

Effect of *Calendula officinalis* Linn in Oral health- A Review

Review Article

Nagaraj NJ^{1*}, Ravikumar N², Mahalaxmi S³, Pallavi S¹

1. Senior Lecturer, Department of Conservative Dentistry and Endodontics, Rajas Dental College and Hospital, Kavalkinaru Junction, Tirunelveli district. Tamilnadu, India.
2. Reader, 3. Professor and Head, Department of Conservative Dentistry and Endodontics, SRM Dental College and Hospital, Ramapuram, Chennai, Tamilnadu, India.

Abstract

Calendula officinalis L., a member of the Asteraceae family, is often known as English Marigold or Pot Marigold. Marigold is an annual or perennial herb traditionally used to treat wounds, ulcers, herpes, scars, skin damage, frostbite, and blood purification. It is mainly used to treat disorders as an anti-diabetic, anti-ulcer, anti-inflammatory, and analgesic activity because of its numerous biological properties. This plant has a high concentration of medicinally active substances such as carotenoids, flavonoids, glycosides, steroids and sterols, quinines, volatile oil, and amino acids. The plant extract, as well as the pure compound derived from it, has been shown to have a variety of pharmacological properties, including anti-cytotoxic, hepatoprotective, and spasmolytic effects, among others. It is used to treat oral mucositis, angular cheilitis, periodontal bone loss, leukoplakia and also used as a root canal irrigant, intracanal medicament, and anti-plaque agent in dentistry. It also helps to heal and manage microbial plaque in gingivitis and periodontitis, boosting immunity. The most significant obstacle and concern is the lack of knowledge regarding the effects of *C.officinalis* on oral tissues, their mechanisms of action, and their adverse effects. Hence, this review has explored the various medicinal properties of *C.officinalis* useful in the multiple fields of dentistry.

Key Words: Anti-inflammatory, *Calendula officinalis*, Flavonoids, Gingivitis, Periodontitis, Healing.

Introduction

Herbal medicines are plant-derived materials or products with medicinal characteristics utilized in traditional medicine for centuries (1). The use of these medicines to prevent and treat oral diseases has risen in recent years; particularly in low-income nations and rural populations. Herbal extracts have attracted a lot of attention worldwide, since they are natural and non-synthetic (2).

Calendula officinalis L., a member of the Asteraceae family, is a medicinal plant native to the Mediterranean region; however, it is now found worldwide (Figure 1). It produces yellow or orange blooms used medicinally as infusions, tinctures, liquid extracts, lotions, or ointments. English marigold and pot marigold are two common names for it. *C.officinalis* contains carotenoids, flavonoids, saponins, sterols, phenolic acids, lipids, and other biologically active constituents. Various plant sections, such as leaves and flowers, have been stated to have therapeutic properties (3). The "Food and Drug Administration" (FDA) and the "Flavors and Extracts Manufacturers

Association" (FEMA) have determined that the plant's components and dried flowers which are often used as spices are safe (4). According to the literature, *C.officinalis* has been widely studied for its various health benefits. It has a wide range of medicinal properties such as antibacterial, anti-fungal, antiviral, anti-HIV, antioxidant, anti-inflammatory, analgesic, hepatoprotective, cardioprotective, gastroprotective, and wound healing properties (5). It is traditionally used as a natural anti-inflammatory agent for wounds that do not heal well, including leg ulcers, burns, scalds, bruises, boils, and rashes (6). In dentistry, it is used to treat oral mucositis (7), angular cheilitis (8), bone loss in periodontitis (9), leukoplakia (10); and also used as a root canal irrigant (11), intracanal medicament (12), anti-plaque and anti-gingivitis agent (13). Despite substantial research on this plant, no assessments or reviews have looked into the possibilities of *C.officinalis* and its benefits in dentistry. This review article will focus on the existing and prospective roles of *C.officinalis* in dentistry.

Pharmacological properties Wound healing

The plant is listed in the 'German Commission European Scientific Co-operative on Phytotherapy, the British Herbal Pharmacopoeia, and World Health Organization monographs for wound healing and anti-inflammatory properties (14). Gunasekaran et al. studied the wound healing activity of *C.officinalis* in

* Corresponding Author:

Nagaraj NJ

Senior Lecturer, Department of Conservative Dentistry and Endodontics, Rajas Dental College and Hospital, Kavalkinaru Junction, Tirunelveli dt, Pin code-627105 Tamilnadu, India.

Email Id: dr.njendo1992@gmail.com

Figure 1: *Calendula officinalis* Linn



rats. They found that it suppressed macrophage activation by preventing the production of pro-inflammatory cytokines and lowering oxidative stress at the wound site, resulting in rapid migration and proliferation of fibroblasts and keratinocytes, both of which are important for wound healing (15). Preethi et al. in their study found that *C.officinalis* extract-treated group had a considerable rise in hydroxyproline and hexosamine levels, indicating that wound healing occurs much quicker than in the control group. As mentioned earlier active biomolecules such as flavonoids, triterpenes, alkaloids, tannins, and others stimulate wound healing. Moreover, because of its antibacterial action, *C.officinalis* may also cause increased cross-linking and inhibition of collagen degrading enzymes, free radical scavenging action, and suppression of inflammation (16).

Anti-inflammatory activity

Triterpenoid esters and carotenoids such as flavoxanthin and auroxanthin are present in *C.officinalis* petals and pollen. Other carotenoids contained in the leaves and stems include lutein, zeaxanthin, and beta-carotene, all of which contribute to its anti-inflammatory effect (17). The *C.officinalis* extract significantly decreased animal paw edema produced by carrageenan and inflammation caused by dextran when administered orally. This effect, according to the findings, may be mediated by a decrease in pro-inflammatory cytokines and CoX-2, as well as the subsequent generation of prostaglandins (18).

Anti-microbial activity

The benefits of employing herbs as anti-microbial agents include low toxicity, cost-effectiveness, improved patient tolerance, and the fact that they are renewable in nature (19). Cetin et al. found that ethanol and chloroform extracts of *C.officinalis* callus inhibited *Staphylococcus aureus* and *Bacillus cereus* (20). Efstratiou et al. revealed that *C.officinalis* showed excellent antibacterial activity against *E. faecalis*, *E. coli*, *K. aerogenes*, *K. pneumonia*, and *P. aeruginosa* (21). According to Muley et al, triterpenoid saponins such as calendulaglycoside, faradiol, isorhamnetin 3-O-neohesperidoside, quercetin, and isorhamnetin are the primary components of *C.officinalis* that are responsible for antibacterial effects. The principal chemical components that contribute to the antibacterial effect of *C.officinalis* essential oil include citral, geraniol, eugenol, menthol, and cinnamic aldehyde [6].

Analgesic activity

Farahmandlou N et al. demonstrated the analgesic effects of *C.officinalis* in male rats; where they found *C.officinalis* extract to dramatically increase the tail-flick latency, indicating that the herb reduced pain. Alkaloids, flavonoids, and saponins have been identified in the hydro-alcoholic extract of *C.officinalis*. The existence of alkaloids in the plant extract gives credibility to the anti-nociceptive property of *C.officinalis* (22).

Anti-fungal activity

Gazim ZC et al. revealed that *C.officinalis* demonstrated anti-fungal activity against a variety of *Candida* species, including those that cause oral candidiasis that was equivalent to nystatin. *C.officinalis* inhibited *Candida albicans*, *Candida parapsilosis*, *Candida glabrata*, *Candida dubliniensis*, *Candida tropicalis*, *Candida guilliermondii*, and *Candida glabrata* species. Essential oils high in cadinene isomers have been demonstrated to have potent anti-candidal properties (23).

Antioxidant activity

C.officinalis reduced tissue lipid peroxidation in vitro and scavenged superoxide and hydroxyl radicals in a concentration-dependent manner. Furthermore, catalase and glutathione levels in the blood and liver were significantly increased following *C.officinalis* therapy. *C.officinalis* has various compounds that have been shown to have antioxidant and anti-clastogenic properties. *C.officinalis*, which has strong antioxidant properties and the capacity to activate cellular antioxidants, can be used to treat various ailments, including heart disease, inflammation, and cancer (24). Quercetin, which has shown antioxidant activity, appears to have a role in this impact, which is related to the existence of two antioxidant pharmacophores inside the quercetin molecule that have the ideal configuration for free radical scavenging (25).

***Calendula officinalis* L. in dentistry**

***C. officinalis* as an intracanal medicament and root canal irrigant**

According to Nagaraj et al., *C.officinalis* can be utilized as an intracanal medicament for long-standing periapical lesions due to its higher resistance to root dentin fracture when compared to calcium hydroxide (12).

The most typically identified organisms in unsuccessful root canal procedures are *E. faecalis* and *C.albicans*. *C.officinalis* exhibits antibacterial and anti-fungal efficacy against *E. faecalis* and *C.albicans*, according to Vinola et al (26). Another research by Yalgi et al. demonstrated the antibacterial activity of *C.officinalis* as a root canal irrigant against *Streptococcus mutans*. Because of its antibacterial qualities, shown excellent results in eradicating microbes and can be utilized as an alternative irrigant. The essential oil of *C.officinalis* contains terpene alcohols and terpene lactones, attributed to its antibacterial properties (11).

***C. officinalis* in treatment and prevention of Periodontitis**

C.officinalis exhibits a potent antibacterial effect against 18 various strains of anaerobic and facultative aerobic periodontal microbes, according to Iauk et al., indicating that it has the potential to eliminate microorganisms that cause disease of the supporting structures of the tooth (27). During a fourteen-day experimental period, Yusoff et al. found that a mouth wash containing *C.officinalis* was highly successful in lowering plaque index by 23% and gingival index by 62% (28). *C.officinalis* mouth rinse will prevent swollen and inflamed gums by utilizing its anti-inflammatory properties, while its antibacterial characteristics will deal with periodontopathic pathogens (27). *C.officinalis* had an anti-resorptive action, reducing bone loss while retaining its topography (29). The major flavonoid in *C.officinalis* extract, quercetin, is mainly responsible for the pharmacological properties of the plant (30). Quercetin substantially improves osteoblast development in vitro and stimulates sialoprotein and osteocalcin mRNA expression in osteoblast culture (31,32). In vivo conditions, quercetin prevented bone loss in rat periodontitis models, elevated serum osteocalcin, and boosted alkaline phosphatase activity, all of which contributes to bone tissue preservation (29,33).

***C. officinalis* in Oral surgical procedures**

EL-Sayed et al. examined the effects of *C.officinalis*-based topical formula as dressing material on palatal wound healing following free palatal graft surgery. It has been shown to have physiologically active qualities such as enhanced proliferation and migration of cultured human fibroblasts and keratinocytes, increased angiogenesis, and reduced collagenase activity (34).

By using *C.officinalis* as an irrigating solution during and after tooth extraction, Uribe-Fentanes et al. examined the efficacy of *C.officinalis* for bone

preservation. During the surgical extraction of third molars, a 10 % diluted *C.officinalis* irrigant was applied at the surgical site. The authors concluded that *C.officinalis* is a phytodrug with a collagenogenic activity that is used as an analgesic, antibacterial, and wound-healing agent, making it a simple and economical therapy for alveolar bone preservation following tooth extraction (35).

***C. officinalis* in treatment of Oral leukoplakia**

Singh et al. reported that using *C.officinalis* gel showed a significant reduction in the size of leukoplakia. For a month, the patients were directed to apply the gel three times daily, after breakfast, lunch, and supper. Patients were asked to apply gel to the lesion location using sterile ear buds. During the initial session, patients were also shown the amount and manner of applying gel to the lesion. The treatment was continued for the next three months. Patients were evaluated on the 30th day to determine the difference in lesion size between baseline and post treatment. Before therapy, the average size of the leukoplakia was 4.14 cm², and after treatment, it was 2.09 cm² and concluded that *C.officinalis* extract is a simple and efficient therapy option for oral leukoplakia (10).

***C. officinalis* in treatment of Oral mucositis**

Several studies have found that *C.officinalis* extract can help to lessen the severity of radiation-induced lesions (7,36). According to Tanideh et al., daily use of *C.officinalis* extract in gel form significantly decreases oral mucositis caused by 5-fluorouracil in hamster mucosa cheek pouches (37). Babae et al. revealed in clinical trial research that *C.officinalis* extract was beneficial in also reducing the severity of radiotherapy-induced oral mucositis. Because *C.officinalis* possesses antioxidant capabilities, it may act against Reactive oxygen species and prevent or postpone the start phase of mucositis. Its potent flavonoid and phenolic phytochemical content, as well as its antioxidant activity, can promote its high radical scavenging activity and subsequent protective impact in radiotherapy-induced oral mucositis (7).

***C. officinalis* in treatment of Angular Cheilitis**

Roveroni-Favaretto et al. utilized 10% *C.officinalis* gel to successfully cure exfoliative cheilitis, which has been demonstrated to be beneficial. The author found that only a little portion of the lower lip near the right commissure developed a discreet desquamation after seven days. Cheilitis has cleared up after fifteen days of application. Because of its stability, penetrability, hydrophobicity and ease of use, *C.officinalis* ointment is suggested for this treatment (8).

***C. officinalis* in treatment of Oral lichen planus**

Machado MA et al. found out that using a gel containing 3% *C.officinalis* extract, 0.05% clobetasol propionate, 100.000 IU/ml of nystatin and 5% pectin reduces the lesion size and pain after application in the gingival region. An ethylene-vinyl acetate sheet was

used to create a custom-fitted tray that covered both the upper and lower tooth arch. Three times a day, the patients were asked to load the tray with the gel and leave it in place for 15 minutes. The lesion showed significant improvement when the 2-week treatment period was completed.

C.officinalis contains triterpenoid fatty acid esters, with the most abundant are the lauryl, myristoyl, and palmitoyl esters of faradiol which have anti-inflammatory effects (38).

To summarize, *C.officinalis* extract found to possess the following biological effects that make them useful in treatment of various dental ailments:

- Anti-inflammatory activity by lowering pro-inflammatory cytokines
- Antioxidant benefits and analgesic effects owing to flavonoids and carotenoids concentration.
- The primary chemical components of *C.officinalis* include triterpenoid saponins such as calendula glycoside, triterpenoid saponins like faradiol, asorhamnetin 3-O-neohesperidoside, quercetin, and isorhamnetin, which are responsible for antibacterial, anti-inflammatory and wound healing activities.

Conclusion

C.officinalis has potential therapeutic effects; nevertheless, there is a scarcity of data on the quality, safety, and efficacy of *C.officinalis* for use in dentistry. More research is needed to investigate the adverse effects, toxicity, and drug interactions of *C.officinalis* in dental applications.

References

1. Pan SY, Litscher G, Gao SH, Zhou SF, Yu ZL, Chen HQ, et al. Historical perspective of traditional indigenous medical practices: the current renaissance and conservation of herbal resources. *Evid Based Complement Alternat Med.* 2014; 2014:525340. doi: 10.1155/2014/525340.
2. Milutinovici R-A, Chioran D, Buzatu R, Macaso I, Razvan S, Chioibas R, et al. Vegetal Compounds as Sources of Prophylactic and Therapeutic Agents in Dentistry. *Plants.* 2021; 10(10):2148. doi:10.3390/plants10102148
3. Ashwlayan VD, Kumar A, Verma M, Garg VK, Gupta S. Therapeutic Potential of *Calendula officinalis*. *Pharm Pharmacol Int J.* 2018;6(2):149–155. doi: 10.15406/ppij.2018.06.00171
4. Chroho M, Drioiche A, Saidi S, Zair T, Bouissane L. Total phenolic and flavonoids contents and in vitro evaluation of antioxidant activity of several *Calendula officinalis* (Marigold) extracts. *J Biol Res.* 2021;94(1). doi:10.4081/jbr.2021.9680
5. Givol O, Kornhaber R, Visentin D, Cleary M, Haik J, Harats M. A systematic review of *Calendula officinalis* extract for wound healing. *Wound Repair Regen.* 2019;27(5):548-561. doi: 10.1111/wrr.12737.
6. Muley B, Khadabadi S, Banarase N. Phytochemical constituents and pharmacological activities of *Calendula officinalis* Linn (Asteraceae): a review. *Trop J Pharmaceut Res* 2009; 8: 455–65. doi:10.4314/tjpr.v8i5.48090
7. Babae N, Moslemi D, Khalilpour M, Vejdani F, Moghadamnia Y, Bijani A, et al. Antioxidant capacity of *Calendula officinalis* flowers extract and prevention of radiation induced oropharyngeal mucositis in patients with head and neck cancers: a randomized controlled clinical study. *Daru.* 2013;21(1):18. doi: 10.1186/2008-2231-21-18.
8. Roveroni-Favaretto LH, Lodi KB, Almeida JD. Topical *Calendula officinalis* L. successfully treated exfoliative cheilitis: a case report. *Cases J.* 2009;2:9077. doi:10.1186/1757-1626-2-9077
9. Lima MDR, Lopes AP, Martins C, Brito GAC, Carneiro VC, Goes P. The Effect of *Calendula officinalis* on Oxidative Stress and Bone Loss in Experimental Periodontitis. *Front Physiol.* 2017;8:440. doi:10.3389/fphys.2017.00440
10. Singh M, Bagewadi A. Comparison of effectiveness of *Calendula officinalis* extract gel with lycopene gel for treatment of tobacco-induced homogeneous leukoplakia: A randomized clinical trial. *Int J Pharm Investig.* 2017;7(2):88-93. doi:10.4103/jphi.JPHI_19_17.
11. Yalgi VS, Bhat KG. Compare and evaluate the antibacterial efficacy of sodium hypochlorite and *Calendula officinalis* against *Streptococcus mutans* as a root canal irrigating solution: An in vivo study. *J. Int. Oral Health* 2020;12(1):74-9. doi: 10.4103/jioh.jioh_164_19
12. Nagaraj NJ, Ravikumar N, Mahalaxmi S, Pallavi S. Comparative Evaluation of Fracture Resistance of Root Dentin Treated with *Calendula Officinalis* L. And Calcium Hydroxide as Intracanal Medicaments- An In vitro Study. *J.Clin.Diagnostic.Res* 2020; 14(12): ZC39-ZC42 doi: 10.7860/JCDR/2020/46524.14351.
13. Khairnar MS, Pawar B, Marawar PP, Mani A. Evaluation of *Calendula officinalis* as an anti-plaque and anti-gingivitis agent. *J Indian Soc Periodontol.* 2013;17(6):741-7. doi: 10.4103/0972-124X.124491.
14. Arora D, Rani A, Sharma A. A review on phytochemistry and ethnopharmacological aspects of genus *Calendula*. *Pharmacogn Rev.* 2013; 7(14):179-187. doi: 10.4103/0973-7847.120520
15. Gunasekaran S, Nayagam AA, Natarajan R. Wound healing potentials of herbal ointment containing *Calendula officinalis* Linn. on the alteration of immunological markers and biochemical parameters in excision wounded animals. *Clin Phytosci.* 2020;6(1):1-8.
16. Preethi KC, Kuttan R. Wound healing activity of flower extract of *Calendula officinalis*. *J Basic Clin Physiol Pharmacol.* 2009;20(1):73-9. doi: 10.1515/jbcpp.2009.20.1.73.
17. Khalid KA, Da Silva JT. Biology of *Calendula officinalis* Linn.: focus on pharmacology, biological

- activities and agronomic practices. *Med Aromat Plant Sci Biotechnol.* 2012;6(1):12-27.
18. Preethi KC, Kuttan G, Kuttan R. Anti-inflammatory activity of flower extract of *Calendula officinalis* Linn. and its possible mechanism of action. *Indian J Exp Biol.* 2009 ;47(2):113-20.
 19. Anand U, Jacobo-Herrera N, Altemimi A, Lakhssassi N. A Comprehensive Review on Medicinal Plants as Antimicrobial Therapeutics: Potential Avenues of Biocompatible Drug Discovery. *Metabolites.* 2019;9(11):258. doi: 10.3390/metabo9110258.
 20. Çetin B, Kalyoncu F, Kurtuluş B. Antibacterial activities of *Calendula officinalis* callus extract. *Int. J. Second. Metab.* 2017; 4 (3, Special Issue 1): 257-63. doi:10.21448/ijsm.372108
 21. Efstratiou E, Hussain AI, Nigam PS, Moore JE, Ayub MA, Rao JR. Antimicrobial activity of *Calendula officinalis* petal extracts against fungi, as well as Gram-negative and Gram-positive clinical pathogens. *Complement Ther Clin Pract.* 2012;18(3):173-6. doi: 10.1016/j.ctcp.2012.02.003.
 22. Farahmandlou N, Shahidi S, Mahmoodi M. Effects of *Calendula officinalis* on pain threshold in male rats. *International Conference on Chemical, Biological and Medical Sciences, Kuala Lumpur (Malaysia) 2012.*
 23. Gazim ZC, Rezende CM, Fraga SR, Svidzinski TE, Cortez DG. Antifungal activity of the essential oil from *Calendula officinalis* l. (asteraceae) growing in brazil. *Braz. J. Microbiol.* 2008; 39(1): 61-63. doi: 10.1590/S1517-838220080001000015.
 24. Preethi KC, Kuttan G, Kuttan R. Antioxidant Potential of an Extract of *Calendula officinalis*. *Flowers in Vitro. and in Vivo. Pharmaceutical biology.* 2006; 44(9): 691-7. doi: 10.1080/13880200601009149
 25. Heijnen CG, Haenen GR, van Acker FA, van der Vijgh WJ, Bast A. Flavonoids as peroxynitrite scavengers: the role of the hydroxyl groups. *Toxicol In Vitro.* 2001;15(1):3-6. doi: 10.1016/s0887-2333(00)00053-9.
 26. Vinola SM, Sekar M, Renganathan SK, Dhiraviam S. Comparative evaluation of *Calendula officinalis* and 2% chlorhexidine against *Enterococcus faecalis* and *Candida albicans*. *J Interdiscip Dentistry* 2021; 11:119-23 doi: 10.4103/jid.jid_28_21
 27. Iauk L, Lo Bue AM, Milazzo I, Rapisarda A, Blandino G. Antibacterial activity of medicinal plant extracts against periodontopathic bacteria. *Phytother Res.* 2003;17(6):599-604. doi: 10.1002/ptr.1188.
 28. Yusoff S, Kamin S. The effect of a mouthwash containing extract of *Calendula officinalis* on plaque and gingivitis. *J Clin Periodontal* 2006; 33:118
 29. Alexandre JTM, Sousa LHT, Lisboa MRP, Furlaneto FAC, do Val DR, Marques M, et al. Anti-inflammatory and antiresorptive effects of *Calendula officinalis* on inflammatory bone loss in rats. *Clin Oral Investig.* 2018 ;22(6):2175-2185. doi: 10.1007/s00784-017-2308-7.
 30. Saini P, Al-Shibani N, Sun J, Zhang W, Song F, Gregson KS, et al. Effects of *Calendula officinalis* on human gingival fibroblasts. *Homeopathy.* 2012; 101(2):92-8. doi: 10.1016/j.homp.2012.02.003.
 31. Zhou Y, Wu Y, Jiang X, Zhang X, Xia L, Lin K, et al. The Effect of Quercetin on the Osteogenic Differentiation and Angiogenic Factor Expression of Bone Marrow-Derived Mesenchymal Stem Cells. *PLoS One.* 2015;10(6):e0129605. doi: 10.1371/journal.pone.0129605.
 32. Satué M, Arriero Mdel M, Monjo M, Ramis JM. Quercitrin and taxifolin stimulate osteoblast differentiation in MC3T3-E1 cells and inhibit osteoclastogenesis in RAW 264.7 cells. *Biochem Pharmacol.* 2013 ;86(10):1476-86. doi: 10.1016/j.bcp.2013.09.009.
 33. Napimoga MH, Clemente-Napimoga JT, Macedo CG, Freitas FF, Stipp RN, Pinho-Ribeiro FA, et al. Quercetin inhibits inflammatory bone resorption in a mouse periodontitis model. *J Nat Prod.* 2013 ;76(12):2316-21. doi: 10.1021/np400691n.
 34. El-Sayed MK, Hommos AM, Kotry GS, Labib GS. The effect of a calendula based topical formula versus oxidized regenerated cellulose on palatal wound healing: a randomized controlled clinical trial. *Alexandria Dental Journal.* 2021; 46(2): 45-53. doi: 10.21608/ADJALEXU.2021.185219
 35. Uribe-Fentanes LK, Soriano-Padilla F, Pérez-Frutos JR, Veras-Hernández MA. Acción del extracto de *Calendula officinalis* en la preservación ósea posterior a extracción [Action of *Calendula officinalis* essence on bone preservation after the extraction]. *Rev Med Inst Mex Seguro Soc.* 2018;56(1):98-105.
 36. Babae N, Moslemi D, Khalilpour M, Vejdani F, Bijani A, akbar Moghadamnia A, et al. Investigation of the effect of *Calendula officinalis* extract on preventing radiotherapy-induced oral mucositis. *Rep Pract Oncol Radiother.* 2013;1(1):3-9.
 37. Tanideh N, Tavakoli P, Saghiri MA, Garcia-Godoy F, Amanat D, Tadbir AA, et al. Healing acceleration in hamsters of oral mucositis induced by 5-fluorouracil with topical *Calendula officinalis*. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2013;115(3):332-8. doi: 10.1016/j.o000.2012.08.450.
 38. Machado MA, Contar CM, Brustolim JA, Candido L, Azevedo-Alanis LR, Gregio AM, et al. Management of two cases of desquamative gingivitis with clobetasol and *Calendula officinalis* gel. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2010;154(4):335-8. doi: 10.5507/bp.2010.050.
