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Expression of *Fibroblast Growth Factor* (FGF) Due to Systemic Application of Probiotics in Healing Wistar Rat (*Rattus Norvegicus*) with Traumatic Ulcers

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Abstract

Background: Oral traumatic ulcers are defined as an impairment to the mucous membranes accompanied by loss of surface and disintegration of epithelial tissue, which is damaged due to trauma. The treatment of traumatic ulcers varies and covers the administration of antiseptics, antibiotics, anti-inflammatories, antihistamines, and corticosteroids. However, the long-term use of certain drugs may cause resistance and disagreeable side effects. This condition led to the increasing need for alternative treatments, such as the use of probiotics, whose potential effect as a wound-healing agent has been proven.

Objective: This review aims to evaluate the effect of probiotics on oral ulcers in animal studies. Furthermore, it demonstrates the results of *in vivo* studies focusing on the expression of fibroblast growth factor (FGF) due to systemic application of probiotics in healing Wistar rats (*Rattus Norvegicus*) with traumatic ulcers.

Materials and methods: Data collected from a secondary data search. Articles were selected and reviewed narratively according to predetermined criteria.

Results: Based on selected studies can be implied that the expression of FGF plays a significant role when *Lactobacillus* and other probiotics components are administered to the animal models because it provides and restores collagen in the new extracellular matrix in response to tissue damage.

Conclusion: Overall, systemic application of probiotics can promote the healing process of traumatic ulcers in Wistar rats (*Rattus Norvegicus*). FGF, as one of the essential modulators for wound healing, plays a significant role by increasing the formation of fibroblasts, the amount of collagen levels, and accelerating fibrosis; thus, the expression of FGF is completely increased in ulcers healing process.

Keywords: Fibroblast Growth Factor, Probiotics, Traumatic Ulcer, Wound Healing

Introduction

Oral traumatic ulcers occur due to the trauma that causes damage to oral epithelial tissue. It is an impairment to the membranes of mucous, accompanied by disintegration, loss of surface tissue, and epithelial tissue necrosis, which causes a burning sensation and pain of inflammation [1]. Moreover, traumatic ulcers can lead to malignancy when they are persistent. The prevalence of traumatic ulcers is 3 to 24% worldwide [2]. The lesions that arise are ulcerative lesions in the lining of the epithelium, which extend beyond the basal membrane and extend to the lamina propria, and are ovoid with a reddish border and prominent with a yellowish-white necrotic pseudomembrane in the center that can be cleaned [3, 4].

The treatment of traumatic ulcers is usually performed by the administration of antiseptics, antibiotics, anti-inflammatories, antihistamines, and corticosteroids both topically and/or systemically [5]. However, the long-term use of antibiotics and steroids can cause resistance and unpleasant side effects that are unpleasant. This condition led to the increasing need for alternative treatments, such as the use of probiotics [2, 6]. Previous studies have proven that systemic use of probiotics can be used as a wound healer, which plays a role in preventing infection and regulating inflammation [7].

The Food and Agriculture Organization of the United Nations (FAO) and the World Health Organization (WHO) state that probiotics are living microorganisms that, when administered in adequate amounts, confer a health effect on the host [8]. The most common microbes used as probiotics are members of the *Lactobacillus* (e.g., *L. rhamnosus, L. acidophilus, L. plantarum, and L. casei*), *Bifidobacterium* (e.g., *Bifidobacterium infantis, Bifidobacterium animalis subsp. Lactis, and Bifidobacterium longum*), and certain yeasts, e.g., *Saccharomyces* [9]. Probiotics, when administered topically, have been shown to prevent infection and regulate inflammation by modulating the immune system to balance the skin microbiota. On the other hand, probiotics systemically work to compete against pathogens, signal immune cells to produce cytokines, and destroy pathogens [10-12].

Based on existing studies, one of the health benefits of probiotics is that they regulate the balance between T helper 1 (Th1), which produces pro-inflammatory cytokines, and T helper 2 (Th2) as which produces anti-inflammatory cytokines [13]. The advantages provided by probiotics are to help build beneficial flora in the intestines and get rid of pathogenic bacteria, as well as to increase immunity, which is called Immunomodulators [10, 14, 15].

Wound healing of oral ulcers initiated by proteins released from immune cells known as growth factors [16]. Vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), collagen type 1 (COL-1), and fibroblast growth factor (FGF) are the first growth factors released by macrophages, fibroblasts, and endothelial cells to initiate tissue regeneration [16, 17]. FGF is a multipotential glycoprotein that boosts the proliferation and differentiation of various cells, including fibroblasts, which can restore defects in the wound area by providing collagen in the new extracellular matrix and producing several cytokines, chemokines, and growth factors in response to tissue damage [18, 19]. The role of FGF in angiogenesis is essential for revascularization, hematopoiesis, and wound healing [18]. As well as during the healing process a new blood vessels are produced, as a product of angiogenesis, transporting fluids, oxygen, nutrients, and immunocompetent cells [19, 20]. Probiotics can stimulate the migration and proliferation of fibroblasts and the formation of new blood vessels in the healing process of oral ulcers, which conforms to the function of FGF [21].

In this regard, this review evaluates the effect of probiotics on oral ulcers in animal studies. Furthermore, it demonstrates the results of *in vivo* studies focusing on the expression of fibroblast growth factor (FGF) due to systemic application of probiotics in healing Wistar rats (*Rattus Norvegicus*) with traumatic ulcers.

Materials and Methods

The method used in this present article is a literature review with a narrative procedure. The present review includes a screening of the most recent studies on the expression of FGF due to probiotics administration against traumatic ulcers. To obtain the most relevant selection of publications, the international databases PubMed, ScienceDirect, Research Gate, and Google Scholar were screened for studies as secondary data. Inclusion criteria were as follows: available full text issued from 2005 to 2021 and use of oral or systemic probiotics for treating wound infections; live bacteria associated with fermented foods, such as yoghurt and kefir, were not included as these do not qualify as probiotics. The types of articles used include research articles, original articles, systematic reviews, and reviews of literature. Articles that match the inclusion criteria were collected, reviewed, and summarized by the authors to form their article as a result of the study.

Results

Growth factors and the cells in the wound beds interact with one another as part of the dynamic process of wound healing, which includes the control of inflammation, cell migration, proliferation, and the synthesis of matrix proteins [22]. The fibroblast growth factor (FGF) family, which consists of 23 members, was one of the mediators in this dynamic process. Keratinocytes, fibroblasts, endothelial cells, smooth muscle cells, chondrocytes, and mast cells can all create FGFs [23]. The basic FGF (bFGF), also known as FGF-2, is the most significant member of the FGF family involved in wound healing. Several studies conducted *in vitro* have shown that bFGF can considerably reduce inflammation, as well as control the production and deposition of different Extracellular Matrix (ECM) components and facilitate fibroblast migration [22].

There is a variety of literature mentioning that FGFs have been linked to several physiological and pathological processes, and it is obvious that FGF signaling is crucial for development. However, the precise role of FGF *in vivo* wounding is still unknown; thus, there is followed by a rising need for observation of FGF expression as described in this present study. According to some earlier investigations, topical bFGF administration speeds up the healing of ocular, retinal, and corneal lesions in animal models as well as the healing of skin wounds [22, 24]. While other studies had proven that bFGF might delay wound development by raising the risk of local infection, regular changes in bFGF expression between skin wounds and transplanted oral mucosa were not discovered in the research by Jiarong Liu *et al* (2015) [22]. In most cases, rats were employed as experimental animals because they provided a suitable model for examining oral tissues and the structures that go along with them. In addition, there were similarities between human and rat oral mucosa; it would be difficult to conduct a similar examination on humans due to ethical reasons [25].

Traumatic ulcers in a few studies may be represented by mechanically induced ulcers as wound models *in vivo*. A study by Dewedar *et al* (2018) evaluated the potential effect of fibroblast (FGF2) and epidermal (EGF) growth factors on the healing of mechanically induced buccal mucosal ulcers in albino rats. EGF and bFGF are well-known important

modulators of wound healing, and based on this study, both growth factors accelerate wound healing compared with the control group, which was given intervention with *phosphate buffer saline* only. Observations were made using the immunohistochemical method, and it was seen that the morphology of the newly formed epithelium grew thicker on day 7 compared to day 4, and the wound was completely closed [25].

The results of a previous study showed that the wound healing process is not the same in young and old age mice. Several rats of different ages were given the same treatment by being given full-thickness wounds. After that, the part of the wound showed that in young mice (8 weeks old), the wound-healing process that occurred was excellent, this was indicated by an increased amount of fibroblast growth factor (FGF). While the amount of fibroblast growth factor (FGF) decreased in old rats (35 weeks old), which exhibited more slowly healing proceeded than in the young mice [26]. This shows that the expression of FGFs may be affected by several factors, which in this study are age.

Gudadappanavar *et al* (2017) have conducted research to study the effect of *Lactobacillus plantarum* and *Lactobacillus acidophilus* on several cutaneous wound models, including resutured incision, excision, and dead space wounds in male Wistar rats. According to histopathological reports, *Lactobacillus* has sped up the normal healing cascade by promoting an orderly process of hemostasis and fibrin deposition that results in an inflammatory cell cascade that is characterized by neutrophils, macrophages, and lymphocytes within the tissue. This is demonstrated by the comparison of the three treatment groups about the change in mean percentage closure of excision wounds from day 4 to days 8, 12, 16, and 18 [27]. On the other hand, Tagliari *et al* (2019) evaluate the effect of perioperative oral administration of a probiotics compound, containing *Lactobacillus paracasei, Bifidobacterium lactis, Lactobacillus rhamnosus,* and *Lactobacillus acidophilus*, on the healing of wounds in rats. One of the parameters observed in this study was the presence of fibrosis, which is the interstitial fiber deposit that marks the onset of the scar and represents the proliferative phase. It was observed that the proliferative phase was faster in the probiotic group on day 7 postoperatively when compared to the controls, resulting in a smaller wound tissue area at that moment. Systemically use of probiotics most likely accelerated fibrosis and increased the formation of collagen, enhancing the healing process. Furthermore, collagen levels in the probiotic group on day 7 postoperatively were comparable to those seen in controls on day 10. Taking into account that FGF can provide collagen in the new extracellular matrix in response to tissue damage, it can be implied from previous research that the expression of FGF plays a significant role when *Lactobacillus* and other probiotic components are administered to the animal models, since it shows a higher amount of fibrosis [28].

Discussion

Many centuries ago, fermented milk was given to accelerate wound healing and prevent infection, even before people were aware that bacteria existed and before they used antiseptics and antibiotics. Consequently, the idea of using bacteria to combat bacteria is an old concept, especially when it comes to the skin. According to Sprunt and Leidy, Cantini made the first attempt to swap out a harmful bacterium for a healthy one in 1885, claiming to do so in the lungs where *Mycobacterium tuberculosis* was present [29]. Today, however, this constitutes a significant shift in the paradigm of both the conventional teaching of "germ theory" and the contemporary philosophy of wound therapy, where the notion of employing bacteria to fight germs is not intuitive [30]. Our study addresses the response of the oral mucosa to the intervention with systemic probiotic administration on animals by observing the expression of FGF as one of the key factors in the wound healing mechanism.

Wound healing is a highly dynamic process involving a complex sequence of cellular and biochemical events, ranging from an immediate response to skin cell damage and invasive microbial signals to inflammatory, angiogenic, and ultimately fibroplasia and scar formation [31-34].

The phenomena occur concurrently, with self-regulated, and each other interfere. It has been divided into three dynamic phases: the inflammatory phase, proliferative phase, and remodeling phase [32, 35]. The interaction between inflammation, cellular, and humoral responses with intense cytokine production and liberation is fundamental for the healing process [33].

Probiotics have played an important role in regulating various biological functions. Many studies and tests were conducted on the intestines and skin, and they made wonderful progress in wound healing [36]. Probiotics can be used topically or systemically. Numerous studies have proven the benefits of applying probiotics topically, because it has a qualitative transfer action in wound healing by reducing bacterial load and increasing tissue repair in rodent wound models [37]. Probiotics' systemic effect can support contact between the gut and the skin microbes, reduce inflammation, and can bring about a change in the components of microbes at both sites. Oral use improves and aids wound healing by absorption of essential nutrients for wound healing, such as vitamins, minerals, and cofactors for key enzymes contribute to accelerating skin healing [34, 37].

FGF mediates the mechanisms of wound healing and tissue repair. They stimulate tissue repair by maintaining pluripotency and aiding self-renewal. Also, FGF stimulates proliferation and inhibits cell senescence and apoptosis. They induce angiogenesis and increase protease expression and aiding in tissue repair and wound healing [38]. Exogenous administration of FGF can affect wound healing by restoring collagen production and inducing rapid wound healing by accelerating the proliferation of new epithelial cells [25]. The significant increase in bFGF expression involves signaling molecules in the TLR4 or TLR2/NF-KB pathways. The activation of TLR2 by probiotics can induce a suppressive effect on the TLR4-mediated inflammatory response. They help modulate the inflammatory response, including alveolar bone remodeling [39]. Thus, we believe that the expression of fibroblast growth factor (FGF) due to systemic application of probiotics would be of impressive scientific value in the healing of human traumatic ulcers.

Conclusion

Probiotics systemic application can promote the process of traumatic ulcer healing in Wistar rats (*Rattus Norvegicus*). FGF, as one of the essential modulators for wound healing, plays a significant role by increasing the formation of

fibroblasts, the amount of collagen levels, and accelerating fibrosis. Thus, the expression of FGF is completely increased in ulcers healing process. Furthermore, systemic administration of probiotics is a recommended method and may be a promising solution to the same problem for the treatment of human traumatic ulcers.

Conflict of Interest

The author declares no conflict of interest.

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References

1. Ayuningtyas NF, Dwi M, Surboyo C, Ernawati DS, Parmadiati AE. The role of liquid smoke and coconut shell in the proliferation phase of an oral traumatic ulcer. Journal of Pharmacy and Pharmacognosy Research. 2020; 8(6):549-557.
2. Arundina I, Diyatri I, Kusumaningsih T, Surboyo M, Monica E, Afanda NM. The Role of Rice Hull Liquid Smoke in the Traumatic Ulcer Healing. European Journal of Dentistry. 2021; 15(1):33-38.
3. Cavalcante GM, Paula RJSD, Souza LPD, Sousa FB, Mota MRL, Alves APNN. Experimental model of traumatic ulcer in the cheek mucosa of rats. Acta Cirúrgica Brasileira. 2011; 26:227-234.
4. Mortazavi H, Safi Y, Baharvand M, Rahmani S. Diagnostic Features of Common Oral Ulcerative Lesions: An Updated Decision Tree. International Journal of Dentistry. 2020; 6014895.
5. Piacentini M, Borghetti RL, Zancanaro de Figueiredo MA, Cherubini K, Gonçalves Salum F. Doxycycline: An option in the treatment of ulcerated oral lesions? Journal of Clinical Pharmacy and Therapeutics. 2019; 44(6):838-843.
6. Negut I, Grumezescu V, Grumezescu AM. Treatment Strategies for Infected Wounds. Molecules. 2018; 23(9):2390-2392.
7. França K. Topical Probiotics in Dermatological Therapy and Skincare: A Concise Review. Dermatology and Therapy. 2021; 11(1):71-77.
8. Morelli L, Capurso L. FAO/WHO guidelines on probiotics: 10 years later. Journal of Clinical Gastroenterology. 2012; 46:S1-S2.
9. Vijayaram S, Kannan S. Probiotics: The Marvelous Factor and Health Benefits. Biomedical and Biotechnology Research Journal. 2018; 2(1):1-6.
10. Hemaiswarya S, Raja R, Ravikumar R, Carvalho IS. Mechanism of action of probiotics. Brazilian Archives of Biology and Technology. 2013; 56(1):113-119.
11. Lopes EG, Moreira DA, Gullón P, Gullón B, Cardelle-Cobas A, Tavaria FK. Topical application of probiotics in skin: Adhesion, antimicrobial, and antibiofilm *in vitro* assays. Journal of Applied Microbiology. 2017; 122(2):450-459.
12. Lee GR, Maarouf M, Hendricks AJ, Lee DE, Shi VY. Topical probiotics: The unknowns behind their rising popularity. Dermatology Online Journal. 2019; 25(5).
13. Azad M, Kalam A, Sarker M, Wan D. Immunomodulatory effects of probiotics on cytokine profiles. BioMed Research International. 2018; 2018:8063647.
14. Markowiak P, Ślizewska K. Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients. 2017; 9(9):1021.
15. Ashraf R, Vasiljevic T, Smith S, Donkor O. Effect of cell surface components and metabolites of lactic acid bacteria and probiotic organisms on cytokine production and induction of CD25 expression in human peripheral mononuclear cells. Journal of Dairy Science. 2014; 97(5):2542-2558.
16. Arundina I, Diyatri I, Surboyo MDC, Monica E, Afanda NM. Growth factor stimulation for the healing of traumatic ulcers with liquid rice hull smoke. Journal of Taibah University Medical Sciences. 2021; 16(3):431-439.
17. Zarei F, Soleimaninejad M. Role of growth factors and biomaterials in wound healing. Artificial Cells, Nanomedicine, and Biotechnology. 2018; 46(sup1):906-911.
18. Akita S, Akino K, Hirano A. Basic fibroblast growth factor in scarless wound healing. Advances in Wound Care. 2013; 2:44-49.
19. Puspasari A, Harijanti K, Soebadi B, Hendarti HT, Radithia D, Ernawati DS. Effects of topical application of propolis extract on fibroblast growth factor-2 and fibroblast expression in the traumatic ulcers of diabetic Rattus norvegicus. Journal of Oral and Maxillofacial Pathology. 2018; 22(1):54-58.
20. Hozzein WN, Badr G, Al Ghamdi AA, Sayed A, Al-Waili NS, Garraud O, *et al*. Topical application of propolis enhances cutaneous wound healing by promoting TGF-beta/Smad-mediated collagen production in a streptozotocin-induced type I diabetic mouse model. Cellular Physiology and Biochemistry. 2015; 37:940-954.
21. Kusumaningsih T, Irmawati A, Ernawati DS, Prahasanti C, Aljunaid M, Amelia S. The differences in the number of fibroblasts and blood vessels after the topical and systemic administration of Lactobacillus casei Shirota probiotics for the treatment of traumatic ulcers in Wistar rats (Rattus norvegicus). Veterinary World. 2021; 14(5):1279-1283.
22. Liu J, Zhao J, Zhu L, Yang P, Han C, *et al*. Comparison of EGF and bFGF Expression *In vivo* and their Effect *In vitro*. Clinical Microbiology. 2015; 4:192.
23. Yu A, Niiyama H, Kondo S, Yamamoto A, Suzuki R, Kuroyanagi Y. Wound dressing composed of hyaluronic acid and collagen containing EGF or bFGF: comparative culture study. Journal of Biomaterials Science, Polymer Edition. 2013; 24(8):1015-1026.
24. Meduri A, Aragona P, Grenga PL, Roszkowska AM. Effect of basic fibroblast growth factor on corneal epithelial healing after photorefractive keratectomy. Journal of Refractive Surgery. 2012; 28:220-223.
25. Dewedar OA, Farid MHM, Adawy HA. Potential Effect of Fibroblast Growth Factor (FGF2) Versus Epidermal Growth Factor (EGF) on Healing of Induced Oral Ulcer in Albino Rats (A Histological and Immunohistochemical Study). AlAzhar Dental Journal for Girls. 2018; 5(1):23-27.
26. Komi-Kuramochi A, Kawano M, Oda Y, Asada M, Suzuki M, Oki J, Imamura T. Expression of fibroblast growth factors and their receptors during full-thickness skin wound healing in young and aged mice. The Journal of Endocrinology. 2005; 186(2):273-289.
27. Gudadappanavar AM, Hombal PR, Timashetti SS,

Javali SB. Influence of Lactobacillus acidophilus and Lactobacillus plantarum on wound healing in male Wistar rats - an experimental study. International Journal of Applied and Basic Medical Research. 2017; 7:233-238.
28. Tagliari E, Campos LF, Campos AC, Costa-Casagrande TA, Noronha L. Effect of probiotic oral administration on skin wound healing in rats. ABCD Arquivos Brasileiros de Cirurgia Digestiva. 2019; 32(3):e1457.
29. Fijan S, Frauwallner A, Langerholc T, Krebs B, Ter Haar Née Younes JA, Heschl A, *et al*. Efficacy of Using Probiotics with Antagonistic Activity against Pathogens of Wound Infections: An Integrative Review of Literature. BioMed Research International. 2019; 2019:7585486.
30. Siddharthan R, Chapek M, Warren M, Martindale R. Probiotics in prevention of surgical site infections. Surgical Infections. 2018; 19(8):781-784.
31. Campos A, Borges-Branco A, Groth A. Cicatrização de feridas. ABCD Arquivos Brasileiros de Cirurgia Digestiva. 2007; 20(1):51-58.
32. Campos A, Groth A, Branco A. Assessment and nutritional aspects of wound healing. Current Opinion in Clinical Nutrition and Metabolic Care. 2008; 11(3):281-288.
33. Salgado F, Artigiani-Neto R, Lopes-Filho G. Growth Factors and Cox2 in Wound Healing: An Experimental Study with Ehrlich Tumors. ABCD Arquivos Brasileiros de Cirurgia Digestiva. 2016; 29(4):223-226.
34. Wilgus T. Immune cells in the healing skin wound: Influential players at each stage of repair. Pharmacological Research. 2008; 58(2):112-116.
35. Castilho T, Campos A, Mello E. Effect of Omega-3 Fatty Acid in the Healing Process of Colonic Anastomosis in Rats. ABCD Arquivos Brasileiros de Cirurgia Digestiva. 2015; 28(4):258-261.
36. Dethlefsen L, McFall-Ngai M, Relman D. An ecological and evolutionary perspective on human-microbe mutualism and disease. Nature. 2007; 449(7164):811-818.
37. Lukic J, Chen V, Strahinic I, Begovic J, Lev-Tov H, Davis S, *et al*. Probiotics or pro-healers: The role of beneficial bacteria in tissue repair. Wound Repair and Regeneration. 2017; 25(6):912-922.
38. Farooq M, Khan AW, Kim MS, Choi S. The Role of Fibroblast Growth Factor (FGF) Signaling in Tissue Repair and Regeneration. Cells. 2021; 10(11):3242.
39. Triwardhani A, Anggitia C, *et al*. The Increased Basic Fibroblast Growth Factor Expression and Osteoblast Number Post Bifidobacterium bifidum Probiotic Supplementation during Orthodontic Tooth Movement in Wistar Rats. Journal of Pharmacy & Pharmacognosy Research. 2021; 9(4):446-453.