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NARRATIVE REVIEW ARTICLE

ROLE OF TOPICAL OXYGEN ORAL THERAPY IN WOUND HEALING OF ORAL AND PERIODONTAL TISSUES: A NARRATIVE REVIEW

FAHAD ALI ALSHEHRI

ABSTRACT

In recent decades, numerous periodontal and peri-implant surgical procedures have been proposed to enhance patients' oral health-related quality of life. However, these surgical procedures may cause acute or chronic wounds in the oral cavity. The success of these procedures largely depends on the wound-healing process. Several adjuvant therapies, such as oxygen therapy, ultrasound techniques, photobiomodulation lasers, biological derivatives, and chemical stimulants, have been proposed for microbial control in the surgical field, reduction of postoperative morbidity, and/or acceleration of tissue-healing processes. Topical oxygen oral therapy has recently gained interest from oral and periodontal care providers to improve wound healing in the oral cavity and control microbial dysbiosis, which hinders optimal wound care. This review aimed to explore how topical oxygen interacts with tissue healing at the wound site and promotes angiogenesis during the proliferative phase of wound healing. A proprietary topical oxygen agent that reportedly increases oxygenation has also been highlighted.

Keywords: *Healing, oral tissues, oxygen therapy, periodontitis, wound.*

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INTRODUCTION

Oral wounds are common clinical conditions involving soft tissue, hard tissue, or both. They can arise from trauma-related injuries, prolonged inflammation, or other postoperative complications.[1] In addition, oral wounds can be caused by invasive dental treatments and oral surgeries, such as periodontal surgical treatments, tooth extractions, dental implant placement, and chemotherapy or radiation therapy.[2,3]

In periodontal practice, oral wounds related to surgical procedures provide access for adequate root surface debridement and establish optimal gingival contours.[4] These types of wounds are typically associated with the resolution of functional or aesthetic alterations, discomfort, pain, or even psychosocial issues, resulting in a substantial enhancement of the patient's quality of life (QoL).[5] Surgical procedures involving the placement of dental implants and bone grafting can cause extensive oral wounds. Furthermore, treating peri-implant infections using surgical methods involves another type of oral wound.[1]

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Oral mucositis in association with chemotherapy or radiation therapy involves non-medically inflicted wounds such as canker sores. Some of these sores recur after remission or fail to heal and are painful, significantly affecting patients' QoL.[2] Successful outcomes of these surgical and therapeutic procedures primarily depend on the healing potential of the oral and periodontal tissues.[6]

Several adjuvant therapies have been proposed for microbial control in the surgical area to reduce postsurgical morbidity and/or accelerate tissue-healing processes.[7] Topical oxygen oral therapy (TOOTh) has recently received interest from oral and periodontal care providers to improve wound healing in the oral cavity and control microbial dysbiosis, which hinders optimal wound healing.[8] This review explores the angiogenesis process of the proliferation phase of wound healing. Among the therapeutic modalities available currently, this review focuses on the topical application of active oxygen agents for promoting neovascularisation of oral wounds. To the author's knowledge, this will be the first review to address the use of TOOTh in wound healing of oral tissues.

Wound Healing in Oral Tissues

After trauma or ulceration, the wound-healing process initiates, occurring in four programmed stages:

haemostasis, inflammation, proliferation, and remodelling.[3,9] Haemostasis and inflammation begin when an injury occurs, lasting up to 4 and 6 days. Proliferation is characterised by the resurfacing of a wound with a new epithelium, angiogenesis, granulation tissue formation, and collagen deposition. During the healing of hard tissue, the supplementary mineralisation phase occurs, beginning on day 4 and lasting until 3 weeks after the soft tissue is injured. Finally, remodelling of the oral soft or hard tissue, or both, occurs and lasts approximately 1 year[3,9] (Figure 1). Healing of wounds in oral soft tissues, oral hard tissues, or both predominantly relies on inflammation and neovascularisation (angiogenesis). Although oxygen plays a critical role in all phases of wound healing, this review focuses mainly on the angiogenesis process in oral wound healing as a critical area influenced by the effect of topical oxygen therapy and as a hallmark activity that plays an indispensable part in wound healing.

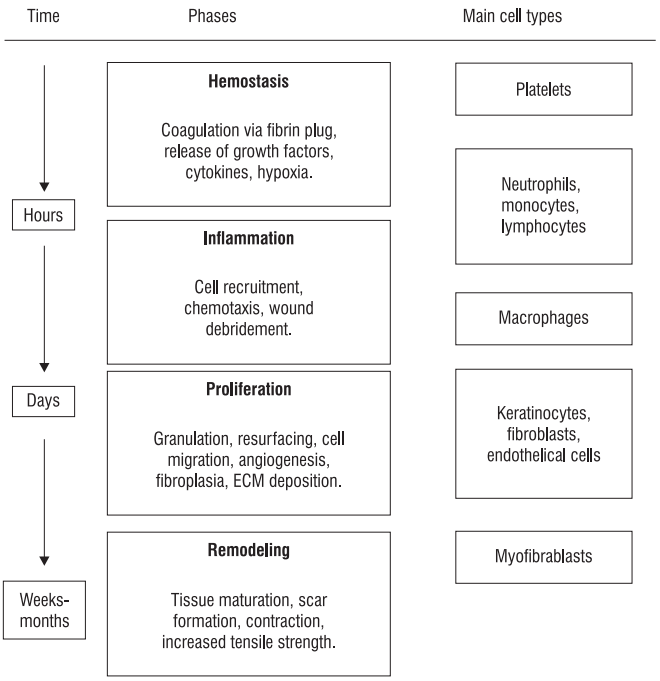

Fig 1: Four phases of wound healing and main cell types. ECM, extracellular matrix.

Angiogenesis in Healing of Oral Wounds

Angiogenesis (neovascularisation) is essential for wound healing.[10] The underlying vascular network is restored during this process, and a new dense yet interwoven network of capillaries is created.[11-13] The dramatic growth of capillaries is critical for optimum wound healing since it supplies oxygen and nutrients while removing cellular waste from tissues undergoing healing.[10] Angiogenesis is a continuous interplay between the cells of the vascular endothelium, angiogenic mediators, and the extracellular matrix (ECM) microenvironment.[13] Pro-angiogenic cytokines include the fibroblast growth factor, vascular endothelial growth factor (VEGF), angiogenin, transforming growth factor β1 (TGF-β1), angiopoietin, and mast cell tryptase.[9,13,14] During wound healing, blood vessels account for as much as 60% of the granulation tissue[13], and fewer new blood vessels are formed as the ECM matures.[2] Individuals with diabetes are more susceptible to impaired wound healing owing to immune system abnormalities and deficient angiogenesis.[2,11] Although angiogenesis is required to supply micronutrients and oxygen to the healing wounds, the functional value of excessive angiogenesis has been re-evaluated in recent years. The current hypothesis is that the oral mucosa heals with a decreased angiogenic burst and is composed of more mature capillaries that supply more oxygen.[11]

Current Therapeutic Means to Promote Angiogenesis

Several techniques promote angiogenesis in the healing of oral wounds during the proliferation stage, including, but not limited to the following:

1. Oxygen therapy (OTs): Ozone therapy[15-20], Hyperbaric Oxygen Therapy (HBOT)[21-24], gas plasma therapy[25-27], and topical OT (TOT)[28-37]
2. Sound (ultrasound)[38-41]
3. Light (photobiomodulation laser)[42-44]
4. Biological derivatives (platelet-rich plasma and platelet-rich fibrin)[45-47] and
5. Chemical stimulants (hyaluronic acid, astaxanthin, and Centella asiatica extract)[48-50]
6. This review provides a critical overview of the involvement of topical oxygen in angiogenesis and the wound-healing process.

Role of Oxygen in Angiogenesis

Oxygen is essential for wound healing since it helps produce energy, synthesize proteins, proliferate cells, promote angiogenesis, and repair tissues. While the oral cavity has adequate blood flow and high tissue metabolism, and oxygen levels fluctuate depending on the anatomical position, wounds are hypoxic. The hypoxic nature of wounds is associated with increasing the risk of infection, nutrients deficiency, and eventually impaired healing (Figure 2).[2,51] Nevertheless, during initial inflammation in wound healing, the hypoxic nature of wounds promotes fibroblast migration and proliferation and changes the normal functioning of stromal cells.

Hypoxia causes fibrotic tissues to secrete more TGF-β1 and, as a result, upregulate the expression of hypoxia-inducible transcription factor 1 (HIF-1) (Figure 3). HIF-1 is a key modulator of oxygen homeostasis

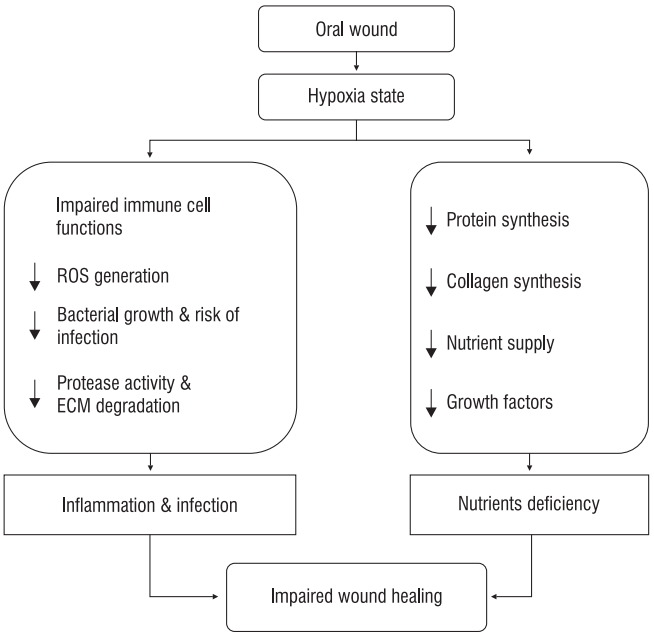

Fig 2: Summary of how hypoxia status results in impaired wound healing. ROS, reactive oxygen species. ECM, extracellular matrix.

and substantially affects the survival of cells and the outcomes of the wound-healing process. HIF-1 is implicated in almost every stage of wound healing, notably cell migration and proliferation, growth factor release, angiogenesis, and ECM attachment. HIF-1 is activated under hypoxia, increasing the levels of proangiogenic mediators, such as VEGF, matrix metalloproteinases (MMPs), angiopoietin 2, and stromal cell–derived factor 1, and causing angiogenesis and tissue remodelling to deliver sufficient oxygen to the healing tissue. HIF-1 targeting for wound therapy is still in development.[52] Elevated MMP gene expression promotes the proliferation and migration of endothelial cells through the formation of granulation tissue on the basement membrane. MMPs also cause keratinocytes to migrate through protein degradation in cell–matrix adhesions to promote the resurfacing of wounds with newly formed epithelia. MMPs, more specifically MMP-2 and MMP-9, are critical in neovascularisation regulation during the healing process because they activate the proangiogenic factors tumour necrosis factor–α, VEGF, and antiangiogenic mediator, causing degradation of the basement membrane and ECM elements so that the damaged tissue is removed [53]. However, when MMPs are overexpressed in chronic wounds, the development of new tissues is hindered, inhibiting wound healing.[53]

In contrast, the production of adenosine triphosphate in mitochondria for chemical energy production, which is required for tissue regeneration, relies on oxygen. Moreover, oxygen contributes to the production of reactive oxygen species (ROS), including superoxide and hydrogen peroxide (H_2O_2), via adenine dinucleotide

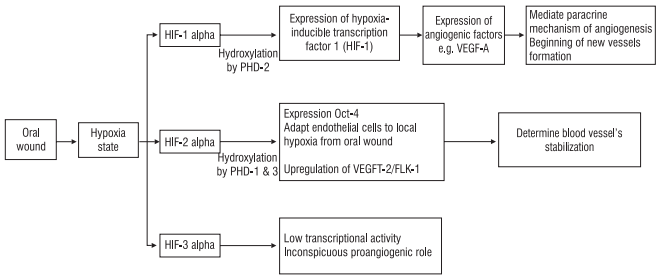

Fig 3: Schematic representation of hypoxia state in oral wound. HIF, hypoxia-inducible transcription factor. PDH, prolyl hydroxylase domain enzymes.

phosphate oxidase. ROS are critical in regulating cell function and homeostasis, upregulating growth factors (VEGF and platelet-derived growth factors), and inducing various human transcription factors that promote phagocytosis and the bacteriostatic effects of H_2O_2 in cellular self-defence.[54]

ROS induce the proliferation of endothelial cells, angiogenesis, vasculogenesis, and the division and migration of fibroblasts for collagen or ECM formation, causing keratinocytes to begin proliferating and migrating during tissue repair. Furthermore, ROS serve as mediating factors in vascular dilatation and constriction via nitrous oxide after platelets are exposed to the ECM. Local ROS signalling for thrombus formation is critical during initial homeostasis [54-56]. During wound healing, angiogenesis is sensitive to autonomic stimulation; therefore, the wound tissue requires sufficient oxygen delivery owing to its high vasoactivity.[57]

Therapies that target increased wound tissue oxygenation can lead to improved wound management (Figure 4). Some therapies that have been shown to improve wound healing are HBOT and topical oxygen.[58] A summary of their possible healing qualities in various diseases has been provided previously.[59]

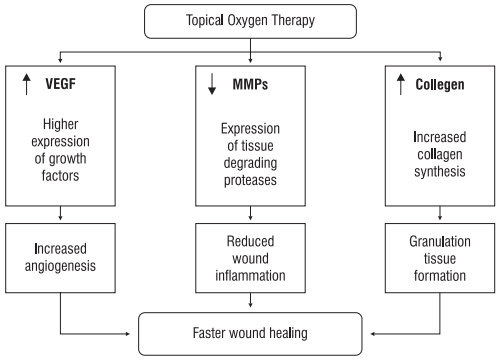

Fig 4: Topical oxygen therapy promotes faster wound healing by increasing angiogenesis and granulation tissue formation, and by reducing wound inflammation.

Oxygen Therapy (OT)

OT encompasses the use of ozone, HBOT, and TOT [60]. Recently, a systematic review and meta-analysis on the application of TOT revealed its high effectiveness and safety in the care of chronic diabetic wounds [61]. Researchers have studied a multitude of hydrogel dressings, including alginic acid, paramylon, fibrinogen, hyaluronan, silk fibroin, and cellulose gum.[62-66], to improve wound healing through angiogenesis while simultaneously scavenging ROS. An alternative approach involves administering TOT to wounds in individuals with peripheral artery disease through a local boot that supplies maximum oxygen to the wound at 1.03 atm.[67] In recent years, the use of TOT in the oral cavity has received considerable attention and is referred to as TOOTh.[8]

Topical Oxygen Oral Therapy (TOOTh)

The application of chemical compounds that can directly supply oxygen to oral wounds is interesting. This treatment approach involves two main modalities: the application of H_2O_2 and oxygen-releasing agents.

H_2O_2 is a source of oxygen and a disinfectant. After exposure to glutathione peroxidase (GPx) and catalase, H_2O_2 biologically decomposes into water and oxygen, with consequent effervescence. Historically, H_2O_2 has been used for wound disinfection and continues to be used for this purpose in developing countries [68]. It is recommended as a ROS to promote the wound-healing process in periodontal surgery. Similarly, H_2O_2 rinsing has been supported as a mild antiseptic for various oral diseases, such as acute necrotising ulcerative gingivitis.[34,69,70] However, H_2O_2 rinses have been linked to negative outcomes under certain circumstances.[71] Approximately 30 years ago, researchers examined the effect of H_2O_2 mouth rinses on the oral mucosa of healthy volunteers. They found significant abnormalities in the mucosa, tissue damage, and multiple subjective complaints, which contributed to the disapproval of mouth rinse usage in oral care.[72] While products incorporating $\leq$3% H_2O_2 for cleansing, promoting minor oral wound healing, and treating gingivitis have been found to be safe[31], the need for a safe, slow, and controlled release of oxygen persists and is of great importance to the dental community.

The current rationale, regimens, and preclinical and patient data regarding various TOOThs using active oxygen-releasing agents that have been used to improve the outcomes of oral wounds are discussed below, with a prime focus on periodontal tissues.

Current Oxygen-Releasing Agents Used in TOOTh

The objective is to provide a localised supply of PEG-32, sodium gluconate, lactoferrin, xanthan gum, and cellulose gum, which have specific functions.[8]

The active ingredients in oxygen-releasing agents that cause the gradual and sustained release of oxygen are sodium perborate, sodium percarbonate, and/or honey (Mel). These are the precursors of H_2O_2. Once these two elements are in contact with saliva or extracellular fluid, they are converted to H_2O_2 at low concentrations (0.003–0.15%).[30] Specifically, in the presence of water, sodium perborate is converted to sodium borate and H_2O_2 at low concentrations (0.003–0.015%). Consequently, H_2O_2 is decomposed by GPx and catalase, enzymes found in almost all living cells, to water and oxygen (Figure 5).

Mel (honey) is an important component in oxygen-releasing agents, with glucose as the main active ingredient. When mixed with water, the glucose in honey is catalysed by the glucose oxidase enzyme D-glucono-1,5-lactone and H_2O_2.[73] The resulting H_2O_2 is further hydrolysed by catalase to oxygen and water, whereas D-glucono-1,5-lactone is sequentially hydrolysed by lactonase to d-gluconic acid. All available glucose in honey is completely converted; thus, there is no risk of caries formation.

Among all oxygen-releasing formulations, the oral gel has the highest amount of oxygen released; therefore, its main effects are bactericidal and enhancing

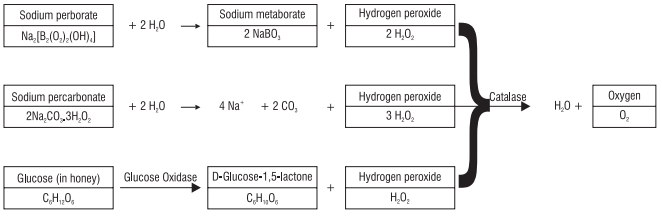

Fig 5: Simplified illustration of how active oxygen is eventually released from three different chemical ingredients used in topical oxygen oral therapy.

oxygen to the wound via external administration, such as with TOOTh. Oxygen-releasing agents are used to deliver a continuous flow of transmucosal non-pressured oxygen to the wound bed at therapeutic concentrations. Such oxygen-releasing products include gels, fluids, mouth rinses, toothpaste, oral sprays, or nanobubble fluids (foam). These formulations are currently manufactured by BlueM (Blue®m, Wijhe, Netherlands) and are commercially available in most oral-care markets worldwide.

Oxygen oral gel formulation was developed by Peter Blijdrop for specific problems in the mouth with the following ingredients: aqua, alcohol, glycerin, honey, silica, sodium saccharin, sodium perborate, citric acid,

tissue healing by promoting angiogenesis and revascularisation, increasing cell metabolism and energy production, promoting growth factor signal transduction, and enhancing collagen synthesis and tensile strength and selective antibacterial activities against anaerobic bacteria.[8]

Current Clinical Indications for TOOTh

Several preclinical and clinical studies have already demonstrated the effectiveness of TOOTh for various oral indications:

Treatment of Gingivitis and Periodontitis

Periodontitis is treated using an active oxygen gel, which targets and destroys the anaerobic bacteria that cause periodontitis to facilitate the restoration of healthy oral microflora.[74] A clinical trial compared the effects of the oxygen-releasing oral gel and chlorhexidine gel in treating periodontitis. The intervention group, treated using oxygen gel, demonstrated a higher likelihood of reduced interdental probing pocket depth. The researchers concluded that comprehensive subgingival scaling and root planing, accompanied by adjunct TOOTh, promoted periodontal pocket reduction.[75]

These findings were supported by an investigation that evaluated the metabolism of the oxygen gel, compared with that of chlorhexidine, in an in vitro model of a multispecies subgingival biofilm. The oxygen gel decreased the bacterial species more than chlorhexidine did during subgingival biofilm formation. However, the oxygen gel was more effective than the chlorhexidine gel in decreasing the number of red complex bacteria, classified as anaerobic bacteria. Even though the oxygen gel decreased the mature 6-day-old multispecies subgingival biofilm, it failed to change the ratio of bacterial complexes on the subgingival biofilms in a manner similar to that of chlorhexidine.[76] A different in vitro investigation demonstrated the oxygen oral gel's bactericidal activity, which was similar to that of chlorhexidine, whereby it impeded *Porphyromonas gingivalis* from growing.[77]

Wound Care After Periodontal Surgery

Concerning the healing action of oxygen-releasing oral gels, a recent investigation revealed that oxygen gel can be used as an effective substitute for Coe-Pak dressing after gingival depigmentation owing to its analgesic effects, acceleration of the wound-healing process, and re-epithelialisation after surgery.[33]

Neovascularisation is a defining process that is essential for wound healing. Supplementation with oxygen during wound healing promotes the oxidative killing of bacteria, induces angiogenesis, accelerates ECM formation, increases fibroblast proliferation, and promotes collagen deposition, thereby promoting rapid healing. Histologically, using oxygen oral gel as a TOT in wound healing demonstrated accelerated healing of skin wounds induced surgically in rats, with elevated angiogenesis and more effective collagen fibre formation. The study also demonstrated a significantly higher VEGF concentration in the participant group in which the Blue®m oral gel was applied, with a slow and persistent oxygen release.[29]

Oxygen oral rinse on surgical wounds in the oral mucoperiosteal tissues has shown a positive effect on tissue healing by decreasing pain and postsurgical inflammation.[36] Human keratinocytes show a higher rate of proliferation after exposure to lower concentrations of the oxygen oral rinse.[32] An earlier systematic review demonstrated that H_2O_2 oral rinses failed to prevent plaque accumulation if utilised as a monotherapy for a relatively short period. In contrast, one study demonstrated that it decreased gingival redness when utilised as long-term adjuvant therapy [32]. However, a more recent systematic review revealed that H_2O_2 oral rinses can influence plaque accumulation and gingivitis.[37]

Treatment of Peri-implantitis

TOOTh has been demonstrated to exert an antioxidant effect while treating peri-implantitis.[78] Peri-implantitis is an infectious disease associated with site-specific plaques that occur in the tissues surrounding dental implants. It is characterised by an inflammatory response in the peri-implant mucosa and ensuing progressive bone loss. Bacterial biofilm formation is regarded as the primary etiological factor.[79] Research investigations focusing on treating peri-implantitis have revealed that anti-infective therapeutic interventions successfully decrease soft-tissue inflammatory responses and suppress disease.[79] Nevertheless, a recent review of surgical procedures for peri-implantitis treatment demonstrated that the available clinical-, radiography-, and microbiology-related data do not support decontamination strategies or show the impact of any specific decontamination method on surgical treatment.[80] Fortunately, H_2O_2 does not cause considerable titanium corrosion, and the induced corrosion can be reversed.[81]

The manufacturing company for these oxygen-releasing agents (BlueM) has TOOTh guidelines for managing peri-implantitis. These guidelines recommend applying a small amount of the oxygen oral gel in the pocket surrounding the implant using a disposable 2.5 mL syringe. The application of this gel as a chemical decontaminant is indicated owing to its bactericidal action. The regimen for home use involves teeth brushing twice using the oxygen toothpaste, mouth rinsing thrice (1 min per rinse) using the oxygen mouth rinse, and two to four interdental applications of oxygen gel

at the site of the implant.

Daily Dental Care Using Toothpaste or Foam

Another approach for delivering oxygen utilises toothpaste as a carrier. Oxygen-releasing toothpaste's anti-plaque and anti-gingivitis effectiveness has been demonstrated in a clinical study conducted by Cunha et al.[28] They showed that compared with toothpaste with triclosan, toothpaste with active oxygen and lactoferrin showed anti-plaque and anti-gingivitis effectiveness.

Recently, oxygen micro or nanobubble water (foam) was tested for wound healing in an animal model containing an oxygen-rich liquid demonstrated to improve the healing of ischaemic wounds.[82]

CONCLUSIONS

Within the scope of this review, the following conclusions can be drawn:

TOOTh appears to play a critical role in acute, chronic, and surgical oral wound healing by promoting angiogenesis and exerting a selective antibacterial effect, primarily against anaerobic bacteria.

Different formulations of TOOThs, including oral gels, fluids, mouth rinses, foams, and toothpaste, serve as efficient active oxygen carriers for delivering controlled and therapeutic concentrations of topical oxygen to oral tissues.

Emerging preclinical and clinical research has indicated that topical oral oxygen can be safely and effectively used for postsurgical oral and periodontal wound care; treatment of acute and chronic forms of periodontal and peri-implant diseases; and management of dry sockets, halitosis, angular cheilitis, and oral ulcerations.

Further studies are necessary to investigate the long-term therapeutic benefits of topical oral oxygen formulations.

REFERENCES

1 Schwarz, F.; Jepsen, S.; Obreja, K.; Galarraga□Vinueza, M.E.; Ramanauskaite, A. Surgical therapy of peri□implantitis. J Periodontology 2022, 88, 145-181.

2 Politis, C.; Schoenaers, J.; Jacobs, R.; Agbaje, J.O. Wound healing problems in the mouth. Frontiers in physiology 2016, 7, 507.

3 Smith, P.C.; Martínez, C. Wound Healing in the Oral Mucosa. In Oral Mucosa in Health and Disease: A Concise Handbook, Bergmeier, L.A., Ed.; Springer International Publishing: Cham, 2018; pp. 77-90.

4 Heitz-Mayfield, L.J.A.; Lang, N.P. Surgical and nonsurgical periodontal therapy. Learned and unlearned concepts. Peridontology 2000 2013, 62, 218-231, doi:https://doi.org/10.1111/prd.12008.

5 Sischo, L.; Broder, H. Oral health-related quality of life: what, why, how, and future implications. Journal of dental research 2011, 90, 1264-1270.

6 Lalla, R.V.; Sonis, S.T.; Peterson, D.E. Management of Oral Mucositis in Patients Who Have Cancer. Dental Clinics of North America 2008, 52, 61-77, doi:https://doi.org/10.1016/j.cden.2007.10.002.

7 Acikan, I.; Sayeste, E.; Bozoglan, A.; Artas, G.; Isayev, A.; Kirtay, M.; Ozercan, I.H.; Yaman, F.; Dundar, S.; Icen, V. Evaluation of the Effects of Topical Application of Chlorhexidine, Ozone, and Metronidazole on Palatal Wound Healing: A Histopathological Study. Journal of Craniofacial Surgery 2022, 33, 1929-1933.

8 Ngeow, W.C.; Tan, C.C.; Goh, Y.C.; Deliberador, T.M.; Cheah, C.W. A Narrative Review on Means to Promote Oxygenation and Angiogenesis in Oral Wound Healing. Bioengineering 2022, 9, 636.

9 Toma, A.I.; Fuller, J.M.; Willett, N.J.; Goudy, S.L. Oral wound healing models and emerging regenerative therapies. Translational Research 2021, 236, 17-34, doi:https://doi.org/10.1016/j.trsl.2021.06.003.

10 Pulito, C.; Cristaudo, A.; Porta, C.L.; Zapperi, S.; Blandino, G.; Morrone, A.; Strano, S. Oral mucositis: the hidden side of cancer therapy. Journal of Experimental & Clinical Cancer Research 2020, 39, 210, doi:10.1186/s13046-020-01715-7.

11 DiPietro, L.A. Angiogenesis and wound repair: when enough is enough. Journal of Leukocyte Biology 2016, 100, 979-984, doi:10.1189/jlb.4MR0316-102R.

12 Honnegowda, T.M.; Kumar, P.; Udupa, E.G.P.; Kumar, S.; Kumar, U.; Rao, P. Role of angiogenesis and angiogenic factors in acute and chronic wound healing. Plastic Aesthetic Research 2015, 2, 243-249.

13 Pettet, G.; Chaplain, M.; McElwain, D.; Byrne, H. On the role of angiogenesis in wound healing. Proceedings of the Royal Society of London. Series B: Biological Sciences 1996, 263, 1487-1493.

14 Tonnesen, M.G.; Feng, X.; Clark, R.A.F. Angiogenesis in Wound Healing. Journal of Investigative Dermatology Symposium Proceedings 2000, 5, 40-46, doi:https://doi.org/10.1046/j.1087-0024.2000.00014.x.

15 AlZarea, B.K. Management of denture-related traumatic ulcers using ozone. The Journal of prosthetic dentistry 2019, 121, 76-82.

16 Isler, S.C.; Unsal, B.; Soysal, F.; Ozcan, G.; Peker, E.; Karaca, I.R. The effects of ozone therapy as an adjunct to the surgical treatment of peri-implantitis. Journal of periodontal implant science 2018, 48, 136-151.

17 Patel, P.V.; Kumar, S.; Vidya, G.; Patel, A.; Holmes, J.C.; Kumar, V. Cytological assessment of healing palatal donor site wounds and grafted gingival wounds after application of ozonated oil: an eighteen-month randomized controlled clinical trial. Acta cytologica 2012, 56, 277-284.

18 Patel, P.V.; Kumar, V.; Kumar, S.; Gd, V.; Patel, A. Therapeutic effect of topical ozonated oil on the epithelial healing of palatal wound sites: a planimetrical and cytological study. Journal of investigative clinical dentistry 2011, 2, 248-258.

19 Shekhar, A.; Srivastava, S.; Bhati, L.K.; Chaturvedi, A.; Singh, S.; Agarwal, B.; Arora, K. An evaluation of the effect of ozone therapy on tissues surrounding dental implants. International Immunopharmacology 2021, 96, 107588.

20 Ta□demir, Z.; Alkan, B.A.; Albayrak, H. Effects of ozone therapy on the early healing period of deepithelialized gingival grafts: a randomized placebo□controlled clinical trial. Journal of periodontology 2016, 87, 663-671.

21 Bennett, M.H.; Feldmeier, J.; Hampson, N.B.; Smee, R.; Milross, C. Hyperbaric oxygen therapy for late radiation tissue injury. Cochrane Database of Systematic Reviews 2016.

22 Condezo, A.B.; Araujo, R.; Koga, D.; Curi, M.; Cardoso, C.J.B.J.o.O. Hyperbaric oxygen therapy for the placement of dental implants in irradiated patients: systematic review and

meta-analysis. British Journal of Oral Maxillofacial Surgery 2021, 59, 625-632.

23 Shah, D.N.; Chauhan, C.J.; Solanki, J.S. Effectiveness of hyperbaric oxygen therapy in irradiated maxillofacial dental implant patients: A systematic review with meta-analysis. The Journal of the Indian Prosthodontic Society 2017, 17, 109.

24 Yin, Y.; Zeng, W.; Jing, W.; Tang, W.; Guo, W.H.; xi, H.; Qiang, k.; zh, y.x.z. Evaluation of hyperbaric oxygen therapy for the osteoradionecrosis of the jaws: Meta-analysis. West China Journal of Stomatology 2021, 39, 690-697.

25 Abonti, T.R.; Kaku, M.; Kojima, S.; Sumi, H.; Kojima, S.; Yamamoto, T.; Yashima, Y.; Miyahara, H.; Okino, A.; Kawata, T. Irradiation effects of low temperature multi gas plasma jet on oral bacteria. Dental Materials Journal 2016, 35, 822-828.

26 Bekeschus, S.; von Woedtke, T.; Emmert, S.; Schmidt, A. Medical gas plasma-stimulated wound healing: Evidence and mechanisms. Redox biology 2021, 46, 102116.

27 Harley, J.C.; Suchowerska, N.; McKenzie, D.R. Cancer treatment with gas plasma and with gas plasma–activated liquid: Positives, potentials and problems of clinical translation. Biophysical Reviews 2020, 12, 989-1006.

28 Cunha, E.J.; Auersvald, C.M.; Deliberador, T.M.; Gonzaga, C.C.; Esteban Florez, F.L.; Correr, G.M.; Storrer, C.L.M. Effects of active oxygen toothpaste in supragingival biofilm reduction: a randomized controlled clinical trial. International journal of dentistry 2019, 2019.

29 Deliberador, T.; Macalossi, J.; Tenorio, C.; Dall'Agnol, G.; Boia, M.; Zielak, J. Oxygen-releasing agent promotes healing of skin wounds in rats. Wound Care 2022.

30 Grootveld, M.; Lynch, E.; Page, G.; Chan, W.; Percival, B.; Anagnostaki, E.; Mylona, V.; Bordin-Aykroyd, S.; Grootveld, K.L. Potential Advantages of Peroxoborates and Their Ester Adducts Over Hydrogen Peroxide as Therapeutic Agents in Oral Healthcare Products: Chemical/Biochemical Reactivity Considerations In Vitro, Ex Vivo And In Vivo. Dentistry Journal 2020, 8, 89.

31 Hasturk, H.; Nunn, M.; Warbington, M.; Van Dyke, T.E. Efficacy of a Fluoridated Hydrogen Peroxide-Based Mouthrinse for the Treatment of Gingivitis: A Randomized Clinical Trial. Journal of periodontology 2004, 75, 57-65, doi:https://doi.org/10.1902/jop.2004.75.1.57.

32 Hossainian, N.; Slot, D.; Afennich, F.; Van der Weijden, G. The effects of hydrogen peroxide mouthwashes on the prevention of plaque and gingival inflammation: a systematic review. International journal of dental hygiene 2011, 9, 171-181.

33 Juliana, H.; Tarek, S. Comparative study of the effect of BlueM active oxygen gel and coe-pack dressing on postoperative surgical depigmentation healing. The Saudi Dental Journal 2022, 34, 328-334.

34 Marshall, M.V.; Cancro, L.P.; Fischman, S.L. Hydrogen Peroxide: A Review of Its Use in Dentistry. Journal of periodontology 1995, 66, 786-796, doi:https://doi.org/10.1902/jop.1995.66.9.786.

35 Mattei, B.M.; Imanishi, S.A.; de Oliveira Ramos, G.; de Campos, P.S.; Weiss, S.G.; Deliberador, T.M. Mouthwash with active oxygen (blue® m) induces keratinocytes proliferation. Open Journal of Stomatology Case Reports in Dentistry 2020, 10, 107.

36 Mattei, B.M.; Imanishi, S.A.; de Oliveira Ramos, G.; de Campos, P.S.; Weiss, S.G.; Deliberador, T.M. Mouthwash with active oxygen (blue® m) reduces postoperative inflammation and pain. Case Reports in Dentistry 2021, 2021, 1-6.

37 Muniz, F.W.M.G.; Cavagni, J.; Langa, G.P.J.; Stewart, B.; Malheiros, Z.; Rösing, C.K. A Systematic Review of the Effect of Oral Rinsing with H 2 O 2 on Clinical and Microbiological Parameters Related to Plaque, Gingivitis, and Microbes. International journal of dentistry 2020, 2020.

38 Harris, M. The conservative management of osteoradionecrosis of the mandible with ultrasound therapy. British Journal of Oral and Maxillofacial Surgery 1992, 30, 313-318, doi:https://doi.org/10.1016/0266-4356(92)90181-H.

39 Hu, B.; Zhang, Y.; Zhou, J.; Li, J.; Deng, F.; Wang, Z.; Song, J. Low-Intensity Pulsed Ultrasound Stimulation Facilitates Osteogenic Differentiation of Human Periodontal Ligament Cells. PLOS ONE 2014, 9, e95168, doi:10.1371/journal.pone.0095168.

40 Maddi, A.; Hai, H.; Ong, S.-T.; Sharp, L.; Harris, M.; Meghji, S. Long wave ultrasound may enhance bone regeneration by altering OPG/RANKL ratio in human osteoblast-like cells. Bone 2006, 39, 283-288, doi:https://doi.org/10.1016/j.bone.2006.01.162.

41 Yang, Z.; Ren, L.; Deng, F.; Wang, Z.; Song, J. Low-Intensity Pulsed Ultrasound Induces Osteogenic Differentiation of Human Periodontal Ligament Cells Through Activation of Bone Morphogenetic Protein–Smad Signaling. Journal of Ultrasound in Medicine 2014, 33, 865-873, doi:https://doi.org/10.7863/ultra.33.5.865.

42 Daigo, Y.; Daigo, E.; Hasegawa, A.; Fukuoka, H.; Ishikawa, M.; Takahashi, K. Utility of High-Intensity Laser Therapy Combined with Photobiomodulation Therapy for Socket Preservation After Tooth Extraction. Photobiomodulation, Photomedicine, and Laser Surgery 2019, 38, 75-83, doi:10.1089/photob.2019.4652.

43 Hosseinpour, S.; Tunér, J.; Fekrazad, R. Photobiomodulation in Oral Surgery: A Review. Photobiomodulation, Photomedicine, and Laser Surgery 2019, 37, 814-825, doi:10.1089/photob.2019.4712.

44 Zand, N.; Fateh, M.; Ataie-Fashtami, L.; Djavid, G.E.; Fatemi, S.-M.; Shirkavand, A. Promoting Wound Healing in Minor Recurrent Aphthous Stomatitis By Non-Thermal, Non-Ablative CO2 Laser Therapy: A Pilot Study. Photomedicine and Laser Surgery 2012, 30, 719-723, doi:10.1089/pho.2012.3301.

45 Blatt, S.; Thiem, D.G.E.; Pabst, A.; Al-Nawas, B.; Kämmerer, P.W. Does Platelet-Rich Fibrin Enhance the Early Angiogenetic Potential of Different Bone Substitute Materials? An In Vitro and In Vivo Analysis. Biomedicines 2021, 9, doi:10.3390/biomedicines9010061.

46 Martínez, C.E.; Smith, P.C.; Palma Alvarado, V.A. The influence of platelet-derived products on angiogenesis and tissue repair: a concise update. Frontiers in physiology 2015, 6, doi:10.3389/fphys.2015.00290.

47 Rengarajoo, J.; Ngeow, W.C.; Ibrahim, N.B. The effects of lyophilised platelet-rich plasma in third molar extraction sockets and its surrounding tissues. Journal of Taibah University Medical Sciences 2022, 17, 289-296, doi:https://doi.org/10.1016/j.jtumed.2021.10.015.

48 Aras-Tosun, D.; Önder, C.; Akdo□an, N.; Kurgan, □.; Aktay, □.; Tuncay, E.; Orhan, K. Astaxanthin Enhances Gingival Wound Healing following High Glucose-Induced Oxidative Stress. BioMed Research International 2022, 2022.

49 Dalessandri, D.; Zotti, F.; Laffranchi, L.; Migliorati, M.; Isola, G.; Bonetti, S.; Visconti, L. Treatment of recurrent aphthous stomatitis (RAS; aphthae; canker sores) with a barrier forming mouth rinse or topical gel formulation containing hyaluronic acid: a retrospective clinical study. BMC Oral Health 2019, 19, 1-10.

50 Sun, B.; Wu, L.; Wu, Y.; Zhang, C.; Qin, L.; Hayashi, M.; Kudo, M.; Gao, M.; Liu, T. Therapeutic potential of Centella asiatica and its triterpenes: A review. Frontiers in pharmacology 2020, 11, 568032.

51 Diego M. Castilla; Zhao-Jun Liu; Velazquez, O.C. Oxygen: Implications for Wound Healing. Advances in wound care 2012, 1, 225-230, doi:10.1089/wound.2011.0319.

52 Hashimoto, T.; Shibasaki, F. Hypoxia-Inducible Factor as an Angiogenic Master Switch. Front. Pediatr. 2015, 3, doi:10.3389/fped.2015.00033.

53 Caley, M.P.; Martins, V.L.C.; O'Toole, E.A. Metalloproteinases and Wound Healing. Advances in Wound Care 2015, 4, 225-234, doi:10.1089/wound.2014.0581.

54 Dunnill, C.; Patton, T.; Brennan, J.; Barrett, J.; Dryden, M.; Cooke, J.; Leaper, D.; Georgopoulos, N.T. Reactive oxygen species (ROS) and wound healing: the functional role of ROS and emerging ROS-modulating technologies for augmentation of the healing process. International Wound Journal 2017, 14, 89-96, doi:https://doi.org/10.1111/iwj.12557.

55 Bryan, N.; Ahswin, H.; Smart, N.; Bayon, Y.; Wohlert, S.; Hunt, J.A. Reactive oxygen species (ROS)–a family of fate deciding molecules pivotal in constructive inflammation and wound healing. Eur Cell Mater 2012, 24, e65.

56 Zorov, D.B.; Juhaszova, M.; Sollott, S.J. Mitochondrial Reactive Oxygen Species (ROS) and ROS-Induced ROS Release. Physiological reviews 2014, 94, 909-950, doi:10.1152/physrev.00026.2013.

57 LaVan, F.B.; Hunt, T.K. Oxygen and Wound Healing. Clinics in Plastic Surgery 1990, 17, 463-472, doi:https://doi.org/10.1016/S0094-1298(20)30621-0.

58 Sen, C.K. Wound healing essentials: Let there be oxygen. the International Journal of Tissue Repair and Regeneration 2009, 17, 1-18, doi:https://doi.org/10.1111/j.1524-475X.2008.00436.x.

59 Sjöberg, F.; Singer, M. The medical use of oxygen: a time for critical reappraisal. Journal of internal medicine 2013, 274, 505-528, doi:https://doi.org/10.1111/joim.12139.

60 Gottrup, F.; Dissemond, J.; Baines, C.; Frykberg, R.; Jensen, P.Ø.; Kot, J.; Kröger, K.; Longobardi, P. Use of oxygen therapies in wound healing: focus on topical and hyperbaric oxygen treatment. Journal of wound care 2017, 26, S1-S43.

61 Sun, X.-K.; Li, R.; Yang, X.-L.; Yuan, L. Efficacy and safety of topical oxygen therapy for diabetic foot ulcers: An updated systematic review and meta-analysis. International Wound Journal 2022, 19, 2200-2209, doi:https://doi.org/10.1111/iwj.13830.

62 Lei, H.; Zhao, J.; Li, H.; Fan, D. Paramylon hydrogel: A bioactive polysaccharides hydrogel that scavenges ROS and promotes angiogenesis for wound repair. Carbohydrate Polymers 2022, 289, 119467, doi:https://doi.org/10.1016/j.carbpol.2022.119467.

63 Li, Y.; Fu, R.; Duan, Z.; Zhu, C.; Fan, D. Artificial Nonenzymatic Antioxidant MXene Nanosheet-Anchored Injectable Hydrogel as a Mild Photothermal-Controlled Oxygen Release Platform for Diabetic Wound Healing. ACS Nano 2022, 16, 7486-7502, doi:10.1021/acsnano.1c10575.

64 Pu, Y.; Wang, P.; Yang, R.; Tan, X.; Shi, T.; Ma, J.; Xue, W.; Chi, B. Bio-fabricated nanocomposite hydrogel with ROS scavenging and local oxygenation accelerates diabetic wound healing. Journal of Materials Chemistry B 2022, 10, 4083-4095, doi:10.1039/D2TB00343K.

65 Soleimanpour, M.; Mirhaji, S.S.; Jafari, S.; Derakhshankhah, H.; Mamashli, F.; Nedaei, H.; Karimi, M.R.; Motasadizadeh, H.; Fatahi, Y.; Ghasemi, A.; et al. Designing a new alginate-fibrinogen biomaterial composite hydrogel for wound healing. Scientific Reports 2022, 12, 7213, doi:10.1038/s41598-022-11282-w.

66 Zheng, Z.; Qi, J.; Hu, L.; Ouyang, D.; Wang, H.; Sun, Q.; Lin, L.; You, L.; Tang, B. A cannabidiol-containing alginate based hydrogel as novel multifunctional wound dressing for promoting wound healing. Biomaterials Advances 2022, 134, 112560, doi:https://doi.org/10.1016/j.msec.2021.112560.

67 Vulakh, G.M.; Hingorani, A.P.; Ascher, E.; Marks, N. Adjunctive topical oxygen therapy for wound healing in patients with peripheral arterial disease. Cardiology and Cardiovascular Medicine 2022, 0, 17085381221080270, doi:10.1177/17085381221080270.

68 Velding, K.; Klis, S.A.; Abass, K.M.; Tuah, W.; Stienstra, Y.; van der Werf, T. Wound care in Buruli ulcer disease in Ghana and Benin. The American journal of tropical medicine and hygiene 2014, 91, 313-318, doi:10.4269/ajtmh.13-0255.

69 Gold, S.I. Early origins of hydrogen peroxide use in oral hygiene. A historical note. Journal of periodontology 1983, 54, 247, doi:10.1902/jop.1983.54.4.247.

70 Wade, A.; Mirza, K. The relative effectiveness of sodium peroxyborate and hydrogen peroxide in treating acute ulcerative gingivitis. Dent Prac 1964, 14, 185-189.

71 Rees, T.D.; Orth, C.F. Oral Ulcerations with Use of Hydrogen Peroxide. Journal of periodontology 1986, 57, 689-692, doi:https://doi.org/10.1902/jop.1986.57.11.689.

72 Tombes M.B.; Gallucci, B. The Effects of Hydrogen Peroxide Rinses on the Normal Oral Mucosa. Nursing research 1993, 42, 332-337.

73 Bauer, J.A.; Zámocká, M.; Majtán, J.; Bauerová-Hlinková, V. Glucose Oxidase, an Enzyme & Its Structure, Function, Production and Properties in the Light of Various Industrial and Biotechnological Applications. Dentistry Journal 2022, 12, 472.

74 Sy, K.; Flamme, J.; Maquet, H.; Chai, F.; Neut, C.; Siepmann, F.; Agossa, K. Antimicrobial effect and physical properties of an injectable "active oxygen" gel for the treatment of periodontitis. Am J Dent 2020, 33, 305-309.

75 Niveda, R.; Kaarthikeyan, G. Effect of Oxygen Releasing Oral Gel Compared to Chlorhexidine Gel in the Treatment of Periodontitis. J. Pharm. Res. Int 2020, 32, 75-82.

76 Shibli, J.A.; Rocha, T.F.; Coelho, F.; de Oliveira Capote, T.S.; Saska, S.; Melo, M.A.; Pingueiro, J.M.S.; de Faveri, M.; Bueno-Silva, B. Metabolic activity of hydro-carbon-oxo-borate on a multispecies subgingival periodontal biofilm: a short communication. Clinical Oral Investigations 2021, 25, 5945-5953, doi:10.1007/s00784-021-03900-0.

77 Deliberador, T.M.; Weiss, S.G.; Rychuv, F.; Cordeiro, G.; Cate, M.C.L.T.; Leonardi, L.; Brancher, J.o.A.; Scariot, R. Comparative Analysis in Vitro of the Application of blue®m Oral Gel versus Chlorhexidine on Porphyromonas gingivalis: A Pilot Study. Advances in Microbiology 2020, Vol.10No.04, 8, doi:10.4236/aim.2020.104015.

78 Ozawa, R.; Saita, M.; Sakaue, S.; Okada, R.; Sato, T.; Kawamata, R.; Sakurai, T.; Hamada, N.; Kimoto, K.; Nagasaki, Y. Redox injectable gel protects osteoblastic function against oxidative stress and suppresses alveolar bone loss in a rat peri-implantitis model. Acta Biomaterialia 2020, 110, 82-94, doi:https://doi.org/10.1016/j.actbio.2020.04.003.

79 Berglundh, T.; Armitage, G.; Araujo, M.G.; Avila□Ortiz, G.; Blanco, J.; Camargo, P.M.; Chen, S.; Cochran, D.; Derks, J.; Figuero, E. Peri□implant diseases and conditions: Consensus report of workgroup 4 of the 2017 World Workshop on the Classification of Periodontal and Peri□Implant Diseases and Conditions. Journal of periodontology 2018, 89, S313-S318.

80 Khoury, F.; Keeve, P.L.; Ramanauskaite, A.; Schwarz, F.; Koo, K.T.; Sculean, A.; Romanos, G. Surgical treatment of peri□implantitis–Consensus report of working group 4. International dental journal 2019, 69, 18-22.

81 Furiya-Sato, S.; Fukushima, A.; Mayanagi, G.; Sasaki, K.; Takahashi, N. Electrochemical evaluation of the hydrogen peroxide-and fluoride-induced corrosive property and its recovery on the titanium surface. journal of prosthodontic research 2020, 64, 307-312.

82 Aoki, K.; Ida, Y.; Fukushima, N.; Matsumura, H. Topical application of oxygen nano□bubble water enhances the healing process of ischaemic skin wound healing in an animal model. International Wound Journal 2022, 19, 1843-1852.