

Nano-emulgel formulation of lemongrass extract (*Cymbopogon citratus*) as herbal-based topical drug for oral mucositis: A review

Brian Limantoro ^{1,*}, Melati Utami ², Felice Kanaya Chandra ¹, Ni Komang Intan Putri Sari ¹, Nadia Jannah ¹, Bayu Cahyo Bintoro ¹, Michelle Ellen Kimberly ¹, Evelyn Nathania Prasetyo ¹, Angelina Moonieque Prasetyo ¹ and Irhenyta Dwi Putri Lestari ¹

¹ Department of Oral Medicine, Faculty of Dental Medicine, Airlangga University, Surabaya, East Java, Indonesia.

² Department of Pharmacy, Faculty of Science, Technology Institute of Sumatera, Bandar Lampung, Lampung, Indonesia.

World Journal of Advanced Research and Reviews, 2024, 24(01), 1672–1679

Publication history: Received on 09 September 2024; revised on 16 October 2024; accepted on 18 October 2024

Article DOI: <https://doi.org/10.30574/wjarr.2024.24.1.3192>

Abstract

Background: Oral mucositis is a condition characterized by inflammation and ulceration of the oral mucosa, commonly affecting cancer patients undergoing chemotherapy or radiotherapy, with MRSA infection as a significant contributing factor. This condition impairs mucosal barrier function, increasing susceptibility to secondary infections, especially from MRSA, which thrives in the moist environment of the oral cavity. Secondary infections by MRSA exacerbate symptoms, delay healing, and complicate the clinical presentation of mucositis through the production of virulence factors like enterotoxins and exfoliative toxins.

Purpose: Explaining the potential of lemongrass extract and its combination with nanoemulgel formulation as herbal intervention against oral mucositis.

Method: A literature review of studies published within the past five years from sources like ResearchGate, ScienceDirect, PubMed, and Google Scholar.

Result: Lemongrass extract comprises prominent amount of citral, emphasizing anti-inflammatory and antioxidant capabilities. Combination with nanoemulgel phase will provide stability and enhanced therapeutic capabilities of lemongrass extract into the targeted oral site.

Conclusion: The formulation of lemongrass extract nanoemulgel equipped can be a futuristic solution as an over-the-counter drug for minimally invasive therapy of oral mucositis.

Keywords: lemongrass extract; Nanoemulgel formulation; Oral mucositis; Topical drug

1. Introduction

Oral mucositis is a condition characterized by inflammation and ulceration of the oral mucosa, often found in cancer patients undergoing chemotherapy or radiotherapy, with Methicillin-Resistant-*Staphylococcus aureus* (MRSA) infection as one of the main contributing factors.^[1] Symptoms of oral mucositis include signs of inflammation such as redness, heat, pain, swelling, and impaired function, as well as ulceration that can interfere with stomatognathic function and articulation.^[1] Research by Kisacik et al. (2023)^[2] showed that the prevalence of oral mucositis in cancer patients ranges from 40–75%, with a higher incidence in cisplatin-based therapy and radiation in the head and neck area. Oral mucositis usually begins with damage to the mucosal epithelial cells due to the cytotoxic effects of chemotherapy or radiotherapy,

* Corresponding author: Brian Limantoro

which triggers the release of proinflammatory cytokines and causes an inflammatory response. This damage impairs the mucosal barrier function, increasing susceptibility to secondary infection by MRSA, which often occurs through contact with dental instruments used by dentists.^[3]

MRSA tends to infect exposed areas because the oral mucosa provides an ideal environment for the growth and virulence of the microorganism due to its favorable moisture and temperature. These secondary infections can delay the healing of oral mucositis, worsen symptoms, and add complexity to the clinical manifestations of mucositis through MRSA virulence factors.^[4] Enterotoxins produced by MRSA can worsen the infection to affect the gastrointestinal tract, while exfoliative toxins support additional damage to the mucous membrane, increasing the aggressiveness of MRSA in the oral mucosa.^[5,6]

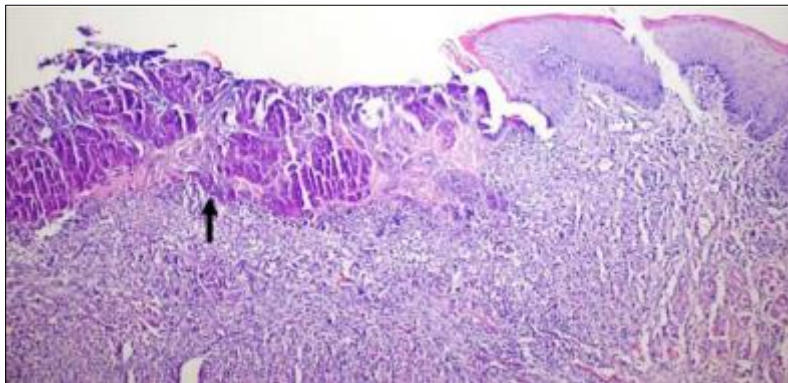


Figure 1 Microscopical Appearances of Oral Mucositis

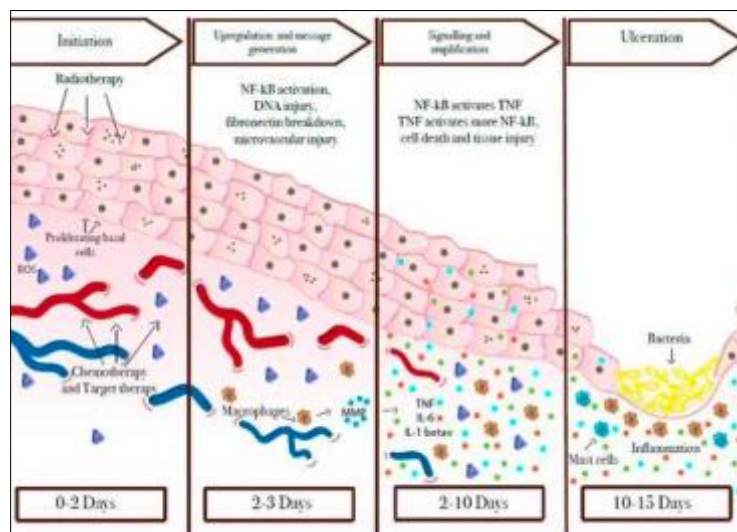


Figure 2 MRSA Invasion During Ulceration Phase of Oral Mucositis

2. Material and methods

A literature review exploring the potential of herbal remedies, specifically lemongrass extract and nanoemulgel formulation, as therapeutic methods for oral mucositis, which can be an early symptom of more severe manifestations, was conducted by searching and compiling scientific articles and data. These form the foundation and provide supporting evidence for arguments favouring the use of lemongrass extract–nanoemulgel formulation in oral mucositis treatment. Articles and data were sourced from reputable scientific databases, such as PubMed, ScienceDirect, ResearchGate, and supplementary databases like Google Scholar, to gather research findings relevant to the situation in Indonesia, which aligns with the objectives of this literature review.

Several key phrases were used to aid the search process, including terms related to lemongrass extract, nanoemulgel formulation, and their abilities against either MRSA infection or oral mucositis. Another aspect considered during the

collection process was ensuring that the articles and data were up-to-date. Only articles published within the last five years were selected, with the oldest articles being from 2014.

A total of 2,986 articles were retrieved through the search process and were gradually filtered based on their relevance to the objectives of the literature review. Ultimately, 21 related articles were used in the preparation of this review.

3. Results and discussion

Currently, oral mucositis therapy requires a very complex approach because many aspects must be considered to ensure its effectiveness and address the root cause comprehensively. Therefore, an invasive approach is considered more promising as a therapeutic option. In the context of oral mucositis, an invasive approach includes not only medical procedures but also pharmacological therapy used. Current standard therapy involves excision procedures, which can increase the risk of MRSA infection, as well as the use of photobiomodulation (PBM) therapy as an anti-inflammatory.^[7] However, recent studies by Kusiak et al. (2020)^[8] and Nugent et al. (2022)^[7] showed that after these procedures, there is often a risk of hypersensitivity and burning sensation. In addition, this orthodox standard procedure still requires pharmacological-based supportive therapy, such as oral and topical drugs. Unfortunately, both types of drugs have significant side effects that are not comparable to their benefits, thus worsening the severity of oral mucositis after therapy.

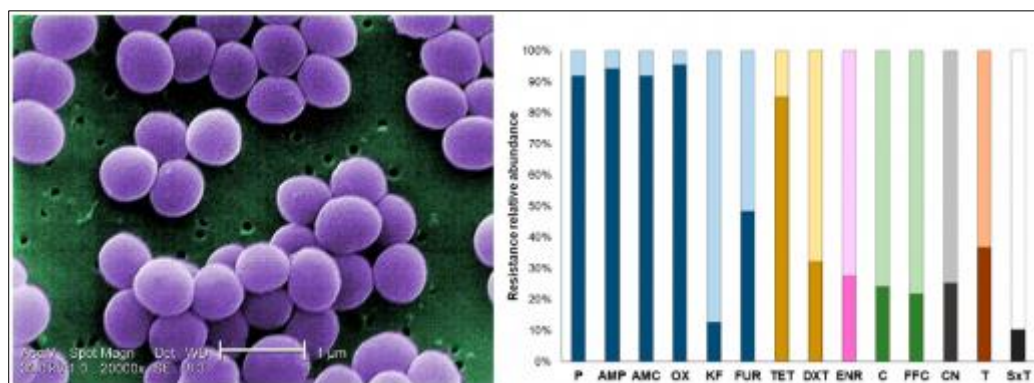


Figure 3 MRSA Profile and Resistance Ability Against Wide Broad Spectrum Antibiotics

Oral drugs such as antibiotics are becoming less effective because MRSA, a mutated strain of *Staphylococcus aureus*, shows resistance to various antibiotics.^[9] Meanwhile, topical drugs that are generally corticosteroids can reduce the body's immune function, increasing the virulence of invasive agents in lesions.^[10] Therefore, the therapy that is currently considered the gold standard requires more attention, considering the low success rate as reported in the study of Gholizadeh et al. (2016)^[11] and the many complex requirements that make it less suitable for rural and lower-class communities. This encourages a shift in the development of conventional therapy towards herbal-based therapy as a more friendly minimally invasive therapy. Practical and economic values are certainly key aspects that are highly considered by the community in encouraging an increase in their quality of life so that topical drugs that are practical, affordable, and light; but still have high efficacy and low side effects, are the best solution that is greatly needed by the entire community for oral mucositis therapy.

Therefore, lemongrass extract–nanoemulgel formulation comes with superior therapeutic capabilities of lemongrass extract for oral mucositis therapy, supported by a better drug delivery system to increase herbal efficacy. Lemongrass (*Cymbopogon citratus*) is a spice widely known to the Indonesian people, its distinctive aroma makes it the most frequently used aromatic ingredient in Indonesian cuisine. The interesting thing about lemongrass features in the medical world includes the citral content which is a characteristic, only found in lemongrass, supported by positive claims related to its extraordinary capabilities; both as anti-inflammatory, antioxidant, and antimicrobial; including the specific ability to target MRSA, the secondary etiology of oral mucositis.



Figure 4 Lemongrass (*Cymbopogon citratus*)

Lemongrass (*Cymbopogon citratus*) is a type of herb with strong aromatic characteristics, with citral compounds dominating 80% of the chemical properties of lemongrass. Chemically, citral is composed of two isomer geometry, consisting of geranial and neral isomers, which are polarly soluble in organic or non-polar solvents.^[12] Through studies conducted by Yan et al. (2016)^[13] and Gutierrez-Pacheco et al. (2023)^[14], citral is able to act as an anti-inflammatory and antioxidant in oral mucositis, especially in the early stages of administration. In addition, claims proven by Long et al. (2019)^[15], show that citral activity in lemongrass is able to inhibit MRSA in in vitro studies.

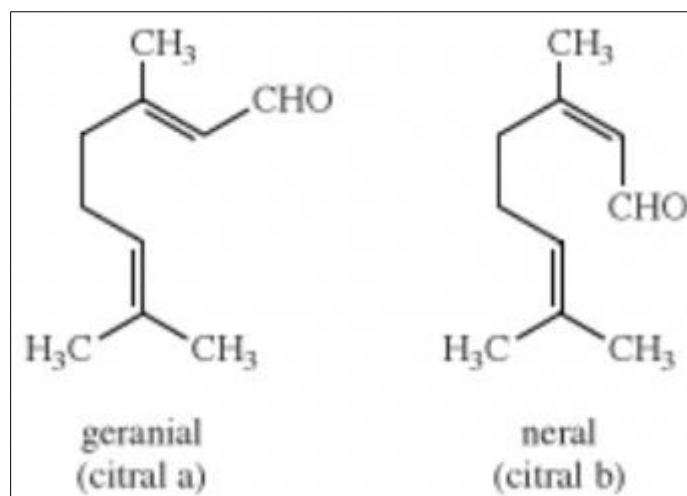


Figure 5 Chemical Structure of Citral, Encompassing Geranial (Citral a) and Neral Isomer (Citral b)

Meanwhile, the role of citral as an anti-inflammatory is shown through inhibition of the excessive release of pro-inflammatory cytokines interleukin (IL-1 β , IL-6, IL-12p70, IL-23, IFN- γ , and TNF- α), where both cytokines play a dominant role in increasing the intensity of vasodilation, causing access for antigens to enter cells to increase.^[16] In addition, its role as an anti-inflammatory and analgesic agent is also very dominant, having very good inhibitory abilities against COX-2 and lipoxygenase (LOX), dominant pro-inflammatory mediators in pain management.^[16] This is also supported by the ability of citral to influence the PPAR- γ signaling pathway and increase suppression of NF- κ B which plays an important role in the gene transcription process of inflammatory cells.^[14] Its role as an anti-inflammatory automatically also describes the role of citral as an antioxidant, through management of pro-inflammatory mediators, coupled with its ability to activate the Nrf2 pathway which plays a key role as an antioxidant in preventing lipid peroxidation, mutually synergistically support each other's role as anti-inflammatories and antioxidants.^[17]

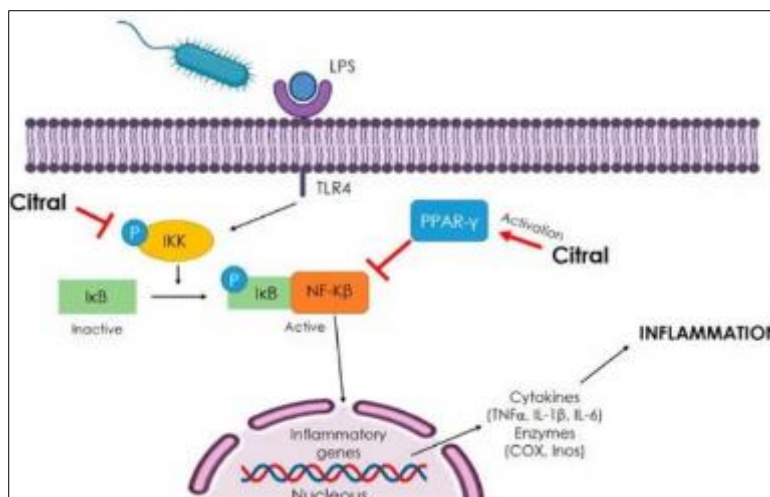


Figure 6 Mechanism of Action (MoA) from Citral

The role of citral does not only stop at its ability as an anti-inflammatory and antioxidant at the beginning of therapeutic action, but also in its capacity as an antimicrobial as an anticipation of the potential for MRSA invasion at the ulceration stage. Citral has good antimicrobial activity against MRSA very well through a very low minimum dose as a minimum inhibitory concentration (MIC). Meanwhile, the mechanism of action of citral as an antimicrobial against MRSA is through the disruption pattern of the integrity of the MRSA cell membrane and inhibition of the formation of MRSA biofilms.^[15] Specifically, literature studies on the citral profile can be accessed through **Table 1** below.

Table 1 Literature Study of Citral Profile

Author(s)	Year Published	Country	Study Design	Scientific Findings
Oliveira et al. ^[16]	2021	Brazil	RCT	Citral at all concentrations, namely 1%, 2%, and 4%, was able to suppress the release of pro-inflammatory cytokines IL-1 β , IL-6, IL-12p70, IL-23, IFN- γ , and TNF- α .
Yan et al. ^[13]	2016	China	RCT	Citral decreases IL-6, TNF- α , total leukocytes, and inhibit NF- κ B activation through lipopolysaccharides (LPS) induction.
Gutierrez-Pacheco et al. ^[14]	2023	Mexico	RCT	Citral activates the PPAR- γ pathway which can then inhibit NF- κ B so that the gene transcription process of inflammatory cells is inhibited and proinflammatory cytokines fail to be released.
Ohnishi et al. ^[17]	2024	Japan	RCT	Citral acts as a renoprotective agent by inhibiting oxidative stress and apoptosis, through early activation of the Nrf2 signaling pathway, in citral treatment of mice at a dose of 200 mg/kg on the 28th day.
Long et al. ^[15]	2019	China	RCT	Citral showed the ability to inhibit the growth of MRSA at a very low minimum dose (MIC) of 0.5%; while the ability to kill bacteria as a whole (bactericidal) against MRSA at a minimum dose (MBC) of 1%.

Thus, citral has been proven to have amazing, complete capabilities and meets all the requirements for oral mucositis therapy. However, challenges have begun to emerge regarding the bioavailability of citral compounds or the herbal properties of lemongrass, considering that herbal properties are known for their very weak mechanical properties, resulting in the extract not being able to reach target cells effectively and efficiently. In other words, herbal bioavailability is a challenge in its application as an independent therapeutic drug, when viewed from a realistic aspect. Therefore, efforts to potentiate herbs as independent drugs that are friendly and friendly to all levels of society must be maximized. Through the development of nanotechnology, efforts to make citral-based lemongrass extract an independent product without the intervention of invasive agents can be realized in real terms, through extract

protection in a nanoemulsion encapsulation so that the bioavailability and efficacy of lemongrass extract can be maximized.

The idea of combining with nanotechnology raises a question, regarding how to incorporate this lemongrass extract with this revolutionary technology, considering that there are actually many nanotechnology options and procedures that can be used for medical purposes. The solution to this problem must be adjusted to the indication and how the approach of the drug administration mode for this case is, but considering all aspects, from the properties and location of the lesion; practical value; to efficacy and bioavailability, the topical administration mode is the most suitable option. Therefore, the type of nanotechnology that is adequate to support this administration mode falls on nanoemulgel, a modification of nanoparticles with a final preparation in gel form.

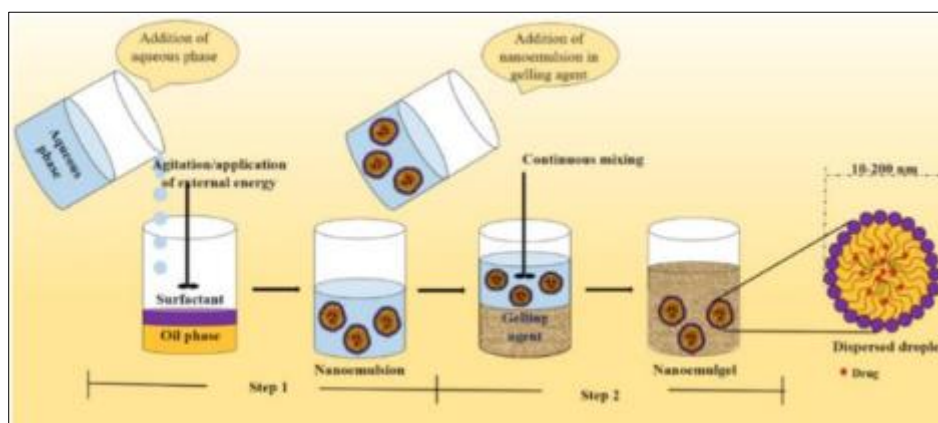


Figure 7 Nanoemulgel Processing

This preparation is formed through two processes that begin with the formation of a nanoemulsion that utilizes an oil phase that can be obtained from the lemongrass extract element and an aqueous phase assisted by an emulsifier compound using the high energy sonication method to form a lemongrass extract that is encapsulated in a nano-sized capsule forming a perfect sphere. Furthermore, the nanoemulsion will be given a polymer-based gelling agent to form a nanoemulsion structure that is applied topically.^[18]



Figure 8 Nanoemulgel Formulation Output

Nanoemulgel itself has obtained various positive claims as shown through literature studies related to nanoemulgel in **Table 2** below. Compared to conventional topical preparations, nanoemulgel facilitates the penetration ability of extracts, penetrates the stratum corneum and reaches the dermis layer, through its very small particle size, plus better distribution ability through incorporation with gelling agents so that distribution becomes more even and well concentrated.^[19] Other features that make nanoemulgel the best option are related to its excellent stability and a more targeted and controlled drug release system.^[19] Reviewing the biocompatibility aspect, the nanoemulgel method has obtained an amazing claim where this method is actually able to reduce all risks of side effects on systemic absorption which are challenges of conventional topical preparations.^[20]

Table 2 Literature Study of Notable Features of Nanoemulgel Compared to Conventional Topical

Author(s)	Year Published	Country	Study Design	Scientific Findings
Rao et al. ^[19]	2021	India	RCT	Nanoemulgel facilitates a better hydrophobic or lipophilic drug delivery system through dimensional stability that tends to be stable; supported by an incorporation system through gelation techniques facilitating a more controlled drug release system.
Alyoussef et al. ^[21]	2021	Saudi Arabia	RCT	Nanoemulgel increases the rate of drug distribution with further and more even penetration. As a result, antioxidant and anti-inflammatory activities increase significantly, and remodeling can be facilitated optimally.
Algahtani et al. ^[18]	2021	Saudi Arabia	RCT	Nanoemulgel with high energy sonication and gelled with Carbopol produces droplets measuring 56.25 ± 0.69 nm with a polydispersity index of 0.05 ± 0.01 ; significantly increasing therapeutic efficacy and mucosal permeability ($p < 0.05$).
Jivani et al. ^[20]	2018	India	RCT	Compared to conventional topical preparations that tend to come in cream form, nanoemulgel produces a smoother and less sticky consistency, resulting in its characteristics not being absorbed systemically so that the potential for systemic toxicity can be minimized.

4. Conclusion

The formulation of lemongrass extract nanoemulgel equipped with adequate comfort features in the form of a smoother and non-sticky texture, can be a futuristic solution that is friendly and environmentally friendly to the community and the ecological environment to be applied as an over-the-counter drug for minimally invasive therapy of oral mucositis.

Compliance with ethical standards

Acknowledgments

We would like to express our sincere gratitude to everyone who contributed to the completion of this study on the utilization of lemongrass extract and nanoemulgel combination against oral mucositis. First and foremost, we thank Fatma Yasmin Mahdani, DDS., MPH. for her invaluable guidance, support, and expertise throughout the research process. We also extend our appreciation to the Airlangga University, Muhammadiyah Yogyakarta University, and xxxx for providing the necessary resources and facilities that enabled us to conduct our experiments. Additionally, we are grateful to our peers and colleagues who provided insights and feedback during the development of this article. Their constructive criticism helped improve the quality of our work. Finally, we would like to acknowledge our families and friends for their unwavering support and encouragement, which motivated us to complete this study.

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Statement of ethical approval

As this article is a review of previously published research, no new human or animal studies were conducted by the authors. Therefore, ethical approval was not required.

Statement of informed consent

This review article is based on previously published studies, and no new human participants were involved. Therefore, informed consent was not required. All cited studies obtained informed consent from their participants as per their respective ethical guidelines.

References

- [1] Bell A, Kasi A Oral Mucositis [Updated 2023 May 29] StatPearls [Internet] Treasure Isl StatPearls Publ 2024 Jan- Available from <https://www.ncbi.nlm.nih.gov/books/NBK565848/> [Internet].
- [2] Gürlek Kısacık Ö, Özdaş A, Coşgun İG Investig Preval oral mucositis Assoc risk factors chronic Obstr Pulm Dis patients A Prospect cross-sectional study Thorac Res Pr 2023;24(3)143-150 [Internet].
- [3] Donkor ES, Kotey FC Methicillin-Resistant Staphylococcus aureus Oral Cavity Implic Antibiot Prophyl Surveillance Infect Dis Res Treat 2020;13 doi101177/1178633720976581 [Internet].
- [4] Allana A, Shamsi U, Rashid Y, Khan FR, Rozi S Oral mucositis oral Heal Relat Qual life women undergoing Chemother breast cancer Karachi, Pakistan A Multicent Hosp based cross-sectional study PLOS ONE 19(4) e0295456.
- [5] Kwapisz, E, Garbacz, K, Kosecka-Strojek, M al Presence egc-positive major clones ST 45, 30 22 among methicillin-resistant methicillin-susceptible oral Staphylococcus aureus strains Sci Rep 10, 18889 (2020).
- [6] Garbacz K, Kwapisz E, Piechowicz L, Wierzbowska M Staphylococcus aureus Isol from Oral Cavity Phage Susceptibility Relat to Antibiot Resist Antibiot 2021; 10(11)1329.
- [7] Nugent M, Bryant V, Butcher C, Fisher H, Gill S, Goranova R, et al. Photobiomodulation in the management of oral mucositis for adult head and neck cancer patients receiving irradiation: the LiTEFORM RCT [Internet]. Vol. 26. p. 46.
- [8] Kusiak A, Jereczek-Fossa BA, Cichońska D, Alterio D. Oncological-Therapy Related Oral Mucositis as an Interdisciplinary Problem—Literature Review. Vol. 17, International Journal of Environmental Research and Public Health. 2020.
- [9] Martin V, Dorte F, Hanne I. Antibiotic Resistance and the MRSA Problem. Microbiol Spectr [Internet]. 2019 Mar 22;7(2):10.1128/microbiolspec.gpp3-0057-2018.
- [10] Youssef J, Novosad SA, Winthrop KL. Infection Risk and Safety of Corticosteroid Use. Rheum Dis Clin North Am [Internet]. 2016;42(1):157–76.
- [11] Gholizadeh N, Sheykhbaehi N, Sadrzadeh-Afshar MS. New Treatment Approaches of Oral Mucositis: A Review of Literature. Adv Hum Biol [Internet]. 2016;6(2).
- [12] Tajidin, N. E. Chemical composition and citral content in lemongrass (*Cymbopogon citratus*) essential oil at three maturity stages. African J Biotechnol. 2012;11(11):2685–93.
- [13] Song Y, Zhao H, Liu J, Fang C, Miao R. Effects of Citral on Lipopolysaccharide-Induced Inflammation in Human Umbilical Vein Endothelial Cells. Inflammation [Internet]. 2016;39(2):663–71.
- [14] Gutiérrez-Pacheco MM, Torres-Moreno H, Flores-Lopez ML, Velázquez Guadarrama N, Ayala-Zavala JF, Ortega-Ramírez LA, et al. Mechanisms and Applications of Citral's Antimicrobial Properties in Food Preservation and Pharmaceuticals Formulations. Vol. 12, Antibiotics. 2023.
- [15] Long N, Tang H, Sun F, Lin L, Dai M. Effect and mechanism of citral against methicillin-resistant Staphylococcus aureus in vivo. J Sci Food Agric [Internet]. 2019 Jul 1;99(9):4423–9.
- [16] Oliveira HBM, das Neves Selis N, Brito TLS, Sampaio BA, de Souza Bittencourt R, Oliveira CNT, et al. Citral modulates human monocyte responses to Staphylococcus aureus infection. Sci Rep [Internet]. 2021;11(1):22029.
- [17] Ohnishi M, Banshoya K, Machida A, Kikuchi N, Yamaguchi S, Akagi M, et al. Aroma of citral repels mice and exerts antioxidant effects as a functional food. Flavour Fragr J [Internet]. 2024 Jul 4.
- [18] Algahtani MS, Ahmad MZ, Nourein IH, Albarqi HA, Alyami HS, Alyami MH, et al. Preparation and Characterization of Curcumin Nanoemulgel Utilizing Ultrasonication Technique for Wound Healing: In Vitro, Ex Vivo, and In Vivo Evaluation. Vol. 7, Gels. 2021.
- [19] Rao SV, Bhagya D, Vani S, Padmalatha K. Topical Nanoemulgel : A Novel Approach for Wound Healing Efficacy. J Chem Pharm Res [Internet]. 2021;13(9):1–09.
- [20] Malay N Jivani CPP and BGP. Nanoemulgel Innovative Approach for Topical Gel Based Formulation.
- [21] Alyoussef A, El-Gogary RI, Ahmed RF, Ahmed Farid OAH, Bakeer RM, Nasr M. The beneficial activity of curcumin and resveratrol loaded in nanoemulgel for healing of burn-induced wounds. J Drug Deliv Sci Technol [Internet]. 2021;62:102360.