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Original Research Article

Jasminum grandiflorum oral gel as an add-on to standard of care in radiation induced grade 2 oral mucositis - an open label pilot clinical trial

A.R. Anuja [a,**], R. Anoop [b], Arun Mohanan [a], N.V. Ramesh [a,*]

[a] *Department of Rasashastra and Bhaishajya Kalpana (Pharmaceuticals), Amrita School of Ayurveda, Amritapuri, Amrita Vishwa Vidyapeetham, India*
[b] *Department of Radiation Oncology, Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India*

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ABSTRACT

Background: Radiation-induced oral mucositis is one of the most critical dose-limiting toxicities associated with radiation therapy for oral cancer which can result in treatment interruption and compromise the quality of the life of cancer patients. *Jati (Jasminum grandiflorum)* is used in Ayurveda to treat oral conditions like stomatitis and mouth ulcers.
Objective: To test the feasibility of *Jati* oral gel as an add on therapy in grade 2 radiation-induced oral mucositis.
Materials and methods: A prospective, open-label, non-randomised pilot trial was conducted on 20 patients with grade 2 radiation-induced oral mucositis at a tertiary cancer hospital. The control group received sodium bicarbonate mouthwash 4–5 times daily as the standard of care, while the intervention arm also received *Jati* oral gel twice daily. We used the ImageJ software for objective assessment and the Visual Analogue Scale for subjective pain assessment. The study was continued for 15 days or until the mucositis progressed to grade 3 or resolved to grade 1.
Result: There was a significant reduction in the mean pain score and mean area of mucositis in the intervention group compared to the control group.
Conclusion: Jati oral gel is a suitable medicament as an add-on therapy in managing grade 2 radiation-induced oral mucositis.

1. Introduction

Radiation-induced oral mucositis (RIOM) is among the most prevalent dose-limiting toxicities in patients undergoing head and neck cancer therapies. According to estimates, up to 80% of patients who receive head and neck cancer radiotherapy suffer RIOM [1]. It is characterised by pain in the oral cavity, oral ulcers, dysphagia, odynophagia and poor nutritional status [2]. Poor oral hygiene, low body mass index, dehydration, and a low protein diet are some risk factors leading to oral mucositis. RIOM usually develops during the second week of radiation therapy and progresses to the subsequent stages if not adequately cared for. It is generally self-limiting as it resolves within a few weeks after radiation therapy. The primary treatment method for RIOM is symptomatic management and preventing complications. Hence an integrated approach with Ayurveda appears promising.

Herbal preparations are currently being tested worldwide for their anticancer properties, and Ayurveda offers a range of prophylactic, palliative, supportive, and curative treatments. RIOM is characterised by inflammation of the oral cavity resulting in ulcers. *Jati* (Jasminum grandiflorum) is mentioned in Ayurveda as a valuable drug in treating oral stomatitis and mouth ulcers. Previous works have shown the anti-ulcer potential of *Jasminum grandiflorum* leaves [3]. A study showed that a mucoadhesive formulation containing *Jasminum grandiflorum* leaves could accelerate the extent of contraction and oral wound healing in animal sample by repair and reconstruction of the connective tissue and the epithelium [4]. RIOM treatment merits a formulation like oral gel that can adhere to the ulcer area and provide sustained drug release. Patient compliance and increased shelf life make oral gel a better choice in RIOM.

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* Corresponding author.
** Corresponding author.
E-mail address: drramesh.adiga@gmail.com (N.V. Ramesh).

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2. Materials and methods

2.1. Preparation of oral gel

2.1.1. Preparation of Jati arka (distillate)

Jati patra arka was prepared in the Quality Control Lab. One part of shade dried *Jati patra churna* (*Jasminum grandiflorum* Linn. leaf powder) was soaked overnight in 12 parts of water. The following day, the *churna* and the water were transferred into a round bottom flask, kept on a Rota mantle. A magnetic bead was added to the distillation flask to avoid bumping. The apparatus was arranged for distillation. The initial few drops were discarded, and 60% distillate was collected.

2.1.2. Preparation of Jati oral gel

A 500 ml glass beaker was filled with 350 ml *Jati patra arka*. 0.35g each of Methyl paraben and Propyl paraben were added to the *arka* and stirred well using a magnetic stirrer to attain a homogenous solution. To this solution, 4.2 g Sodium bicarbonate was added and mixed well. 7g of Carbopol was added portion-wise to the homogenous solution and was stirred for 1 h in a mechanical stirrer. The beaker was kept aside for one day. The next day the mixture was again stirred in a mechanical stirrer for 1 h. On the third day, around 4 to 5 drops of vanillin essence were added to the beaker and stirred for 1 h. Later it was packed in tubes of 30g and was sealed and labelled. It was stored in cool and dry place, away from direct sunlight.

2.2. Analysis of Jati oral gel

Organoleptic evaluation and physico-chemical analysis were conducted at Quality Control Lab. The prepared gel's gas chromatography-mass spectrometry (GCMS) was carried out at the Sophisticated Analytical Instrument Facility, IIT Mumbai.

2.3. Clinical trial

2.3.1. Study design

The pilot study followed an open-label, non-randomised clinical trial with a sample size of 20. Patients satisfying the inclusion criteria were screened and recruited. The patients were equally divided into trial and control groups.

2.3.2. Objective

The primary objective of the trial is to assess the feasibility of *Jati* oral gel as an add on medicament in the management of grade 2 Radiation induced oral mucositis.

2.3.3. Inclusion criteria

- Patients between 20 and 70 years of age, clinically diagnosed with squamous cell carcinoma of the oral cavity
- Patients undergoing curative-intent radiation therapy with IMRT technique and with grade 2 oral mucositis (area of <1.5 cm^2) according to the Radiation Therapy Oncology Group scale

Patients received a total median dose of 60 Gy during the radiation therapy session. They were treated with the conventional fractionation schedule which divides the dose into 30 units delivered every week day over six weeks.

2.3.4. Exclusion criteria

- Patients undergoing concurrent chemotherapy.
- Patients having chemotherapy-induced oral mucositis
- Oral ulcers due to ill-fitting dentures
- Patients with Collagen vascular disease and Diabetes Mellitus.

Ethical approval

The study protocol was reviewed and approved by the Institutional Ethical Committee and registered prospectively at CTRI (CTRI/2020/03/024136).

2.3.5. Intervention

The treating physician monitored all patients for oral mucositis daily from the start of radiation treatment. Patients were divided into the Trial group and Control group once the grade of oral mucositis progressed to Grade 2. The patients in the trial group were instructed to apply *Jati* oral gel (approximately 500 mg) twice daily using clean fingertips along with Sodium bicarbonate mouthwash 4–5 times daily. *Jati* oral gel was applied 1 h after radiation therapy, under the supervision of the Principal Investigator, to avoid the susceptibility of the drug compromising the efficacy of treatment. Patients in the trial group were asked to do sodium bicarbonate mouth wash only after 1 h after gel application to ensure the adherence of gel to oral mucosa. The control group received Sodium bicarbonate mouthwash alone 4–5 times daily. The trial continued for 15 days until the mucositis progressed to grade 3 or resolved to grade 1.

2.3.6. Outcome measures

The Radiation Therapy Oncology Group Scale was used to assess the grade of oral mucositis. The area of the oral mucositis was measured using ImageJ software. The radiation oncologist analysed and validated the photographs of the oral mucositis using a Waldent Intraoral camera with 5 Mega Pixels. The intensity of pain was assessed using Visual Analogue Scale (VAS) and scored from 0 to 10. We evaluated them at the beginning of the trial and after completion.

2.3.7. Statistical method

Statistical analysis was done using SPSS VER. 20. We did an Independent Sample *t*-test to analyse the group differences. Paired *t*-test was done to interpret the time of significance in each group separately.

3. Results

3.1. Analytical results

Jati oral gel was prepared with *Jati patra arka*. The organoleptic characters and physico-chemical parameters of *Jati* churna were within the limits mentioned in API [5].

3.1.1. Organoleptic characters of Jati oral gel

The organoleptic characters of the prepared *Jati* oral gel are provided in Table 1.

3.1.2. Physico-chemical parameters of Jati oral gel

The prepared gel's pH was 7.025, and its viscosity was 1,43,150 cP. Gas Chromatography and Mass Spectrometry analysis revealed the presence of compounds having antimicrobial, antioxidant, analgesic and anti-inflammatory properties (Table 2) (Appendix A).

3.2. Effects on clinical outcomes

One hundred thirty-nine patients were screened between December 2020 and May 2021, out of which 20 patients satisfying the inclusion

Table 1
Organoleptic characters of *Jati* oral gel.

Parameter	Observation
Colour	Colourless
Odour	Smell of vanilla
State	Gel consistency
Taste	Not specific

Table 2
Compounds present in *Jati*oral gel.

Property	Compounds
Antimicrobial compounds	Undecanoic acid,11-bromo-methyl ester, Octadecanoic acid, 9,10-dichloro-methyl ester, Tetra decanoic acid, 12-methyl-methyl ester, Tridecanoic acid, methyl ester, Pentadecanoic acid, methyl ester, Cyclopropane decanoic acid, 2-octyl methyl, Narcissidine, Pentadecanoic acid, 14- methyl-methyl ester, Octadecanoic acid, 10-methyl -methyl ester, β-santalol acetate, Benzoic acid, 3-hydroxy, Benzoic acid, 4- [amino sulfonyl].
Antioxidant compounds	Octadecanoic acid, methyl ester, Methyl tetra decanoate, Eicosanebioic acid, dimethyl ester, Hexadecenoic acid, methyl ester, Eicosanoic acid, methyl ester, Cyclopropane decanoic acid, 2-octyl methyl, Pentadecanoic acid, 14-methyl-methyl ester, Octadecanoic acid, 10-methyl -methyl ester, Undecanoic acid, 10-methyl-methyl ester, β santalol acetate
Analgesic compounds	Morphinan-6-one,3,4-dimethoxy-14-hydroxy-17, Narcissidine, Drotebanol, Oxycodone.
Anti-inflammatory compounds	Eicosanoic acid, methyl ester, Eicosanebioic acid, dimethyl ester, Pregn-4-ene,3,15,20-trione,17- hydroxy

criteria were enrolled in the study. The CONSORT flow chart depicts the screening, allocation, intervention, dropouts, and assessment (Fig. 1).

The demographic details of the participants are provided in Table 3.

Outcome measure assessment, including the mean area of mucositis, the number of patients in each grade on trial termination, the average number of days, and the mean pain score, are depicted in Table 4.

In the trial group, the average area of the mucositis significantly decreased after treatment, whereas the area increased in the control group. Among the ten patients in the trial group, the mucositis grade of six dropped to grade 1 with an average of 9.5 days. In contrast, no patients in the control group resolved back to grade 1. One patient in the trial group continued in grade 2 throughout the study with an average of 15 days. In contrast, three patients in the control group continued in grade 2 oral mucositis with an average of 14.6 days. In the trial group, three patients progressed from grade 2 to grade 3 with an average of 14.6 days, whereas in the control group, seven patients progressed to grade 3 with an average of 8.28 days.

The trial group had a statistically significantly lower mean area of mucositis (0.78 ± 1.035) compared to the control group (2.7 ± 0.92), $t(18) = -4.286$, $p = 0.0001$. There was a statistically significant increase in the mean area of mucositis in the control group, from 1.35 ± 0.107 to 2.66 ± 0.927 ($p < 0.0005$).

The mean pain score in the trial group reduced from 2.2 to 0.9. At the same time, the mean pain score increased from 1.8 to 2 in the control group. There was a statistically significant decrease in the pain score, from 2.200 ± 0.4216 to 0.900 ± 0.8756 ($p < 0.0005$) in the trial group.

Hence we observe that the wound healing and the reduction in pain score were significantly better in the trial group. No adverse drug events were reported during the entire course of the trial. Fig. 2 depicts a sample image of patients in the trial and control groups.

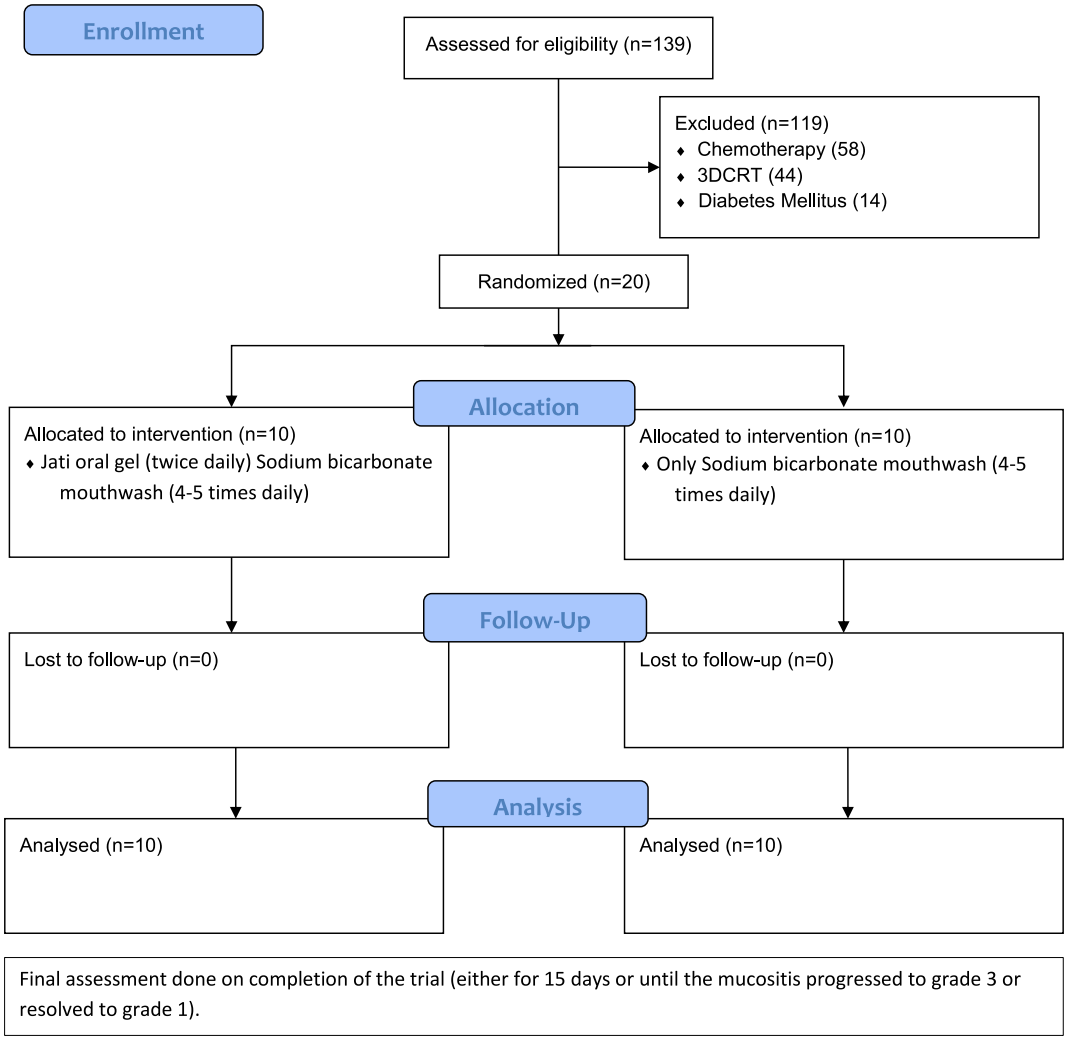

Fig. 1. Consort flow chart.

Table 3
Demographic details of the participants

Variables	Trial group	Control group
Gender		
Male	9	9
Female	1	1
Mean	5	5
Standard Error	4	4
Age group		
11–20	0	0
21–30	0	0
31–40	5	2
41–50	1	3
51–60	2	4
61–70	2	1
Mean	46.4	49.5
Standard Error	3.86	2.77
Diet		
Vegetarians	2	1
Non- Vegetarians	8	9
Mean	5	5
Standard error	3	4
Tobacco usage		
Users	6	7
Non users	4	3
Mean	5	5
Standard error	1	2
Alcohol intake		
Alcoholic	4	5
Non alcoholic	6	5
Mean	5	5
Standard error	1	0

Table 4
Assessment of the outcome measures

Parameters	Trial group	Control group
Mean area of mucositis (cm^2)		
Before treatment	1.354	1.35
After treatment	0.778	2.662
Number of patients in each grade on trial termination.		
Grade 1	6	0
Grade 2	1	3
Grade 3	3	7
Average number of days		
Average number of days taken for resolving to Grade 1 from Grade 2.	9.5	0
Average number of days the patient continued in Grade 2.	15	14.6
Average number of days taken for progression to grade 3.	14.6	8.28
Mean pain score		
Before treatment	2.2	1.8
After treatment	0.9	2

4. Discussion

Oral mucositis is an adverse effect significantly related to ionising radiation used to treat cancer. It can limit radiation dose, alter dosimetry, and negatively impact patients' quality of life. There is a need to address this condition immediately since it affects treatment continuity. The topical application of medicine is one of the treatment procedures mentioned in managing RIOM [6]. Ayurveda mentions different formulations for topical therapy [7]. Incorporating the formulation into a gel makes it more convenient for patients. Oral gel was dispensed in tubes. Tubes reduces the chance of cross contamination of the medicament using the simple squeeze dispersion method. The small tube openings reduce the amount of medication that is exposed to the air. Additionally, the gel is protected from light deterioration by the opaque tube exterior.

The physico-chemical parameters of *Jati* churna (powder) met the standards in Ayurvedic Pharmacopeia of India, which suggests that the drug was genuine. *Rasapancaka* (five pharmaco-therapeutic principles of substance) of *Jati* is *tikta kasaya rasa* (bitter astringent taste), *laghu guna* (lightness), *usna virya* (hot potency), and *katu vipaka* (pungent post digestive state) [8]. *Tikta rasa* of *Jati* result in *lekhana* (scraping effect), *krimigna* (disinfectant) and does the *sosana* of *kleda* (removes moisture content) [9]. *Kasaya* rasa have *vrana ṣodhana* (wound cleansing), *ropana* (wound healing) and *twakprasadana* (skin tone improving) action [10]. *Jasminum grandiflorum* has several pharmacological actions, including anti-inflammatory, analgesic, wound healing, antioxidant, antiulcer, and antimicrobial effects [11]. As per the Drugs and Cosmetic Rules, 1945, Amendment on 2016, the shelf life of gel preparations are 3 years.

A case report was published briefing the action of *Jatiarka* mouthwash in the management of Recurrent Aphthous Stomatitis [12]. A clinical trial was conducted to compare the efficiency of *Jati arka* mouthwash and *Jati kvatha* (decoction) in managing *mukhapaka*, concluding that *Jati arka* mouthwash was more effective in controlling the disease. Therefore, to prepare the oral gel, *Jati arka* was used, which further ensured the uniformity of drug content throughout the product. Soaking *Jati* churna overnight helps transfer water-soluble principles from the drug into water. The evaporated and condensed volatile principles are collected during the distillation process. Mucoadhesive property of Carbopol 934 aids gel adhesion into the mucous membrane, resulting in the targeted drug release for an extended period of time [13]. A formulation with higher viscosity possesses higher mucoadhesive properties. If the gel has a lower viscosity, it cannot adhere to the mucous membrane and gets washed up with saliva [14]. The cooling nature of gel helps to reduce the burning sensation and pain associated with mucositis. The average pH of the prepared gels was 7, which was within the limits of the pH of the oral mucosa (6.7–7.3). Sodium bicarbonate was added to the gel to adjust its pH [15]. The patients undergoing radiation therapy will have decreased saliva production and high chances of sensitive mucous membranes. An increase or decrease in the pH of the prepared gel from the limit may cause further irritation to the skin membrane making the condition vulnerable. Radiation to the head and neck damages taste buds and salivary glands, resulting in taste changes [16]. Adding vanillin flavour to the gel improves its palatability and compliance.

Tannins [17], flavonoids [18], and triterpenoids [19] are the primary agents responsible for wound healing. Antioxidant compounds accelerate healing by controlling wound oxidative stress and faster regeneration of skin cells. It also prevents the further deterioration of injuries [20]. Opioid analgesics like Narcissidine, Oxycodone, and Drotebanol relieve pain by binding to opioid receptors in the central nervous, spinal cord, and peripheral nervous systems. Cell migration stimulated by opiates can facilitate wound healing by modulating cell proliferation and survival [21]. A study has reported the efficacy of Morphine mouthwash for the management of pain in head and neck cancer patients [22]. The anti-inflammatory compounds work by inhibiting the effect of cyclooxygenase enzymes. The antimicrobial compounds present in oral gel prevent secondary infection, thereby accelerating wound healing.

The mean area of mucositis was reduced in the trial group compared to the control group, which implies that most of the mucositis healed in the trial group. In the trial group, the mean area decreased from 1.35 cm^2 to 0.778 cm^2; in the control group, the mean area increased from 1.35 cm^2 to 2.662 cm^2. The enhanced wound healing activity in the trial group may be due to the presence of chemical compounds that possess antioxidant, antimicrobial and antiulcer activities. There was a significant reduction in pain in the trial group compared to the control group. In the trial group, the mean pain score decreased to 0.9 from 2.2, whereas in the control group, the pain increased from 1.8 to 2. Pain reduction may be due to chemical compounds that possess analgesic and anti-inflammatory action. An increased rate of wound healing may also aid in the reduction of pain scores. 70% of the patients in the control group progressed to grade 3 mucositis after the trial, whereas only 30%

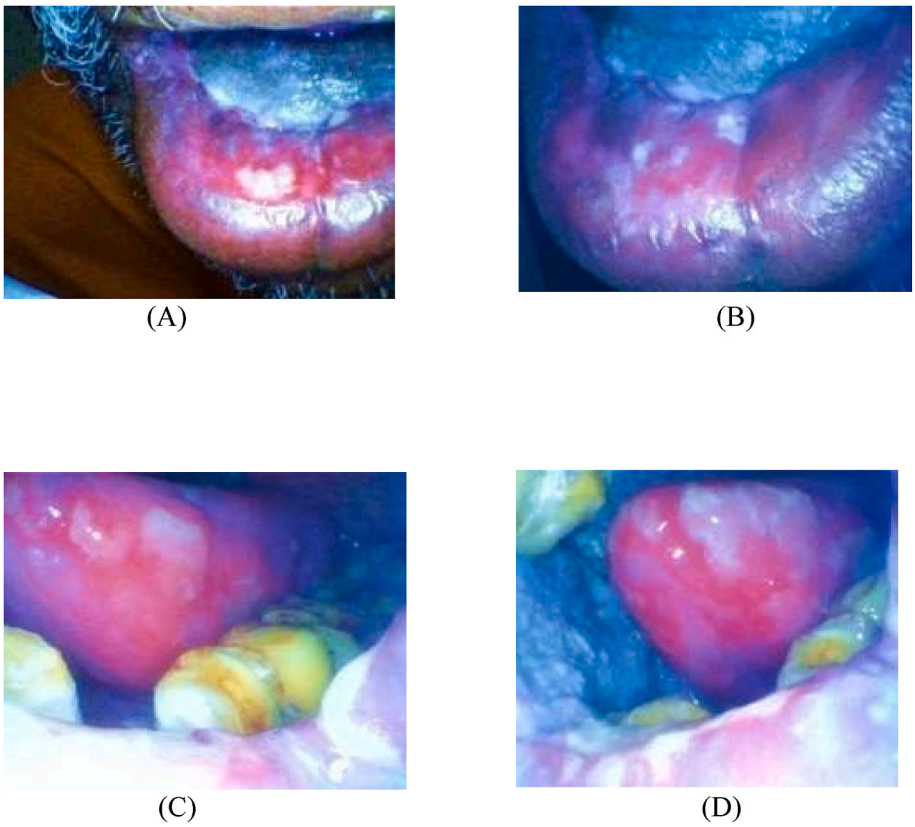

Fig. 2. Images of Radiation-Induced Oral Mucositis. (A) Before treatment in the trial group (B) After treatment in the trial group (C) Before treatment in the control group (D) After treatment in the control group.

in the trial group showed worsening. In the control group, the progression from grade 2 oral mucositis to grade 3 happened within an average of 8.28 days. In the trial group, this progression took 14.6 days, suggesting that we could delay the average time taken for the progression. 60% of the patients in the trial group resolved to grade 1 oral mucositis after the trial, but no patients in the control group resolved back to grade 1.

4.1. Limitations

Due to the COVID-19 pandemic conditions, the study's sample size was limited to 20. The study was conducted without blinding and randomisation. While duly considering the disease's prevalence, oral gel's efficacy has to be proved in a large sample size as an independent medicine.

5. Conclusion

On application of the oral gel, most patients in the trial group resolved back to grade 1 RIOM, whereas no patients resolved back to grade 1 RIOM in the control group. We observed a longer average progression time from grade 2 RIOM to grade 3 RIOM in the trial group following the application of the oral gel. After statistical assessment between the groups and within the group, we observed a significant reduction in pain and the mean area of mucositis in the trial group. No untoward side effects were reported for the newly formulated *Jati* oral gel during the study period. While considering all these facts, *Jati* oral gel can be regarded as a suitable medicament as an add-on therapy in managing grade 2 RIOM, which needs to be confirmed by more extensive studies.

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Declaration of Generative AI in Scientific writing

None

Author Contributions

Anuja A. R.-Conceptualization, Methodology/Study design, Formal analysis, Investigation, Data curation, Writing original draft. Anoop R.-Conceptualization, Methodology/Study design, Validation, Data curation, Writing-review and editing, Supervision. Arun Mohanan-Conceptualization, Methodology/Study design, Validation, Data curation, Writing-review and editing, Supervision. Ramesh N. V. - Conceptualization, Methodology/Study design, Validation, Data curation, Writing-review and editing, Supervision.

Declaration of Competing Interest

Nil.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaim.2024.100925.

References

[1] Maria OM, Eliopoulos N, Muanza T. Radiation-induced oral mucositis. Front Oncol 2017;7:89. https://doi.org/10.3389/fonc.2017.00089. PMID: 28589080; PMCID: PMC5439125.

[2] Ps SK, Balan A, Sankar A, Bose T. Radiation induced oral mucositis. Indian J Palliat Care 2009;15(2):95–102. https://doi.org/10.4103/0973-1075.58452. PMID: 20668585; PMCID: PMC2902123.

[3] Umamaheswari M, Asokkumar K, Rathidevi R, Sivashanmugam AT, Subhadradevi V, Ravi TK. Antiulcer and in vitro antioxidant activities of Jasminum grandiflorum L. J Ethnopharmacol 2007;110(3):464–70. https://doi.org/10.1016/j.jep.2006.10.017. Epub 2006 Oct 21. PMID: 17125945.

[4] Mortazavi H, Mashhadiabbas F, Mortazavi SAR, Rezaeifar K, Farhangi M. Formulation of a Jasmine Grandiflorum containing mucoadhesive and evaluation of its healing effect on oral biopsy ulcers. Clin Oral Invest 2020;24(4):1591–7. https://doi.org/10.1007/s00784-019-03171-w. Epub 2020 Jan 8. PMID: 31916035.

[5] Ayurvedic Pharmacopoeia of India, Part-1(vol 3). 1st ed. Ministry of Health & Family Welfare, Government of India, Department of Indian Systems of medicine & Homeopathy; Year. p 71.

[6] Podlesko AM, Ramacciati N, Panzolini S, Saldi S, Fiorucci S, Pierini D, Mancini M, Merolla MS, Lancellotta V, Aristei C. Effects of topical polydeoxyribonucleotide on radiation-induced oral mucositis. Tech Innov Patient Support Radiat Oncol 2018;7:17–9. https://doi.org/10.1016/j.tipsro.2018.05.003. PMID: 32095577; PMCID: PMC7033775.

[7] Prof K, Srikantha Murthy R, Samhita Sarangadhara. Uttarakhanda chapter 10, verse 17, Chaukhambha Orientalia. 2012. p. 234.

[8] National Institute of Indian Medical Heritage (NIIMH). Hyderabad/central Council for research in Ayurvedic Science (CCRAS). New Delhi: Department of AYUSH, Ministry of Health and Family Welfare, Government of India; 2023. Retrieved on March 6, https://niimh.nic.in/ebooks/e-Nighantu/?mod=search.

[9] Srikanta Murthy KR, Hridaya Aṣṭāṅga. Chowkhamba Krishnadas Academy. Sutrasthana 2011;I:146. 10/14.

[10] Srikanta Murthy KR, Hridaya Aṣṭāṅga. Chowkhamba Krishnadas academy. Sutrasthana 2011;I:147. 10/20.

[11] Sharma PC, Yelne MB, Dennis TJ. Database on medicinal plants used in Ayurveda, vol. 3. New Delhi,India: Documentation and Publication Division, CCRAS; 2005. p. 332.

[12] Balakrishnan Geethu, Vineeth K, Mohanan Arun, Ramesh V. Effect of jati (jasminum grandiflorum) mouthwash in ras: a case report. Int Res J Pharm 2018;9:81–4. https://doi.org/10.7897/2230-8407.09346.

[13] Abu-Huwaij R, Obaidat RM, Sweidan K, Al-Hiari Y. Formulation and in vitro evaluation of xanthan gum or carbopol 934-based mucoadhesive patches, loaded with nicotine. AAPS PharmSciTech 2011;12(1):21–7. https://doi.org/10.1208/s12249-010-9534-5. Epub 2010 Dec 15. PMID: 21161460; PMCID: PMC3066338.

[14] Kassab Hanan, Vartanian Lena, Jabir Saba. Development and physical characterization of a periodontal bioadhesive gel of gatifloxacin. Int J Appl Pharm 2017;9:31. https://doi.org/10.22159/ijap.2017v9i3.7056.

[15] Madeswaran S, Jayachandran S. Sodium bicarbonate: a review and its uses in dentistry. Indian J Dent Res 2018;29(5):672–7. https://doi.org/10.4103/ijdr.IJDR_30_17. PMID: 30409952.

[16] Cheng SC, Wu VW, Kwong DL, Ying MT. Assessment of post-radiotherapy salivary glands. Br J Radiol 2011;84(1001):393–402. https://doi.org/10.1259/bjr/66754762. PMID: 21511748; PMCID: PMC3473647.

[17] Chokotho L, van Hasselt E. The use of tannins in the local treatment of burn wounds - a pilot study. Malawi Med J 2005;17(1):19–20. https://doi.org/10.4314/mmj.v17i1.10866. PMID: 27528993; PMCID: PMC3346037.

[18] Zulkefli N, Che Zahari CNM, Sayuti NH, Kamarudin AA, Saad N, Hamezah HS, Bunawan H, Baharum SN, Mediani A, Ahmed QU, Ismail AFH, Sarian MN. Flavonoids as potential wound-healing molecules: emphasis on pathways perspective. Int J Mol Sci 2023;24(5):4607. https://doi.org/10.3390/ijms24054607. PMID: 36902038; PMCID: PMC10003005.

[19] Kindler S, Schuster M, Seebauer C, Rutkowski R, Hauschild A, Podmelle F, Metelmann C, Metelmann B, Müller-Debus C, Metelmann H-R, et al. Triterpenes for well-balanced scar formation in superficial wounds. Molecules 2016;21(9):1129. https://doi.org/10.3390/molecules21091129.

[20] Comino-Sanz IM, López-Franco MD, Castro B, Pancorbo-Hidalgo PL. The role of antioxidants on wound healing: a review of the current evidence. J Clin Med 2021;10(16):3558. https://doi.org/10.3390/jcm10163558. PMID: 34441854; PMCID: PMC8397081.

[21] Rosenblum A, Marsch LA, Joseph H, Portenoy RK. Opioids and the treatment of chronic pain: controversies, current status, and future directions. Exp Clin Psychopharmacol 2008;16(5):405–16. https://doi.org/10.1037/a0013628. PMID: 18837637; PMCID: PMC2711509.

[22] Sarvizadeh M, Hemati S, Meidani M, Ashouri M, Roayaei M, Shahsanai A. Morphine mouthwash for the management of oral mucositis in patients with head and neck cancer. Adv Biomed Res 2015;4:44. https://doi.org/10.4103/2277-9175.151254. PMID: 25789270; PMCID: PMC4358035.