systems by free radicals ravaging influence that subsequently results in stomach oxidative injury.

Results revealed that aspirin increased the oxidative damage and disturbs antioxidant parameters levels. In an acidic milieu of stomach aspirin gets an easy access to the interior of epithelial cells where it gets trapped and causes local injury, uncouples mitochondrial oxidative phosphorylation, alters mucosal barrier function including physicochemical characteristics of mucus and reduces epithelial surface hydrophobicity [26]. Results showed that, aspirin increased MDA levels as well as decreased activities of SOD and GSH in the stomach of aspirin-ulcerated rats because of lipid peroxidation and over production of free radicals resulting in mucosal damage. SOD plays an important antioxidant role and is occasionally used to prevent the damage caused by radicals in aerobic organisms. This enzyme reduces intracellular levels of superoxide radicals. It converts superoxide anion (O_2 -) into H_2O_2, which then decomposes into water via CAT and glutathione peroxidase (GSHPx). MDA is the main product of lipid peroxidation. Thus, measurement of gastric MDA level can estimate indirectly the level of lipid peroxidation [27]. Subsequently, the low gastric GSH level increased the rate of lipid peroxidation, which mediates gastric tissue damage.

Functional oligosaccharides have been used as a good alternative to antibiotics in recent decades. The best-known functional oligosaccharides include xylooligosaccharides (XOS). The XOS are a new type of prebiotic, and studies show greater improvement in antioxidant parameters levels with XOS [28]. XOS, like other functional oligosaccharides, are not hydrolyzed by digestive enzymes; therefore, they reach the distal parts of the intestinal intact and are assimilated by the gastrointestinal microbiota, particularly probiotic bacteria, which produce short-chain fatty acids (Patel and Goyal, 2011). Prebiotics supplementation with a gastric ulcer diet (GU+PreB) was found to effective in reducing MDA levels and increasing the content of GSH and the activity of SOD, CAT and GSH in serum of rats. These results suggested that dietary supplementation of prebiotic in the form of xylooligosaccharides (XOS) might attenuate the damage of oxidative stress induced by aspirin through modulating antioxidant defense system and have a beneficial effect for human health. The levels of antioxidant parameters showed no differences in healthy rats supplemented with prebiotics (G3) as compared with control healthy rats. The effect of prebiotic addition to probiotic cultures has been reported by in vitro study of Le et al., [29], who observed an inhibition in the proliferation of Caco-2 cell lines when XOS were added to a fermented soymilk by bacteria cultures of L. rhamnoses.

The results of the present study demonstrated that supplementation with probiotic (GU+PreB) significantly improved the level of oxidative stress markers. In vitro studies on the antioxidative

properties of lactobacilli were performed using strains originating from human or mouse GI tracts. Independent of their origin, L. plantarum strains demonstrated an ability to break down H_2O_2, which requires catalase enzyme activity. In fact, the mechanisms and uses of the antioxidative properties of this species have been studied frequently (Zanoni et al., 2013). Supplementation of probiotics had significantly improved the overall levels of serum SOD and GSH and decreased the contents of serum MDA when compared with ulcerative rats. Previous studies provided evidence that some probiotics belonging to the Bifidobacterium genus are characterized by the ability of counteracting the occurrence of oxidative stress at intestinal level [30].

As for the antioxidative mechanism of probiotics, several explanations were supposed. Bacillus subtilis treatment caused the down-regulate in the expressions of antioxidative genes, such as glutathione reductase, and xanthine oxidase [31]. Other mechanisms included modulating mitochondria-mediated apoptotic pathways and reducing inflammatory enzymes [32,33]. It has been reported that some probiotics result in increased activity of antioxidative enzymes or modulation of circulatory oxidative stress, which protects cells against carcinogen-induced damage. These enzymes include glutathione S-transferase, glutathione, glutathione reductase, GPX, SOD, and CAT [34]. Some authors hypothesize that probiotics exert their defensive effects against oxidative stress by re-establishment of the gut flora [35]. Most lactobacilli species have scavenging systems for oxygen free radicals. Some lactobacilli possess antioxidant activity and can decrease the risk of accumulation of ROS during ingestion of food [36]. Metabolic activities of probiotic bacteria may have shown the antioxidative effect through the scavenging of oxidant compounds or the prevention of their generation into the intestine [37]. Some lactobacilli possess antioxidative activity and can decrease the risk of accumulation of ROS during the ingestion of food [38].

5. CONCLUSION

In conclusion, the antioxidative property of probiotics has been the subject of many studies in recent times, and a few patents have been granted recently in this area on the use of Bifidobacterium lactis BS and Lactobacillus acidophilus LA [39]. Treatment with prebiotics or probiotics efficiently reduces gastric injury, oxidative stress and proinflammatory cytokines. Comparing treatment groups showed that, Probiotics as a therapeutic group was the most potent demonstrated a hopeful role against gastric ulcer.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors

CONSENT

It is not applicable.

ETHICAL APPROVAL

Experiment will be approved by the Ethical Committee of King Fahd Medical Research Center. Jeddah, KSA.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
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