

The Effect of Kersen (*Muntingia calabura L.*) Leaf Extract Nanogel on Stomatitis

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ABSTRACT

Background: Recurrent aphthous stomatitis (RAS) is common painful mucosal condition affecting the 5%-60% world's population and become the third largest oral disease in Indonesia. Despite their high prevalence, RAS treatment is currently still dominated by the use of chemicals that scientifically have adverse side effects. Therefore, it is necessary to develop new approach using herbal product with no side effects. This literature review summarizes the potential of kersen leaf extract (*Muntingia calabura L.*), its dosage forms, and the possibility using nanotechnology that can speed up the drug delivery process. **Objective:** to determine the possibility effect of nanoparticle cherry leaf extract in gel form on decreasing number of macrophages and stimulating collagen in stomatitis. **Methods:** literature search using the PRISMA method with Science Direct, PubMed, Scielo, NCBI, Research gate, and Google Scholar databases of 1107 articles with keywords "Muntingia calabura L. leaves extract", "nanogel", "flavonoid", "quercetin", "fisetin", "macrophage", "collagen", "soft tissue healing process" and "recurrent aphthous stomatitis". The results of the literature selection found 22 articles. **Results:** flavonoids in cherry leaf extract can reduce the number of macrophages and increase collagen stimulation. The mechanism of action begins by inhibiting the production of pro-inflammatory cytokines, inhibiting macrophage migration and adhesion, stimulating the production of growth factors by macrophages for collagen synthesis, and decreasing collagenase. Nano gel form may increase retention time and drug penetration. **Conclusion:** Nanogel based cherry leaf extract may reduce the number of macrophages and stimulating collagen in minor RAS.

Keywords: Kersen leaf, Nanoparticle, Collagen, Macrophage, RAS

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INTRODUCTION

Dental and oral health is a very important aspect of a person's life. However, Indonesian people's awareness of the importance of maintaining dental and oral health is still low. This is consistent with the fact that there has been an increase in the prevalence of dental and oral diseases in Indonesia from 2013 to 2018 by 25.9% to 57.6%.^{1,2} Recurrent aphthous stomatitis (RAS) is the third largest oral disease in Indonesia with a prevalence of 8%, reaching 5%-60% of the world's population.³ The prevalence of RAS is very high in developing countries and 80% of people experience RAS before the age of 30 years.⁴

Recurrent aphthous stomatitis (RAS) is the most common ulcerated condition of the oral mucosa with characteristic round, painful ulcers, surrounded by a reddish area, and covered by a pseudomembrane.⁵ The etiology of RAS is unknown, but it is associated with various predisposing factors such as a family history of RAS, mechanical trauma, hormonal imbalance, stress, food allergies, bacterial and viral infections, immunological factors, iron deficiency, nutrition, and smoking.^{6,7} Management of RAS aims to reduce pain, speed healing, reduce the number and size of ulcers, and increase the disease-free period^[8].

Drugs used for the treatment of RAS include topical anti-inflammatory steroids (Hydrocortisone hemisuccinate, Triamcinolone acetonide, and Betamethasone valerate), topical antiseptics (Chlorhexidine, Triclosan), topical non-steroidal anti-inflammatory drugs (Benzydamine Hydrochloride, Diclofenac) and systemic drugs (Tetracycline, Colchicine, Dapsone, thalidomide). Generally, RAS treatment uses topical steroids.⁹ However, long-term and/or repeated use of steroid drugs have side effects such as adrenal suppression, candidiasis, and burning sensation, bad taste in the mouth, mucosal atrophy, nausea, sore throat, and xerostomia.^{10,11} Currently, the use of herbal medicines is more widely developed because it has no side effects and 85% comes

from plant extracts.^{12,13} Therefore, the author wants to know the effect of herbal ingredients, namely cherry plants, on the healing of RAS.

Cherry plant is a flowering plant from the Elaeocarpaceae family which is widely found in tropical areas such as Malaysia, India, South America, Central America, and Indonesia.¹⁴ Several studies have proven that the content in cherry leaves has anti-inflammatory and antioxidant activity^[13,14,16]. Cherry leaves contain flavonoid compounds, tannins, triterpenes, saponins, and polyphenols with the highest flavonoid concentration of 70%^[17]. The types of flavonoids found in cherry leaves include flavones, flavonols, flavans, and biflavans^[18]. Flavonoids themselves are known as anti-inflammatory and antioxidant bioactive substances that can accelerate the healing of RAS.¹⁹

Flavonoids are compounds with low solubility in water, very hydrophobic, and chemically unstable under physiological conditions. Flavonoids are very sensitive to environmental factors such as temperature, pH, and light. The low solubility causes limitations on the use of flavonoids and the acceptance of flavonoids as herbal medicines.²⁰ The most effective way of drug delivery for poorly soluble bioactive molecules such as flavonoids is to use nanoparticles. Nanoparticles have the highest drug loading efficiency and can protect flavonoids from degradation due to physiological conditions (especially due to endogenous enzyme activity).^{20,21} Flavonoids in cherry leaf extract can work optimally in treating recurrent aphthous stomatitis (RAS) if it is in the form of nanogels. Based on the problems above, the authors wanted to know the effect of cherry leaf extract (*Muntingia calabura* L.) on the reduction of the number of macrophages and stimulation of collagen as an alternative treatment for stomatitis based on nanogels.

PURPOSE

To determine the effect of cherry leaf extract nanogel on decreasing the number of

macrophages and collagen stimulation in stomatitis.

METHODS

The research design used is a systematic literature review (SLR) by using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) method. Systematic literature review is a research method to identify, evaluate and interpret all relevant research results related to certain research questions and topics.²²

The journals used in the literature review were obtained through a database of international journal providers, namely Science Direct, PubMed, Scielo, NCBI, Research Gate, and Google Scholar. The relevant sources are then stored as a reference for selection. The keywords used for the journal search were "Muntingia calabura L. leaves extract", "nanogel", "flavonoid", "quercetin", "fisetin", "macrophage", "collagen", "soft tissue healing process" and "recurrent aphthous stomatitis". The data search was taken based on the inclusion criteria. The inclusion criteria in this literature review include literature that is included in the category of journal articles (original article), published in English, fully accessible, belongs to the health sciences group, published from 2011-2021, and must contain research data related to keywords

RESULTS

As shown in the image below (Figure 1), based on online search of the database, 1,107 articles were found. Furthermore, they were selected using the Preferred Reporting Items for Systematic Review and Meta Analyses (PRISMA) method. The final results of the selection were 22 literatures.

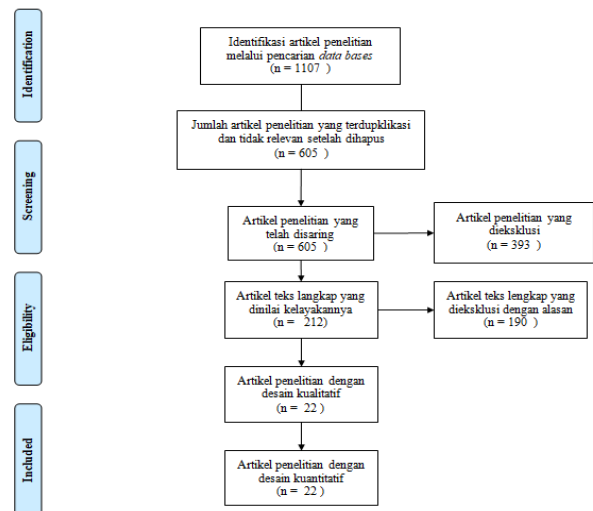


Figure 1. PRISMA Diagram

DISCUSSION

This literature review discusses the effect of cherry leaf extract (*Muntingia calabura* L.) as a nanogel-based topical drug on the treatment of Recurrent Aphthous Stomatitis (SAR) with variable number of macrophages and collagen stimulation. Recurrent aphthous stomatitis (RAS) is a common oral lesion with unclear etiology, but has predisposing factors such as stress and nutritional deficiency. In RAS patients there is an excessive inflammatory process. SAR treatment itself aims to reduce pain and speed up the healing process. Research Pandya et al. in 2017 showed that flavonoid compounds from herbal ingredients were able to provide analgesic, antibacterial, anti-inflammatory effects, and without side effects in patients with minor RAS.²⁴

Cherry leaves through a maceration process with 70% and 96% ethanol solvents produced the highest amount of flavonoids. Types of flavonoid compounds in cherry leave include rutin, quercetin, and fisetin. However, the type of flavonoid compound that has the highest concentration is quercetin. The concentration of quercetin in cherry leaves reached 10.255%.

25, 18, 26, 27, 28, 29

Cherry leaf extract (*Muntingia calabura* L.) was then developed into nanoparticles and processed into a gel-based topical preparation.

The application of nanotechnology in drug delivery aims to protect flavonoids from degradation due to oxidative and enzymatic environments. The gel preparation was chosen because it has advantages such as stabilizing the application of nanoparticles, prolonging drug contact time with the mucosa, increasing bioavailability, and providing a protective layer on the lesion from mechanical irritation and bacterial contamination.^{30,31,24} Research by Karavana et al. in 2012 also proved that nanogel preparations increase retention time and penetration of bioactive ingredients to the mucosal surface thereby accelerating the healing process of RAS.³²

The mechanism of action of flavonoids in suppressing excessive inflammation in RAS is by reducing the number of inflammatory cells such as macrophages, neutrophils, and lymphocytes, suppressing the production of pro-inflammatory cytokines (IL-6, IL-1, TNF-, NF-B), and reducing pro-inflammatory cytokines and

release of reactive oxidative stress (ROS) by macrophages.^{28,33,34,35,36,37,38} The research of Cui et al. in 2019 also explained the effect of flavonoids on macrophage activity including by inhibiting Nitric Oxide (NO) production, migration, and macrophage adhesion.³⁹ The mechanism of action of flavonoids in the wound healing process (ulcer) in RAS includes stimulating macrophages to produce growth factors (TGF- β , FGF-2, and VEGF) and reducing collagenase (MMP-9 and MMP-13). Increased TGF- will induce fibroblast cell proliferation and increase collagen synthesis, deposition, and maturation. Increased fibroblast growth factor (FGF-2) will increase the synthesis and formation of collagen. Increased vascular endothelial growth factor (VEGF) will stimulate angiogenesis so that it can induce the process of migration, proliferation, and differentiation of endothelial cells. Proliferation of capillary blood vessels is needed as an oxygen and nutrient pathway for tissue growth.^{35,40,41,31,42,43,44}

Table 1. Literature review

No	Name	Year	Title	Objective	Research Methods	Research Results	Conclusion
1.	Nguyen and Thao	2020	Wound Healing Activity of <i>Crassocephalum crepidioides</i> (Benth.) S. Moore. Leaf Hydroethanolic Extract	Histological observation using H&E staining	Observation of TNF- α , NF-B, TGF- β , and VEGF numbers using Quantitative Real-Time PCR.	The quercetin-type flavonoid increases TGF- β and VEGF. Elevated TGF- induces fibroblast proliferation and increases collagen synthesis, deposition, and maturation. Quercetin can also decrease the number of inflammatory cells such as macrophages and pro-inflammatory cytokines (TNF- α , NF- κ B).	Quercetin-type flavonoids can reduce the number of inflammatory cells such as macrophages and increase the synthesis, deposition, and maturation of collagen.
2.	Pertiwi, R. D., Suwaldi, Martien, R., & Setyowati, E. P.	2020	Radical Scavenging Activity and Quercetin Content of <i>Muntingia calabura</i> L. Leaves Extracted by Various Ethanol Concentration	Determination of the amount of flavonoids	Determination of flavonoids using colorimetric and the amount of quercetin using thin layer chromatography (TLC)	Cherry leaf ethanol extract contains flavonoids, tannins, saponins, and phenols. The highest number of flavonoids was obtained with 96% ethanol solvent. The highest amount of quercetin was obtained by using 50% ethanol as solvent.	Cherry leaf ethanol extract contains flavonoids, tannins, saponins, and phenols.

3	Prayitno and Rahim	2020	Comparison of Extracts (Ethanol and Aqueous Solvents) <i>Muntingia calabura</i> Leaves on Total Phenol, Flavonoid, and Antioxidant (Ic ₅₀) Properties	Determination of the number of flavonoids and analysis of the antioxidant activity of cherry leaves.	Extraction using the maceration method was then carried out by the DPPH method.	The number of flavonoids using 96% ethanol and aqueous solvents, respectively, was 42.46 mg of QE/g and 16.22 mg of QE/g.	The highest number of flavonoids was obtained from cherry leaf extraction using 96% ethanol.
4	Sari, A. S., Mellya, E., Nasir, M. M., Muhammad, R. A. R.	2020	Identification of Active Compounds on <i>Muntingia calabura</i> L. Leaves Using Different Polarity Solvents	To identify the content of cherry leaf extract with polar solvents (ethanol, ethyl acetate, and n-hexane).	.Mayer- Dragendorff test (alkaloids), Shinoda test (flavonoids), saponin (H ₂ O) test, iron chloride test (tannins and phenols), and Salkowski test (terpenoids)	The content of cherry leaves is higher in polar solvents such as ethanol than in non-polar solvents. Cherry leaf ethanol extract contains high flavonoids, tannins, saponins, alkaloids, and terpenoids.	Cherry leaf content was higher in polar solvents such as ethanol than non-polar. Cherry leaf ethanol extract contains high flavonoids, tannins, saponins, alkaloids, and terpenoids.
5	Setyadewi, C. M., Suzery, M., Agustina, L. N. A., & Bambang, C.	2020	The Comparison of Spectrophotometric and TLC-Densitometric for DPPH Radical Scavenging Activity Analysis of Three Medicinal Plant Extract.	To identify flavonoid compounds and antioxidant activities.	DPPH and TLC.	Cherry leaf extract contains high levels of flavonoids. The highest type of flavonoid is quercetin with a concentration of 10.255%.	Cherry leaf extract contains high levels of quercetin-type flavonoids.
6	Cui, S., Wu, Q., Wang, J., Li, M., Qian, J., & Li, S	2019	Quercetin Inhibits LPS-induced Macrophage Migration by Suppressing the iNOS/FAK/Paxillin Pathway and Modulating The Cytoskeleton	To determine the effect of quercetin on migration, adhesion, and production of NO in macrophages.	Histological testing with crystal violet staining, method of Transwell cell culture chambers.	Quercetin inhibits NO production, migration and adhesion of macrophages.	Quercetin type flavonoids can inhibit macrophage production.
7	Permatasari, D. A., Karliana, D., Iskandarsyah, I., Arsianti, A., & Bahtiar, A.	2019	Quercetin Prevent Proteoglycan Destruction by Inhibits Matrix Metalloproteinase-9, Matrix Metalloproteinase-13, A Disintegrin and Metalloproteinase with	To find out the number of MMP.	The in vivo test was then carried out histological test.	Quercetin nanogels were able to reduce the number of MMP-9 and MMP-13 so that they could reduce ECM (collagen) degradation.	The quercetin type flavonoid nanogel can reduce ECM (collagen) degradation.

			Thrombospondin Motifs-5 Expression on Osteoarthritis Model Rats				
8	Rhimi, W., Hlel, R., Ben Salem, I., Boulila, A., Rejeb, A., & Saidi, M.	2019	<i>Dittrichia viscosa</i> L. Ethanol Extract Based Ointment with Antiradical, Antioxidant, and Healing Wound Activities	To determine the number of inflammatory cells and collagen fibers.	In vivo test. Histological observations using H&E staining	Flavonoids (quercetin) can reduce the number of inflammatory cells and increase collagen fiber proliferation.	Flavonoids (quercetin) can increase collagen fiber proliferation.
9	Roodbordei, F., Afshar, M., Haji Abas Tabrizi, F., Chooapani, S., Torkaman, G., Moayer, F., & Salimi, M.	2019	Topical Hydrogel Containing <i>Fumaria vaillantii</i> Loisel. Extract Enhances Wound Healing in Rats.	To determine the amount of quercetin type flavonoid and its use in the wound healing process	Determination of quercetin using HPLC. Histopathological observation of collagen with H&E staining.	Quercetin-type flavonoid hydrogel has anti-inflammatory activity and increases collagen synthesis. Hydrogel preparations are suitable for promoting wound healing.	The preparation of quercetin type flavonoid in gel form is suitable for promoting wound healing.
10	Desrini, S., Mashita, A. I., Rosary, A. N., Hidayah, U. N., & Farm, S.	2018	Antibacterial Activity Screening of <i>Muntingia Calabura</i> L. Leaves Methanol Extract on Three Bacterial Pathogens	To determine the content of cherry and its antibacterial activity.	A phytochemical test of cherry leaf extract using TLC, then an in vitro test was carried out.	Cherry leaf extract contains flavonoid, tannin and saponin compounds. These compounds possess antibacterial activity.	Cherry leaf extract contains flavonoid, tannin and saponin compounds.
11	Ernawati and Ade	2018	Expression of Vascular Endothelial Growth Factor and Matrix Metalloproteinase-9 in <i>Apis mellifera</i> Lawang Propolis Extract Gel-Treated Traumatic Ulcers in Diabetic Rats	To determine the effect of flavonoids in propolis gel on the amount of VEGF and MMP-9 chronic traumatic ulcers in the oral cavity.	In vivo test, then immunohistochemical imaging was also performed using monoclonal antibody combined with antigen reaction.	Flavonoids stimulate macrophages to produce VEGF and FGF-2 thereby inducing angiogenesis, and can increase the synthesis of ECM (collagen). Flavonoids also decrease MMP-9 expression.	Flavonoids can increase ECM (collagen) synthesis.

12	Jin, Y., Lin, X., Song, L., Liu, M., Zhang, Y., Qi, X., & Zhao, D.	2017	The Effect of Pudilan Anti-Inflammatory Oral Liquid on the Treatment of Mild Recurrent Aphthous Ulcers	To determine the effect of flavonoids on RAS.	Experimental.	Flavonoids can inhibit the production of pro-inflammatory mediators (NO, PGE2, TNF- α , and IL-6) macrophages.	Flavonoids can inhibit macrophage production.
13	Pandya, M., Kalappanavar, A. N., Annigeri, R. G., & Rao, D. S.	2017	Relative Efficacy of Quercetin Compared with Benzydamine Hydrochloride in Minor Aphthae: A Prospective, Double-Blind, Active Control, Preliminary Study	To prove that flavonoid gel (quercetin) is effective, safe, and faster in curing minor RAS compared to Benzydamine Hydrochloride.	Randomized, prospective, parallel-group, and active-controlled.	The flavonoid gel (quercetin) cured minor SAR faster than Benzydamine HCL 0.15% in 7 days. Quercetin is able to provide analgesic, antibacterial, and anti-inflammatory effects on the patient. Giving quercetin has no side effects.	Flavonoid gel (quercetin) heals minor RAS more quickly.
14	Quagliarillo, V., Iaffaioli, R. V., Armenia, E., Clemente, O., Barbarisi, M., Nasti, G., Berretta, M., Ottaiano, A., & Barbarisi, A.	2017	Hyaluronic Acid Nanohydrogel Loaded with Quercetin Alone or in Combination to a Macrolide Derivative of Rampamycin RAD001 (Everolimus) as A New Treatment for Hormone-Responsive Human Breast Cancer.	To determine the effectiveness of quercetin nano hydrogel.	Nanotechnology	Nano technology as a drug delivery flavonoid type quercetin was developed as a drug protector from oxidative and enzymatic environments.	The nanogel formulation improves drug delivery.
15	Zaccaria, V., Curti, V., Di Lorenzo, A., Baldi, A., Maccario, C., Sommatitis, S., Mocchi, R., & Daglia, M.	2017	Effect of Green and Brown Propolis Extracts on the Expression Levels of microRNAs, mRNAs and Proteins, Related to Oxidative Stress and Inflammation	To determine the effect of flavonoids on the inflammatory process.	Real-Time PCR Test.	Flavonoids can inhibit the production of pro-inflammatory cytokines (TNF- α) by macrophages.	Flavonoids as an anti-inflammatory compounds.
16	Krishnappa, P., Venkatarangaiah, K., Venkatesh, Shimoga	2016	Wound Healing Activity of <i>Delonix elata</i> Stem Bark and Its	To determine the effect of quercetin-type flavonoids on the amount of collagen in the	In Vivo test was then carried out histopathological observation of collagen with	The flavonoid gel (quercetin) increases collagen synthesis through up-regulation of Col 1.	Flavonoid gel (quercetin) can increase collagen synthesis.

	Rajanna, S. K., & Kayattukan dy Balan, R.		Isolated Constituent Quercetin-3-rhamnopyranosyl-(1-6) Glucopyranoside in Rats	wound healing process.	H&E staining. The amount of collagen was calculated using the Neuman and Logan method.		
17	Albaayit, S. F. A., Abba, Y., Rasedee, A., & Abdullah, N.	2015	Effect of <i>Clausena excavata</i> Burm. F. (Rutaceae) Leaf Extract on Wound Healing and Antioxidant Activity in Rats	To find out the role of quercetin in the wound healing process.	In vivo test. Histopathological observations using H&E staining and Masson trichome.	Flavonoids (quercetin) reduce the inflammatory response, increase collagen synthesis and maturation, increase angiogenesis.	Flavonoid (quercetin) has anti-inflammatory activity and can increase collagen synthesis.
18	Kim, J. H., Kim, M.-Y., Kim, J.-H., & Cho, J. Y.	2015	Fisetin Suppresses Macrophage-Mediated Inflammatory Responses by Blockade of Src and Syk	To determine the effect of fisetin on macrophages.	In Vitro test.	Fisetin is a type of flavonoid compound that functions as a suppressor of the macrophage cell inflammatory response.	Flavonoids (Fisetin) have anti-inflammatory activity.
19	Gavanji, S., Larki, B., & Bakhtari, A.	2014	The Effect of Extract of <i>Punica granatum</i> var. <i>Pleniflora</i> for Treatment of Minor Recurrent Aphthous Stomatitis	To determine the effect of <i>Punica granatum</i> alcohol extract flavonoids on minor RAS	Double-blind.	Flavonoids can inhibit pro-inflammatory cytokines (IL-1 and IL-6) and oxidative stress produced by macrophages.	Flavonoids have anti-inflammatory activity.
20	Zakaria, Z. A., Sani, M. H. M., Cheema, M. S., Kader, A. A., Kek, T. L., & Salleh, M. Z.	2014	Ant nociceptive Activity of Methanolic Extract of <i>Muntingia calabura</i> Leaves: Further Elucidation of The Possible Mechanism	Determination of cherry content and types of flavonoids.	Phytochemical screening using HPLC analysis then performed ant nociceptive assays.	Cherry leaf ethanol extract contains flavonoids, triterpenes, saponins, and tannins. The types of flavonoids found in cherry leaves are rutin, quercetin, and fisetin. Quercetin can inhibit pro-inflammatory cytokines.	Cherry leaf ethanol extract contains the flavonoids of rutin, quercetin, and fisetin.
21	Karavana, S. Y., Gökçe, E. H., Rençber, S., Özbal, S., Pekçetin, Ç., Güneri, P., & Ertan, G.	2012	A New Approach to The Treatment of Recurrent Aphthous Stomatitis with Bio adhesive Gels Containing Cyclosporine A Solid Lipid Nanoparticles : in vivo/in	To determine the effectiveness of gel formulations with Nano technology for SAR treatment.	In Vivo test and In Vitro test.	Nano gel preparations increase retention time and penetration of bioactive ingredients to the mucosal surface thereby accelerating the healing process of RAS.	Nanogel preparations are suitable for RAS treatment

			vitro Examinations				
22	Machado, J. L., Assunção, A. K. M., da Silva, M. C. P., Dos Reis, A. S., Costa, G. C., Arruda, D. de S., Rocha, B. A., Vaz, M. M. de O. L., Paes, A. M. de A., Guerra, R. N. M., Berretta, A. A., & do Nascimento, F. R. F.	2012	Brazilian Green Propolis: Anti-Inflammatory Property by Immunomodulatory Activity	To determine the effect of flavonoids in propolis on the inflammatory response.	In Vivo test	Flavonoids can reduce the number of inflammatory cells (macrophages, neutrophils, and lymphocytes).	Flavonoids can reduce the number of macrophages.

CONCLUSION

Based on a literature review study that has been carried out by the authors of 22 journals, it can be concluded that the cherry leaf extract (*Muntingia calabura L.*) may have effect on healing minor type of recurrent aphthous stomatitis (RAS). This is because the content of flavonoids in cherry leaves as an anti-inflammatory can reduce the number of macrophages and increase collagen synthesis. Further research in the laboratory is needed to determine the effectiveness of cherry leaf (*Muntingia calabura L.*) as a nanogel-based herbal medicine for recurrent aphthous stomatitis (RAS).

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