

Exploring Melatonin as a Treatment for Oral Ulcers

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Thesis Committee

Faculty Advisor: Sandra Hope, PhD

Honors Coordinator: R. Paul Evans, PhD

Faculty Reader: Roy Silcox, PhD

Project Purpose

A correlation between salivary melatonin levels and aphthous ulcerations may be implicated from a study about melatonin and periodontal disease, but has not yet been investigated (1). The purpose of this project is to review and connect the available literature on melatonin with that of aphthous stomatitis.

Project Importance

Canker sores, or aphthous stomatitis, are painful and common, non-contagious oral ulcers. Aphthous ulcers are the most common type of ulcerative disease and are associated with a number of health conditions (2). Recurrent aphthous stomatitis (RAS) may be influenced by diet, stress level, genetic predisposition, viral and bacterial infection, microelement deficiency, hormone level fluctuation, mechanical injury, systemic disease, and potentially a number of other factors (2). Despite the pervasiveness of RAS, its etiopathogenesis is still unclear (3).

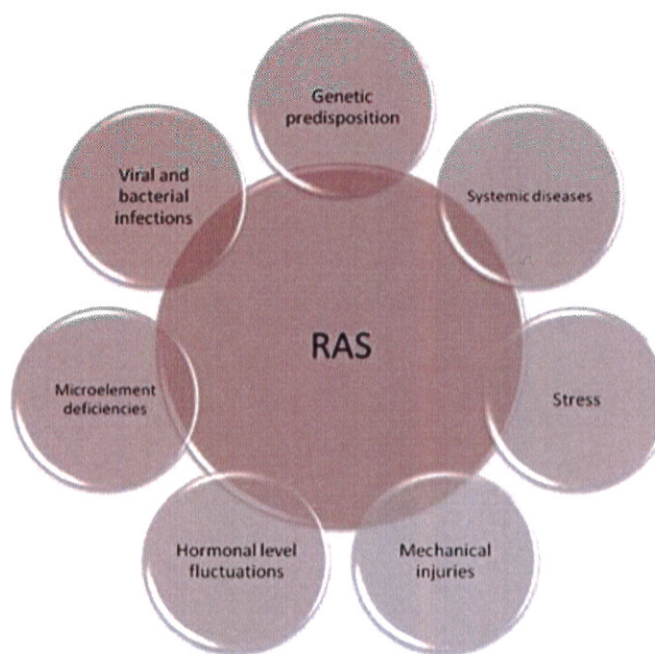


Figure 1: Slebioda, et al. 2014

The many causes of aphthous stomatitis and limited understanding of its etiopathogenesis have made treatment difficult. A variety of home remedies are commonly recommended for pain relief, but there is little evidence for a substantial, effective treatment (4). Current methods include:

- Topical anaesthetic gel (ie. Orajel: Benzocaine, menthol, and zinc chloride)

- Analgesic patch (ie. Pain-Relieving Patch: Camphor, Menthol & Methyl Salicylate)
- Homeopathic method (ie. Hyland: Borax, Calendula, Causticum, Mezereum, Natrum Muriaticum)
- Home remedies (ie. Milk of magnesia, antiseptic mouth rinse, baking soda/water mouth rinse, and many more)

Although the hormone melatonin is best known for its role in the human sleep-wake cycle, it has many more implications (5). Melatonin has demonstrated anti-inflammatory and antioxidant effects that have not been fully explored in oral health (1). It has been explored as an alternative analgesic and anxiolytic due to its promising safety profile (5). A correlation between salivary melatonin levels and aphthous ulcerations may be derived from a study about melatonin and periodontal disease (1). It is possible that these characteristics of melatonin could affect aphthous ulcers wound healing. Melatonin has been used to treat a number of gastrointestinal ulcers, including duodenal ulcers (6), but no study has reported its effects on aphthous stomatitis.

Connecting the available literature of melatonin and aphthous stomatitis may contribute to improved treatment of oral ulcers, determining the etiopathogenesis of RAS, and a better understanding of melatonin's action in the oral cavity. These implications will be explored through a literature review, which will be the final product of this Honors Thesis.

Project Overview

This review will explore and synthesize the available literature on both melatonin and aphthous stomatitis. Since the scope of this Honors Thesis is limited to a literature review, it will not necessitate IRB or FDA approval.

The format will be as follows:

- **Title Page**
- **Body of the review**
 - Aphthous stomatitis
 - Possible causes (Grouped)
 - Group A
 - Group B
 - Group C
 - Treatment attempts
 - Topical gels
 - Analgesic patches
 - Homeopathic methods
 - Home remedies

- Melatonin
 - Natural physiological function (Not as a treatment)
 - Sleep/wake cycle
 - Other functions
 - Use as a medication
 - Sleep/wake cycle
 - Wound healing
 - Alternative uses
- Discussion
 - Significance of findings
 - Limitations of findings
 - Unexpected findings
 - Implications for future research
- Conclusion
 - Limitations of this literature review
 - Restate most significant findings
 - Overall significance of this review
- Reference section
 - Journal of Bacteriology format

The Hope Lab is preparing for a clinical trial that evaluates melatonin's effect on size, pain, time to heal, and color in aphthous stomatitis. This thesis will provide context for Dr. Hope's research. We expect the results from this thesis and ongoing study to contribute to a better understanding of the etiopathogenesis of RAS. We also expect this review and the results from future clinical trials to add to the understanding of melatonin's action in the body, especially in the oral cavity.

Thesis Committee Qualifications

My faculty advisor is **Dr. Sandra Hope** from the MMBIO Department. Dr. Hope has an impressive history of Microbiology research, including the development of Macrophage Fas-Induced Apoptosis (MAFIA) transgenic mice for the study of macrophages through the absence of macrophages. Additionally, she also pioneered a novel method for DNA delivery via nanoinjection. She is currently the director of the Research Instrumentation Core (RIC) facility in the Life Science Building. I took Dr. Hope's MMBIO 121: Intro to Health and Disease course during the Winter 2017 semester and have been a teacher's assistant for that class during the 2018 and 2019 Winter semesters. We have been collaborating on this melatonin study since March of 2019. My honors coordinator is **Dr. R. Paul Evans** from the MMBIO Department. He has been the MMBIO coordinator for many years and thus has extensive experience and exposure to Honors Theses. He is actively involved in academic research as well. I have not had the opportunity to work with Dr. Evans in the past, but I am looking forward to his insight on my

project. My faculty reader is **Dr. Roy Silcox** of the PDBIO Department. I took his PDBIO 305: Human Physiology course last year, and I felt that his expertise would enhance the quality of my work. Like Dr. Evans, Dr. Silcox has been involved with the Honors Program for many years, serving as the Honors Coordinator for PDBIO students.

Project Timeline

The proposed timeline is as follows:

March 2019: We began reading research and review articles about melatonin and aphthous stomatitis.

April - May 2019: I continued reading articles on melatonin and aphthous stomatitis. I met with Dr. Sandra Hope each week to discuss my readings.

June - October 2019: Background research on melatonin safety, monograph, FDA information on dietary supplements. Prepare thesis proposal for thesis committee approval.

November 2019: Dr. Hope and I consulted with Leslie R. Halpern, MPH, DDS, MA, MPhil, MD, PhD at the University of Utah to present preliminary findings on melatonin and its implications for wound healing. Dr. Hope and I consulted with a biochemist to discuss the mechanism of melatonin and its possibility for wound healing. I met with my Honors Coordinator and Faculty Reader to review and revise my Honors Thesis Proposal. I submitted Honors Thesis Proposal after meeting with Dr. Hope (Faculty Advisor) to discuss revisions.

December 2019: I unsuccessfully submitted my Honors Thesis Proposal twice and it is now on hold in the Honors Program Office. Due to finals and dental school interviews, I had to postpone completion until Winter semester.

January - February 2020: I am registered for MMBIO 494R (Advanced Mentored Research) credit in order to dedicate time to work on this project. I met weekly with my Faculty Advisor and our lab. I have given regular updates to the Honors Program Office regarding my status. I met with Dr. Greg Nelson to learn about managing citations for my thesis submission.

March - April 2020: Finalize my proposal and meet with my Honors Coordinator. I set a deadline with Dr. Hope for March 23, 2020, by which I will have a thesis draft submitted. We will follow up on March 26, 2020 to discuss revisions. I will synthesize the literature and prepare my thesis poster prior to the March 28, 2020 deadline, as a summary of my literature review. I will meet weekly with my Faculty Advisor to assess my progress. I will follow the proposed literature review outline (listed above) and prepare a second thesis draft by the April 16, 2020 Reading Day. Meet with Honors Coordinator to discuss progress before the end of finals week.

May - June 2020: Revise thesis according to feedback from Faculty Advisor, Honors Coordinator, and Faculty Reader. Finalize literature for thesis write-up under my Faculty Advisor's supervision. I will submit my Thesis Defense Information Form prior to the May 15, 2020 deadline and have my thesis final draft submitted a week prior (May 8, 2020). I will defend my thesis prior to the June 10, 2020 deadline.

Summary of Timeline

Year	Winter	Spring	Summer	Fall
2019	Conceptualize project, begin background research.	Further research on melatonin and weekly meetings with Faculty Advisor.		Submit thesis proposal and revisions to scope of project.
2020	Submit 3 rd thesis proposal revision 3/2/20. Thesis Draft 3/23/20. Submit thesis poster 3/28/20. Second draft of thesis 4/16/20. Weekly meetings with Faculty Advisor.	Finalize thesis draft 5/8/20. Revise and continue research as necessary. Thesis Defense Info form by 5/15/20. Defend thesis by 6/10/20.	Dental School matriculation July 2020.	

IRB Approval

This Honors Thesis does not require IRB approval.

Funding

No funding will be requested.

Culminating Experience

Due to a shorter timeline before graduation, no Culminating Experience is expected. I will likely withhold publication to preserve the patentability of our research.

Works Cited

1. **Cutando, A., P. Galindo, G. Gómez-Moreno, C. Arana, J. Bolaños, D. Acuña-Castroviejo, and H. Wang.** 2006. Relationship Between Salivary Melatonin and Severity of Periodontal Disease. *Journal of Periodontology*. **77**:1533-1538. doi: 10.1902/jop.2006.050287.
2. **Slebioda, Z., E. Szponar, and A. Kowalska.** 2014. Etiopathogenesis of recurrent aphthous stomatitis and the role of immunologic aspects: literature review. *Arch. Immunol. Ther. Exp.* (Warsz). **62**:205-215. doi: 10.1007/s00005-013-0261-y.
3. **Preeti, L., K. Magesh, K. Rajkumar, and R. Karthik.** 2011. Recurrent aphthous stomatitis. *J. Oral Maxillofac. Pathol.* **15**:252-256. doi: 10.4103/0973-029X.86669.

4. **Edgar, N. R., D. Saleh, and R. A. Miller.** 2017. Recurrent Aphthous Stomatitis: A Review. *J. Clin. Aesthet. Dermatol.* **10**:26-36.
5. **Yousaf, F., E. Seet, L. Venkatraghavan, A. Abrishami, and F. Chung.** 2010. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomized trials. *Anesthesiology.* **113**:968-976. doi: 10.1097/ALN.0b013e3181e7d626.
6. **Osadchuk, M. A., A. A. Sibriaev, N. V. Kireeva, and I. M. Kvetnoi.** 2012. The influence of melatonin included in the combined treatment of antihelminth therapy on immunohistochemical characteristics of gastric epitheliocytes from patients with duodenal ulcer. *Klin. Med. (Mosk).* **90**:48-52.