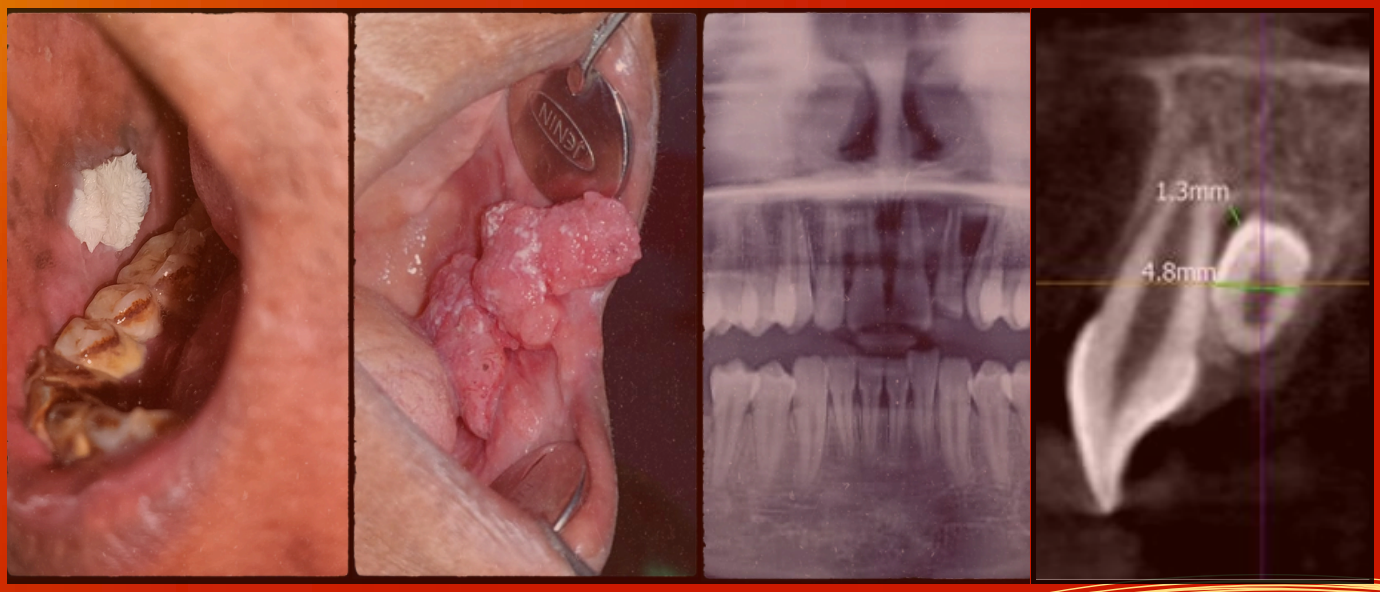
Journal of IAOMR, Karnataka State Branch



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- Karnataka State Branch

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JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY:

KARNATAKA STATE BRANCH

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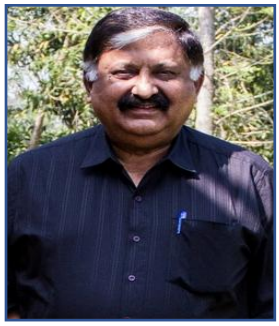
DR. K. S. GANAPATHY



I deem it an honour and privilege to write this message to the 3rd issue of e-journal of IAOMR, Karnataka State Branch.

I take this opportunity to congratulate the Editor-in-Chief Dr. Suman B, and the other members of the Editorial Board for the well deserved success in bringing out two issues of the E-journal as on date. I really appreciate the time and energy that you have put into your efforts, to bring out a standard journal. It is said, success in every field is 99% perspiration and 1% inspiration. Your success in your efforts has amply proved the truth of this statement. It is indeed a moment of joy and satisfaction.

Lots of responsibility lies on the shoulders of the editorial board in general and Chief Editor in particular to keep up the academic standard of the journal by screening and reviewing the quality of the articles.

I wish the entire Editorial Board led by Dr. Suman B., all the very best in their future endeavours.

Regards

DR. K. S. GANAPATHY

MESSAGE BY

DR. SRI KRISHNA K

PRESIDENT – IAOMR

Dear Colleagues and Members of the Karnataka Branch of the Indian Academy of Oral Medicine and Radiology (IAOMR),

It gives me great pleasure to extend my warm greetings to all the esteemed members of the Karnataka Branch of IAOMR.

Karnataka holds a place of singular importance in the history of our Academy, with our Academy registered under the Karnataka Societies Act, and Bengaluru holding the place of our Registered Office. From the early days of our Academy, Karnataka has nurtured some of the finest minds and leaders in our specialty, and it continues to be a vibrant hub of academic excellence, clinical innovation, and professional leadership.

The IAOMR members from Karnataka have always stood at the forefront of academic excellence and clinical innovation in our specialty. The consistent efforts of the branch in promoting scientific temper, encouraging research, and building a strong community of Oral Medicine and Radiology professionals are truly commendable. These initiatives should serve as a model for other branches across the country and contribute meaningfully to the growth of our Academy at the national level.

As we collectively strive to elevate the standards of education, diagnosis, and patient care in Oral Medicine and Radiology, I encourage each one of you to continue engaging with passion and purpose. Let us remain committed to collaboration, knowledge-sharing, and upholding the highest standards of ethical and evidence-based practice.

I congratulate the Office Bearers of the Karnataka branch of IAOMR for their continued contributions and for bringing out this e-journal, which serves as an important medium to connect, reflect, and inspire.

With best wishes for continued success and academic excellence,

Jai Hind,

Warm regards,
DR. SRI KRISHNA K.
PRESIDENT
INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY

MESSAGE BY

DR. SHIVA PRASAD S.

HONORARY GENERAL SECRETARY - IAOMR

It is good to hear that the IAOMR Karnataka State Branch will be releasing the journal for the year 2025.

The office Bearers of IAOMR Karnataka state branch need to be lauded for the commendable work during their tenure, be it hosting a successful UG convention at Raichur, CDE programmes, and community service programmes to the benefit of the members of IAOMR and the public as a whole.

This year will be remembered for the achievement of the Head office for instituting the Research fund through the interest incurred by the fixed deposit from the Research fund for the members of IAOMR. This will definitely help the coming out with new treatment modalities. Let's take this opportunity to congratulate the Editor on bringing out this journal.

Thank you all,

DR SHIVA PRASAD S

HONORARY GENERAL SECRETARY

IAOMR – HEAD OFFICE

MESSAGE BY

DR. MANISHA M. KHORATE

EDITOR - JIAOMR

Dear Readers,

‘Writing well, is thinking made visible’

In today’s fast paced world, one must remember that the single concept that has been accepted is that clear, compelling language can change opinions, inspire action and may even win support. For students of health sciences, cultivating good writing habits early ensures they are equipped to contribute meaningfully to academic discourse, to submit research that withstands peer review, and to participate in the ongoing dialogue that shapes their profession.

To all the participants who took the time and effort to contribute to this competition, your commitment to writing is commendable. Each entry represents not just words on paper, but hours of thought, reflection, and perseverance. You have engaged in the process of turning complex ideas into clear communication—an ability that will serve you throughout your careers.

To the prize winners, I extend my warmest congratulations. Your achievement is a testament to both your intellectual clarity and your dedication to excellence. In a profession where precision, empathy, and communication matter deeply, you have demonstrated that writing is as much an art as it is a skill. The recognition you receive today is not merely for the strength of your writing, but for the discipline and creativity that it reflects. May this recognition encourage you to continue honing your craft. Whether you write research papers, clinical notes, or reflections on your professional journey, let every word you write carry clarity, purpose, and impact. In doing so, you contribute not only to your personal growth but also to the advancement of your profession and the betterment of patient care.

For students and young professionals, the benefits of developing strong writing skills extend beyond academia. The ability to craft persuasive grant proposals, articulate ideas in competitive examinations, or prepare impactful presentations can significantly influence career trajectories. Employers and institutions value individuals who can communicate ideas effectively in writing, because such professionals are better able to advocate for themselves, their teams, and their patients. In this light, writing competitions such as the one we celebrate today are not mere extracurricular activities—they are training grounds for essential professional competencies.

They encourage participants to synthesize knowledge, think critically, and express themselves clearly under the discipline of structure and word limit.

More importantly, they instil confidence in participants to share their voices, reminding them that their perspectives matter and deserve to be heard. Many congratulations to both participants and the winners. May your words continue to inspire, inform, and illuminate.

Regards

DR. MANISHA M. KHORATE

EDITOR IN CHIEF - JIAOMR

MESSAGE BY

DR. RAMAMURTHY T. K.

PRESIDENT – IAOMR- KSB

I am truly pleased to learn about the upcoming third volume of the e-journal of the IAOMR Karnataka State Branch. As the President of the IAOMR Karnataka State Branch and Head of the Department of Oral Medicine and Radiology at Vydehi Institute of Dental Sciences and Research Centre, I am immensely proud to witness the continued academic contributions and editorial excellence demonstrated through this initiative.

I appreciate the dedicated efforts of your entire editorial team in creating a meaningful platform that highlights scholarly work and promotes academic exchange in our specialty.

Wishing you and the team continued success in all your endeavours.

Warm Regards

DR. RAMAMURTHY T. K.

PRESIDENT – IAOMR KSB

MESSAGE BY

DR. RAMNARAYAN B. K.

HONORARY SECRETARY – IAOMR-KSB

It gives me immense pleasure to pen down this message for our Academy journal. The journal has always been a reflection of our commitment to academic excellence, professional growth, and collective progress. It serves not only as a platform to showcase research and innovations but also as a medium to connect, share, and inspire.

As Secretary, I am grateful for the dedicated efforts of our editorial team, contributors, and members, whose passion and hard work have made this publication possible. The diverse range of articles, case studies, and updates included in this issue are highlights of the dynamic spirit of our fraternity and its ongoing contribution to society.

I extend my heartfelt appreciation to all members for their active participation in the association's endeavours. Together, let us continue to uphold the values of learning, service, and collaboration, while working towards new milestones of excellence.

Wishing the journal, a great success and hoping it will serve as a source of knowledge and inspiration to all readers

Regards

DR. RAMNARAYAN B. K.

HONORARY SECRETARY, IAOMR-KSB

JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY: KARNATAKA STATE BRANCH

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Information for Authors

About the Journal:

Journal of Indian Academy of Oral Medicine and Radiology, Karnataka State Branch (JIAOMR-KSB), an annually published, peer-reviewed electronic journal affiliated to Indian Academy of Oral Medicine and Radiology, Karnataka State Branch. The journal does not charge for submission and processing the manuscripts.

Scope of the Journal:

JIAOMR-KSB scope includes all the aspects of oral medicine, diagnosis, dental and maxillofacial radiology, and its related subjects. The journal provides a platform for the academic contributions of undergraduate students enrolled in all the dental institutions in the state of Karnataka. The journal focuses on quality work and on publishing novel and innovative scientific content elated to all aspects of oral and maxillofacial diseases ranging from standard diagnostic and management guidelines to various advanced modalities with relevance to oral manifestations of systemic disease. Preference has been given to the manuscripts that have bagged prizes in the Karnataka State Undergraduate IAOMR conference adding an extra layer of appreciation to the efforts taken by the undergraduate students and their esteemed teachers as well.

The Editorial Process:

- Initial Review: Manuscript will be reviewed for possible publication with the understanding that authors would authorize one of them to correspond with the journal for all matters related to the manuscript. All manuscripts received are duly acknowledged. On submission, editors review all submitted manuscripts initially for suitability for formal review.
- Plagiarism: The journal follows a strict policy against plagiarism and follows the guidelines dictated by the Committee on Publication Ethics (COPE) and International Committee of Medical Journal Editors.
- Double Blind Review: Suitable manuscripts will undergo a double-blind peer review, wherein the reviewers as selected by the editor and the authors remain anonymous.
- Opinions & Revisions: The feedbacks received from reviewers are conveyed to the *Corresponding author. If required, the author is requested to provide a point-by-point response to reviewer's comments and submit a revised version of the manuscript. This process continues until satisfaction is obtained.
- Editing: Accepted manuscripts are copy edited for grammar, punctuation, print style and format.
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- Screening: Manuscripts received from Editorial board members will be screened by the Editor-in-Chief and sent to external peer reviewers without sharing the details of the editorial board member. The editorial board members who are authors will be excluded from publication decisions. If the articles are authored by the editorial board, the conflict of interest must be clearly stated. In case of any conflicts arise, the manuscript will be submitted for internal review and experts review and finally, the Editor-in-Chief will decide based on consolidated suggestions.

Authorship criteria:

Authorship credit should be granted based on substantial contributions to conception, design, analysis, drafting and final approval of the manuscript.

Each contributor should have participated sufficiently in the work to take public responsibility for appropriate portions of the content of the manuscript.

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Conflicts of Interests/ Competing Interests:

All authors must disclose any and all conflicts of interest they may have with publication of the manuscript or an institution or product that is mentioned in the manuscript and/ or is important to the outcome of the study presented. Authors should also disclose conflict of interest with products that compete with those mentioned in their manuscript.

Submission Guidelines:

All manuscripts must be submitted by mail to kiaomrjournal@gmail.com. The submitted manuscripts that are not as per the "Instructions to Authors" would be returned to the authors for technical correction before they undergo editorial/ peer review. Generally, the manuscript and/ or is important to the outcome of the study presented. Authors should also disclose conflict of interest with products that compete with those mentioned in their manuscript.

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e. References:

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- Instead, they should be cited in parentheses at the appropriate place in the text. Reference list format should conform to that set forth in "Uniform Requirement for Manuscripts Submitted to Biomedical Journals" (Ann Intern Med 1997; 126:36-47).

c. Contributors' / Copyright Transfer Form:

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Kindly refer the summarized uniform requirements and specific requirement of Journal of Indian Academy of Oral Medicine and Radiology, Karnataka State Branch as summarized below.

Ensure that the latest instructions have been complied before submitting the manuscript.

JIAOMR-KSB accepts manuscripts written in American English.

Only original manuscripts will be considered for publication. Proper preparation of the manuscript by the author will expedite the reviewing and publication procedures.

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Types of Manuscripts:

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a. Ethics:

- Ensure procedures comply with ethical standards, referencing the responsible committee on human experimentation, institutional or regional guidelines, and the Helsinki Declaration (1975, revised in 2000).
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- The age for assent may vary as per regional and/or national guidelines.
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- Provide evidence of ethical committee approval on request.
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- The ethical standards of experiments must be in accordance with the guidelines provided by the CPCSEA and World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Humans for studies involving experimental animals and human beings, respectively.
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b. Study Design:

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  Reference established methods, including statistical methods; briefly describe methods that are published but not well known, and provide reasons and evaluations for new or modified methods.

  Precisely identify all drugs and chemicals used, including generic names, doses, and routes of administration.

  Reports of randomized clinical trials should include all major study elements, such as the protocol, randomization methods, allocation concealment, and blinding method, following the CONSORT Statement.
- *Sample size estimation*: Include the formula and derivation used to calculate the sample size, making provisions for dropouts, etc.
- *Reporting Guidelines for Specific Study Designs:*
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c. Statistics:

- **Quantification**: Quantify findings and present them with indicators of measurement error or uncertainty, such as confidence intervals.
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- **Results Summary**: Specify the statistical methods used when summarizing data in the Results section.
- **Statistical Terminology**: Avoid non-technical uses of statistical terms like 'random,' 'normal,' 'significant,' 'correlations,' and 'sample.' Define statistical terms, abbreviations, and symbols.
- **Software**: Specify the software used for statistical analysis.
- **P-Values**: Use upper italics (P 0.048). Include the exact P-value, not just 'less than 0.05' or 'less than 0.001.' Provide confidence intervals for mean differences in continuous variables, proportions in categorical variables, and relative risks, including odds ratios and hazard ratios.

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- **Numeric Results**: Provide absolute numbers alongside percentages and specify the statistical methods used to analyse the data.
- **Tables and Figures**: Restrict tables and figures to those needed to support the paper's argument. Avoid duplicating data in graphs and tables.
- **Data Analysis**: Include analyses of the data by variables such as age and sex where appropriate.

Discussion:

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- **Strengths and Limitations**: Discuss the strengths and limitations of the study, covering study design, data collection, analysis, and interpretation.
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- **Controversies and Future Research**: Address any controversies raised by the study and suggest directions for future research.
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- **Focus**: Manuscripts should review the current status of a given topic, diagnosis, or treatment modality, focusing on contemporary thought rather than an exhaustive literature review.
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    - Abstract (unstructured, 150 words)
    - Keywords (MeSH terms)
    - Introduction (150 words)

    - Case Report
    - Discussion
    - References (up to 10)
    - Tables and Legends
- **Case Report Section**: Divide into clinical findings, diagnostic assessment, surgical or therapeutic intervention (including dose), follow-up, and outcome.
- **Figures and Tables**: Include up to 3 tables or 3 figures.
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EDITORIAL

EDITOR-IN-CHIEF:

DR. SUMAN B.
Associate Professor,
Department of OMR, GDCRI, Bengaluru

Season's greetings to all,

It is with great pleasure that I welcome to you the latest issue of the Journal of Indian Academy of Oral Medicine and Radiology – Karnataka State Branch. It has been my proud privilege to have served as the Editor-in-chief of this journal for the past 2 years. This opportunity enabled me to interact with knowledgeable fraternity in Oral Medicine and Radiology. We bring forth their ardent efforts in mentoring and shaping the academic prowess of budding undergraduate students of dentistry who have secured prizes in the 3rd Karnataka State Undergraduate Conference – 2024, organized by IAOMR - KSB. Our primary goal currently is to provide an accessible and supportive platform for these young innovative minds.

We have strived to maintain the integrity and quality of the scientific manuscripts to facilitate scholarly exchange of knowledge in Oral Medicine and Radiology by adopting a rigorous peer review and offered the authors constructive feedback to further strengthen and improve the quality of their manuscripts with the sole intention of growth of the academic quality of this journal.

At present this journal is non-indexed and whole-hearted efforts are underway to meet the requirements of obtaining indexing and in this regard, I thank the authors, reviewers, editorial board members, and the office bearers of IAOMR-KSB for their valuable support.

Thank you all,

Dr SUMAN B

ASSOCIATE PROFESSOR

DEPARTMENT OF ORAL MEDICINE AND RADIOLOGY

GOVERNMENT DENTAL COLLEGE AND RESEARCH INSTITUTE, BENGALURU

JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY: KARNATAKA STATE BRANCH

Elastography: A New Dimension in Oral and Maxillofacial Imaging

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ABSTRACT

Various diagnostic imaging modalities have emerged in the past few decades for the detection of pathological lesions in the body. Palpation was the earliest and most common method of assessing a lesion based on its hardness. Ultrasound elasticity imaging is an extension of the ancient art of palpation. Elastography is the method for assessing tissue hardness by imaging the tissue strain with an underlying principle of tissue compression that produces strain within the tissue which is lower in hard tissue than in soft tissue and this change in strain pattern is imaged as bright and dark respectively. The major clinical applications of elastography in the maxillofacial region are differentiating benign from malignant lesions, reactive and malignant lymph nodes, assessing masseter stiffness, and evaluating focal lesions in major salivary glands. This review highlights a novel, non-invasive diagnostic modality, elastography, its principles of action, and clinical applications and advantages over conventional ultrasonography.

INTRODUCTION:

The assessment of tissue hardness has been a fundamental diagnostic method in medicine.[1] Historically, palpation was the earliest and most widely practiced method by physicians to detect differences in tissue stiffness, dating back to the era of Hippocrates. The relationship between tissue elasticity and hardness depends on the basic principle that, for an object to be palpable, there must be changes in consistency compared to the surrounding tissues. During palpation, the pressure receptors at various points on the skin covering the fingers sense the local stress over the region of interest.[2] Ultrasonographic imaging is a dynamic, non-invasive, accessible, and patient-friendly technique that is particularly useful in the examination of superficial structures [3] and has a wide range of applications in maxillofacial imaging.

Indication of ultrasound in the maxillofacial region [4]

1. Assessment of lymph nodes
2. Assessment of the salivary gland and thyroid gland
3. Assessment of soft tissue cysts
4. Ultrasound-guided biopsy
5. Assessment of tumor thickness

In recent decades, ultrasound has evolved significantly from conventional grey scale imaging to color and power Doppler techniques, and recently to elasticity imaging. Elastography is a novel imaging method described by Ophir et al in 1991 that assesses tissue compliance and tissue stiffness.[5] This review aims to highlight this emerging imaging modality, its principle, clinical applications, and advantages over conventional ultrasonography.

THEORY OF ELASTOGRAPHY

Elastography, which is based on the principle of physical elasticity, involves applying pressure to a medium and estimating the induced strain distribution by tracking the tissue motion. It is based on the concept of Young's modulus (E), which describes longitudinal deformation as strain (fractional change in length) in response to longitudinal stress (force per unit area). Additionally, the shear modulus (G) relates the transverse strain to transverse stress and describes the shear wave propagation in the isotropic homogenous media, while the Bulk Modulus (K) of elasticity reflects the changes in volume of a material to an external stress. Young's modulus and shear modulus of the tissue are related by a scaling factor of three (E=3G). The high-water content in the biological tissues allows them to deform easily under compression while maintaining constant volume.

MECHANISM OF ELASTOGRAPHY

Elastography enables the evaluation of the elastic properties of various tissues, and the images obtained are compared to those

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before and after compression.[7] Tissue elasticity varies among different tissues, like fat, collagen, etc., and in the same tissue during different pathologic states, like inflammation and malignancy.[8] Tissue stiffness tends to change (usually increase) with the disease and can be imaged by measuring the tissue distortion under applied stress.[9] The resulting high-contrast images contribute to the early detection of the disease processes. The data are then compared using a cross-correlation technique to determine the amount of displacement each small region of tissue undergoes in response to the compression applied by the ultrasound transducer.[10]

The development of elastography has been driven by interdisciplinary research. When stress (or displacement) is applied, all points in the elastic medium experience longitudinal strain, most prominently along the axis of compression. If tissues have different stiffness parameters, the level of strain will vary, and a stiffer tissue element will generally experience less strain than the softer tissues. Longitudinal (axial or lateral) strain is estimated from the analysis of ultrasonic signals obtained from standard diagnostic ultrasound equipment.[11] This process involves acquiring a set of digitized radio-frequency echo lines from the tissue, applying slight compression using the ultrasonic transducer along the ultrasonic radiation axis, and subsequently acquiring a second set of post-compression echo lines from the same region of interest. [8,9]

TECHNIQUE OF ELASTOGRAPHY

Elastography techniques have been developed for use with both ultrasound and MR imaging.[12] US elastography, also known as sonoelastography, relies on reproducible variations in the backscattered ultrasound signals resulting from compression of tissues of varying stiffness.[12] Image representation of tissue hardness can be obtained using a conventional sonography machine with special software and a conventional ultrasound probe.[5]

The procedure involved in the production of an elastogram (image produced with elastography) includes [10]

1. Elastography receives digitized radiofrequency echo lines from the tissue.
2. The transducer applies slight compression along the radiation axis to induce tissue displacement
3. Post-compression digitized radiofrequency echo is received from the same tissue.
4. Data undergoes processing, and ultimately, an elastogram is displayed on the monitor.

Elastogram may appear in grayscale or color. The hard and soft areas appear in the gray scale histogram as dark and bright, respectively. In the color elastogram, increasing tissue hardness appears in ascending order as red, yellow, green, and blue. These colors represent the relative hardness of the tissues in the elastogram.[13]

MR elastography is a quantitative method that relies on shear pressure waves and elastic displacement of tissue.[12] It obtains information about the stiffness of tissue by assessing the propagation of mechanical waves through the tissue with a special MRI technique, which essentially involves the 3 steps:[16]

1. Generating shear waves in the tissue.
2. Acquiring MR images depicting the propagation of the induced shear waves.
3. Processing the images of the shear waves to generate quantitative maps of tissue stiffness, called an elastogram.

APPLICATIONS OF ELASTOGRAPHY

A wide variety of organs and diseases are potential targets for elastographic evaluation, including superficial organs such as the breast, scrotum, neck, thyroid, and superficial masses in other organs. Deeper organs that can be accessed with pressure from an intracavitary transducer, such as the uterus, ovaries, and prostate gland, as well as the structures that are subject to physiological displacements like arterial walls, liver, and brain, are also ideal for elastography. Specific applications of elastography in the above organs are being explored in various studies and have shown satisfactory results. [1,12,17,18,19]

ELASTOGRAPHY IN THE MAXILLOFACIAL REGION

Elastography serves as an excellent diagnostic adjunct for pathologies involving the maxillofacial region. It is useful in the following aspects:

1. Assessment of cervical lymph nodes – to differentiate between reactive and malignant nodes
2. Differentiate benign and malignant lesions
3. Measure muscle stiffness in MPDS
4. Evaluate focal lesions in major salivary glands

CERVICAL LYMPH NODES

Lymph nodes in the maxillofacial region typically appear as well-defined, fusiform, or kidney bean-shaped, with an intermediate to low reflectivity, homogenous cortex, and a highly reflective central hilus. The dimension of the short axis is considered more valuable than the length of the node, which does not exceed 10mm. A width-to-length ratio greater than 0.5 implies a rounded abnormal node, and the more rounded a node, the more likely it is to contain metastatic disease. The submandibular and submental lymph nodes appear to be more rounded, so shape alone should not be used as an isolated predictor of malignancy.[3]

Cervical lymph nodes are readily accessible and can efficiently be compressed against the underlying structures with the use of an ultrasound probe for elastography. Information on lymph node stiffness would be useful clinically for guidance of percutaneous biopsy and/ or nodal dissection which helps in early detection of cancer recurrence.[13]

For the assessment of cervical lymph nodes, qualitative criteria are used, called the grayscale criterion, which includes the lymph node visibility, relative brightness, margin regularity, and margin definition- as well as the quantitative criterion strain index, which was obtained by comparing the absolute values of lymph node strain with the absolute values of surrounding muscle strain. Using a strain index of greater than 1.5 as a threshold for diagnosing tumors resulted in a sensitivity of 85% and a specificity of 98%- considerably better than the best grayscale criterion.[21] The combination of B-mode US, US elastography, and positron emission tomography, computed tomography (CT) could prove to be a powerful set of tools for assessment of nodal metastasis.[21]

Lyshchik et al,[13] studied the accuracy of sonoelastography in differentiating benign and metastatic cervical lymph nodes in patients suspected of thyroid cancer using histopathology as a

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standard reference. He reported that the most benign nodes have the same brightness as surrounding anatomic tissues and were not clear on the US elastogram, whereas the most malignant nodes appeared darker with better marginal delineation. In another study, Alam et al,[17] evaluated the diagnostic performance of sonoelastography and B-mode sonography of enlarged lymph nodes and found that elastography significantly improved sonography in the diagnosis of enlarged metastatic cervical lymph nodes.

SALIVARY GLANDS

Salivary gland masses are typically superficial and determining their pathological type using imaging techniques remains notoriously difficult. Elastography has shown potential in differentiating benign from malignant salivary gland masses, thereby assisting surgeons in selecting appropriate surgical procedures[20]. Dana Dumitriu[21]` et al. investigated the efficacy of real-time sonoelastography for the differential diagnosis of salivary gland tumors, using histopathological confirmation as the standard for comparison. While the study demonstrated differences in elastographic scores between benign and malignant tumors, detailed analysis did not yield consistent results. Thus, sonoelastography proved to be a limited technique for reliably distinguishing between benign and malignant salivary gland masses. However, elastography can detect glandular fibrosis, which is associated with inflammation in Primary Sjögren's syndrome and in glands exposed to radiation.

Elastography, particularly sonoelastography, has emerged as a valuable adjunct imaging tool in the evaluation of salivary gland pathologies. It provides information about tissue stiffness, aiding in the differentiation between benign and malignant lesions. While conventional ultrasound offers morphological details, elastography adds functional insight by assessing tissue elasticity, which can be altered in malignancy, inflammation, or fibrosis. Several studies [20] have explored its diagnostic utility in salivary gland tumors, with mixed results. Though differences in elasticity scores between benign and malignant lesions have been reported, the overlap in values limits its standalone diagnostic accuracy. In inflammatory conditions like Primary Sjogren's syndrome and post-radiation changes, elastography can detect glandular fibrosis, making it useful for disease monitoring. Despite some limitations, elastography serves as a non-invasive, real-time, and repeatable technique that complements conventional imaging in the assessment of salivary gland disorders.

Muscle stiffness

Estimation of individual muscle force could provide considerable insight into neuromuscular physiology, motor control, biomechanics, and robotics. It can also contribute to improved diagnosis and management of both neurological and orthopaedic diseases.[22] Surface electromyography (EMG) has been traditionally used to measure muscle activity level; however, there are several limitations inherent to this technique that can preclude an accurate estimation of muscle force.[23] Muscle stress is linked to its elastic modulus.[24] Consequently, muscle stiffness could provide an estimation of muscle force during contraction, which can be assessed with elastography. Various muscle pathologies that can be evaluated are: myospasm, myositis, myositis ossificans, hematoma, and tumors of muscles.

Masseter muscle stiffness can be evaluated using elastography. It is known that the hardness of muscle in men is higher than in women.[25] Ariji et al,[26] conducted a study with sonoelastography to assess the stiffness of the masseter muscle for investigating the correlation of muscle stiffness with the most comfortable massage pressure in MPDS patients.

Elastography is a valid support in the study of skeletal muscle pathology, because not only does it give an appraisal of the entity of the lesion, but also shows the state of the peri lesional area indispensable in the clinical and therapeutic follow-up of muscular lesions, allowing thus a more correct evaluation of the functional recovery in relation to the actual condition of muscular fibers involved in the repair process.[27]

ADVANTAGES:

1. A finer definition of tissue components with better margin delineation.
2. Differentiation of benign from malignant lesions.
3. Can complement B-mode US images with more diagnostic information.
4. A clinically useful guide for percutaneous biopsy or nodal dissection.
5. Early detection of cancer recurrence.

LIMITATIONS: [4]

1. Inability to control the extent of tissue compression by the transducer.
2. Some strain images of large lymph nodes can be suboptimal due to inadequate probe contact over a large area.
3. Artifacts can be caused by the movement of surrounding tissues and vessels.

RECENT ADVANCES IN ELASTOGRAPHY

A recent development in the elastographic technique, shear wave elastography [12] uses focused beams of ultrasound energy from conventional transducers to produce movement in the order of several microns at a depth of up to 6cm beneath the transducer. The speed of shear wave propagation is directly proportional to tissue elasticity, with a faster speed in stiffer tissues. This method has the advantage of being quantitative, reproducible, and operator-independent and is suitable for monitoring changes over time. The ARFI imaging technique has been introduced to overcome the inability to control the extent of tissue compression.[29] It uses radiation impulses to induce localized displacement of tissue and then monitor the dynamic response to individual tissue displacement.[30] To equalize the pressure over the tissue, balloon systems indicating the force of compression have been integrated into the probes.[30]

CONCLUSION

Elasticity imaging has received considerable attention due to its intuitive source of mechanical contrast and the significant diagnostic potential. We have every reason to believe that with continued development, elastography will become a more objective, non-invasive diagnostic tool in the future, and its prospective promises to be valuable in every way.

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JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY: KARNATAKA STATE BRANCH

Novel natural product Foeniculum vulgare on Candida species and comparison with Fluconazole on Candida species causing Oral Candidiasis- An in-vitro study.

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ARTICLE INFO

Keywords:
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Candida species
Fluconazole

ABSTRACT

Background: Candidiasis can be present as a cutaneous, mucosal, or deep-seated organ infection, caused by more than 20 types of Candida species with Candida albicans being the most common. Over the years there has been a definite increase in yeast infections, the drugs available for their management, and the emergence of resistant isolates making antifungal drug susceptibility testing an important component of current health care management.
Aim: To evaluate the antifungal property of Foeniculum vulgare herb against Candida species and to screen antifungal susceptibility of cells compared to Fluconazole.
Materials and methods: The study was undertaken to investigate the possible antifungal action of the ethanolic and methanolic extract of Foeniculum vulgare and to determine Minimum Inhibitory Concentration [MIC], Disc Diffusion method & Time Kill Assay.
Results: Both extracts exhibited antifungal activity on the subcultures of Candida species. The methanolic extract of Foeniculum vulgare against Candida albicans showed a maximum inhibitory zone in relation to the Standard drug Fluconazole. The methanolic extract shows maximum sensitivity against C. krusei followed by ethanolic extract against C. albicans. Antifungal activity against C. albicans and C. krusei was observed by time-kill assay. C. glabrata showed the least activity.
Conclusion: Foeniculum vulgare herb gives the best inhibitory effect, and it has good potential to control the growth of Candida species. In the future this study can be used in the infected patients with candidiasis as this herb is natural do not have any toxic effects. Further clinical studies are required for its efficacy.

INTRODUCTION:

Candida is one of the most common causes of fungal infections. Candida is a type of yeast or single-celled fungi that exists as a part of the natural microflora.[1] Candida species are human fungal pathogens capable of initiating various recurring superficial mycoses, especially in the oral mucosa.[2]
Presently, oral infection is one of the most prevalent types of disease and is a growing health problem around the world.[3] Mycological studies have shown that Candida albicans represents over 80% of isolates from all forms of human candidiasis.[4]
There are no drugs that can be used effectively to treat oral infections caused by Candida.[3] All the drugs from plants are substances with particular therapeutic actions that are extracted from plants.[3,5]
Natural products play a major role in controlling infections and treatment by inhibiting the growth of responsible pathogens.[5] Foeniculum vulgare, commonly known as fennel, is a flavourful culinary herb and medicinal plant. They are packed with nutrients such as vitamin C, Calcium, Magnesium, Potassium, and Manganese. They also contain potent antioxidants like Chlorogenic acid, limonene, and quercetin.[6]
Fennel seeds have been associated with various health benefits, including antioxidant, anti-inflammatory, and antifungal, antibacterial effects, digestive health, heart health, and potential anti-cancer properties.[6,7]
Even the essential oil of Foeniculum vulgare has been found to have antifungal activity against Candida albicans.[8]
The present study has been undertaken to evaluate the in vitro action of Foeniculum vulgare against Candida albicans, Candida glabrata, and Candida krusei.

OBJECTIVES:

1. To evaluate the antifungal activity of Foeniculum vulgare herb against Candida species.
2. To find the antifungal activity of Foeniculum vulgare seed extracts prepared in 2 different solutions (methanol and ethanol) against opportunistic pathogens Candida albicans, Candida glabrata, and Candida krusei.
3. To screen antifungal susceptibility of cells compared to Fluconazole.

MATERIALS AND METHODS:

The seed extract of Foeniculum vulgare was prepared in methanolic and ethanolic solutions chosen for the investigation of in vitro antifungal activity. The study was carried out within the Institute at the Central Research Laboratory.

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1.1. Extract preparation:

Fennel seeds were uniformly ground using a mechanical grinder to yield fine powder. 250g of the powder was mixed with 1000mL of methanol and ethanol separately in a conical flask & kept in an automatic shaker. The mixture was filtered using Whatman filter paper. Using a horizontal ROTA evaporator, it was concentrated, i.e., it was reduced from 1000mL to 60mL, then kept in an incubator at 37 °C to reduce it to 40mL.

1.2. Disc Diffusion Method

Sterile cotton dip was swabbed into the inoculum and swabbed to the entire surface of the agar plate, which was at room temperature, then the inoculated plate was allowed to stand for 3 minutes. A hollow tube of 5mm diameter was taken, heated, and pressed on the above inoculated agar plate, and removed immediately by making a well in the plate. Likewise, 4 wells were made on each plate. With the help of a micropipette, 75µl/ml, 50µl/ml, 25µl/ml, and 10µl/ml were added in each well and then incubated for 18-24 hours at 37 °C in an incubator.

1.3. Minimum Inhibitory Concentration

9 dilutions of each extract were done with Brain Heart Infusion [BHI] Broth for MIC. In the initial tube, 20mL of extract was added to 380Ml of BHI broth. For dilutions, 200mL of BHI broth was added into the next 9 tubes separately. Then, from the initial tube, 200mL was transferred to the first tube containing 200mL of BHI broth. This was considered a 10: 1 dilution. From a 10:1 diluted tube, 200mL was transferred to a second tube to make a 10:2 dilution. Then, serial dilution was repeated up to 10:9 dilution for each extract, 5mL of the organism was taken and added into 2mL of BHI broth. In each serially diluted tube, 200mL of the above culture suspension was added. Tubes were incubated for 24hours and observed for turbidity.

1.4. Time Kill Assay

An equal quantity of the broth with the organism and compound was mixed, then immediately it was plated; this was noted as 0 minutes. Tubes were kept in a CO_2 jar till further notice. The further time slots were 30 minutes, 1 hour, and 2 hours. It was cultured or plated and incubated according to the growth requirement, i.e., in a CO_2 jar and an Anaerobic jar. After 48-72 hrs. of incubation, the plates were removed, and the colony count was noted.

RESULTS:

The antifungal activity of ethanolic and methanolic extracts of Foeniculum vulgare with standard Fluconazole was analysed in the present study, and the results were tabulated. The zone of inhibition increases in a dose-dependent manner. Among the three concentrations [25,50,75µl/ml], maximum inhibitory zone was observed for Fluconazole, followed by Methanolic extract of Foeniculum vulgare against C. albicans. The results shown are better seen in C. albicans than in the other two Candida species tabulated in [Table 1].

Table 1:

Sl No.	Samples	75 µl/ml	50 µl/ml	25 µl/ml	Fluconazole
Candida albicans					
1.	Foeniculum vulgare Ethanolic extract	15mm	13mm	10mm	35mm
2.	Foeniculum vulgare Methanolic extract	25mm	18mm	15mm	40mm
Candida glabrata					
1.	Foeniculum vulgare Ethanolic extract	R	R	R	45mm
2.	Foeniculum vulgare Methanolic extract	R	R	R	48mm
Candida krusei					
1.	Foeniculum vulgare Ethanolic extract	08mm	R	R	40mm
2.	Foeniculum vulgare Methanolic extract	12mm	10mm	R	43mm

The MIC results showed that C. albicans showed the most sensitivity towards the standard drug Fluconazole. The sensitivity of ethanolic extract of Foeniculum vulgare against C. albicans was seen till concentrations 6.25µl/ml, which was better seen than the methanolic extract, which showed sensitivity only till 50µl/ml, which in relation to Fluconazole was till 1.6µl/ml [Table 2]. The sensitivity of ethanolic and methanolic extracts of Foeniculum vulgare against C. glabrata was almost seen same [Table 2]. The sensitivity of the methanolic extract of Foeniculum vulgare against C. krusei was seen till concentrations 3.12µl/ml which was better seen than the ethanolic extract, which showed sensitivity only till 12.5µl/ml, which in relation to Fluconazole was till 0.8µl/ml [Table 2].

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Table 2:

Sl No.	Samples	100 µl/ml	50 µl/ml	25 µl/ml	12.5 µl/ml	6.25 µl/ml	3.12 µl/ml	1.6 µl/ml	0.8 µl/ml	0.4 µl/ml	0.2 µl/ml	B+C	B+O
Candida albicans													
1.	Foeniculum vulgare Ethanolic extract	S	S	S	S	S	R	R	R	R	R	S	R
2.	Foeniculum vulgare Methanolic Extract	S	S	R	R	R	R	R	R	R	R	S	R
3.	Fluconazole	S	S	S	S	S	S	S	R	R	R	S	R
Candida glabrata													
1.	Foeniculum vulgare Ethanolic extract	S	S	S	R	R	R	R	R	R	R	S	R
2.	Foeniculum vulgare Methanolic Extract	S	S	S	R	R	R	R	R	R	R	S	R
3.	Fluconazole	S	S	S	S	S	S	S	S	S	R	S	R
Candida krusei													
1.	Foeniculum vulgare Ethanolic extract	S	S	S	S	R	R	R	R	R	R	S	R
2.	Foeniculum vulgare Methanolic extract	S	S	S	S	S	S	R	R	R	R	S	R
3.	Fluconazole	S	S	S	S	S	S	S	S	R	R	S	R

The time kill kinetics of ethanolic and methanolic extracts of Foeniculum vulgare against C. albicans showed a reduction in the number of cells with an increase in time, as shown in [Graph 1].

The time kill kinetics of ethanolic extract against C. glabrata showed a reduction in the number of cells with an increase in time. And with methanolic extract, there were the fewest cells seen at 0 minutes, which was accompanied by an increase in cells and then reduced at 2 hours [Graph 1].

The time kill kinetics of ethanolic and methanolic extracts of Foeniculum vulgare against C. krusei showed a reduction in the number of cells with an increase in time, as shown in [Graph 1].

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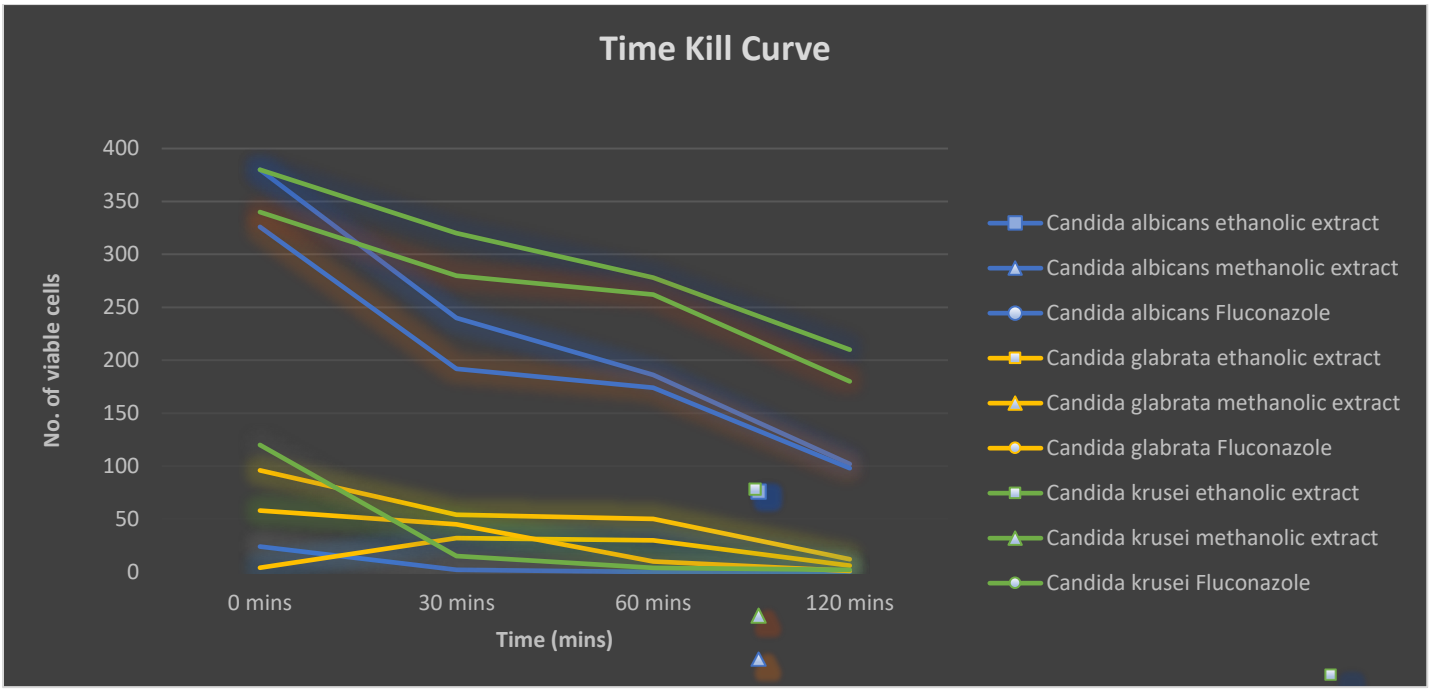
GRAPH: 1



DISCUSSION:

The indiscriminate use of commercially available antifungal drugs has led to multiple drug resistance in human pathogenic microorganisms. The resistant strains of C. albicans, a causative agent for Oral Candidiasis, have become a cause of major health concerns, and novel antifungal agents are required to tackle this issue. This situation obligated scientists to search for new and effective antifungal agents to replace the current regimens.[9]

Natural products are in great demand for their extensive biological properties and their bioactive components, which have been proven to be useful against a large number of causative agents of diseases.[10]

Fennel seeds are reported to have effective reducing power, free radical scavenging, superoxide anion radical scavenging, and hydrogen peroxide scavenging activities.[11]

In a 2009 study, researchers from Pakistan's University of Agriculture tested fennel seed extracts against bacteria and fungi and also found them to be significantly antibiotic and antifungal[12]. The current study investigated the antifungal activity of Foeniculum vulgare against Candida albicans, Candida glabrata, and Candida krusei obtained from oral candidiasis cell culture. According to the results obtained in the current study, the Methanolic extract showed maximum inhibitory zone against Candida albicans. The ethanolic and methanolic extract of Foeniculum vulgare showed the least/no inhibitory zone against Candida glabrata and Candida krusei.

The low candidal activity of these agents may be improved via the use of different solvents and different extraction procedures, considering the polarity of the active compounds.[13]

Further, from the current study, the efficacy of ethanolic and methanolic extracts was tested by obtaining their MIC values. It showed that the MIC value of the ethanolic extract for Candida albicans and the methanolic extract for Candida krusei was better than Candida glabrata.

In the current study, colony count samples were obtained at 0,30,60,120 minutes. The colony count decreased with an increase in time.

According to Pfaller et al, an antifungal is said to have fungicidal activity if there is a decrease in the number of colonies by 99% or 3 log 10 units in CFU/ml compared to the initial inoculum.[14] In this study, we observed the growth of Candida species using the time kill curve, and the fungicidal activity was observed for Candida albicans.

CONCLUSION:

The findings of this suggested that Foeniculum vulgare in specific solution can be best used in the treatment of oral infection by Candida species, as the herb used is natural without any toxic effects. The effective herbs can be used to treat infection at very low cost by using the effective herbal components in toothpastes, oral gels, ointments, as by use of these products will totally vanish the fungal colony from the oral cavity without resulting in any side effects or toxicity like drugs. As the use of chemical antimicrobial agents also enhances the resistance character of microbes or fungi, but these herbal products will not show any effect on enhancing the resistance character of this pathogenic fungus, this might also be the best of its use.

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Fusion Imaging: Emerging Trend in Therapeutics

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ABSTRACT

Medical imaging technology involves several techniques, which include conventional X-rays, ultrasound imaging, Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Positron Emission Tomography (PET), and Single Photon Emission Tomography (SPECT). All these imaging modalities have their advantages and disadvantages. By using the method of fusion imaging, we can combine multiple modalities and get more specific details about the lesion. These modalities act synergistically with each other and give an enhanced view to diagnose, treat, and compare the prognosis. This review article gives a broader idea of fusion imaging and its various applications.

INTRODUCTION:

Medical imaging involves creating images of the human body to assist medical practitioners in effective clinical diagnosis. Several imaging techniques have been developed over time that not only help in anatomical diagnosis but also assist in functional diagnosis. The imaging scenario has continuously evolved from X-ray film and cassettes to using computers and digital techniques. Such reinventions in imaging techniques aim to provide excellent patient care, without compromising on the accuracy of diagnosis, but also assist in functional diagnosis. As technology evolved, for accurate diagnosis, different imaging modalities were being used one after another. The clinicians obtained physiological and anatomical information on separate machines. These images were viewed together after using special registry software to superimpose images from each of the participating modalities. Recently, there has been an increased need to utilise different modalities together for effective diagnosis, and this has promoted a novel hybrid technology called fusion imaging.

Medical imaging can be classified as anatomical imaging and molecular imaging.

ANATOMICAL IMAGING:

Anatomical imaging is the fundamental approach, which includes X-ray imaging, ultrasound imaging, CT, and MRI. In this type, pathologies are detected according to the structural alteration of the affected area in comparison with normal surrounding structures; these changes are not always related to the cancer. Similarly, small cancers are undetected by this kind of imaging, but this helps in the initial cancer evaluation to look for local spread, to know the primary nodal status, and preoperative anatomy .[4]

Different modalities of anatomical imaging are explained in Chart 1.

MOLECULAR IMAGING:

In 2005, the Radiological Society of North America (RSNA) and the Society of Nuclear Medicine (SNM) jointly convened a definition as follows: techniques directly or indirectly monitor and record the spatiotemporal distribution of molecular or cellular processes for biochemical, biologic, diagnostic, or therapeutic applications.[5]

This imaging technique provides the visualization, characterization, and quantification of biologic processes taking place at the cellular and subcellular level. This is achieved by contrast and radiotracers and is also known as functional or physiologic imaging. (Reba 1995, Massoud and Gambhir 2003)

Different modalities of molecular imaging with advantages and disadvantages have been explained in Chart 2.[6]

FUSION IMAGING/HYBRID IMAGING:

Fusion imaging is defined as the process of coalescing multiple images from multiple imaging modalities to obtain a fused image with a large amount of information, increasing the clinical applicability of medical images.[7]

Most commonly used hybrid imaging modalities include:

- PET-CT
- SPECT-CT
- PET-MRI
- SPECT-MRI
- Ultrasonogram and MRI

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- Ultrasonogram and CT
- MRI and CT

Ideally, the final image after the fusion should retain the information from the source images, but it should reduce the misregistration and noise as much as possible and not generate any new information or artifacts.[8]

There are multiple methods and multiple approaches in the field of image fusion. Commonly used steps include decomposition and reconstruction, the image fusion rule, and image quality assessment.[8]

At first, the input image is decomposed into a series of sub-images with low and high frequency components with the help of algorithms from the image, and then rules in the image fusion are used to merge more than one feature from the low or high frequency component into sub-images at different resolutions. Later, the fused image is regenerated from the fused sub-images by using image reconstruction algorithms. Finally, the image quality assessment is done.[9,10]

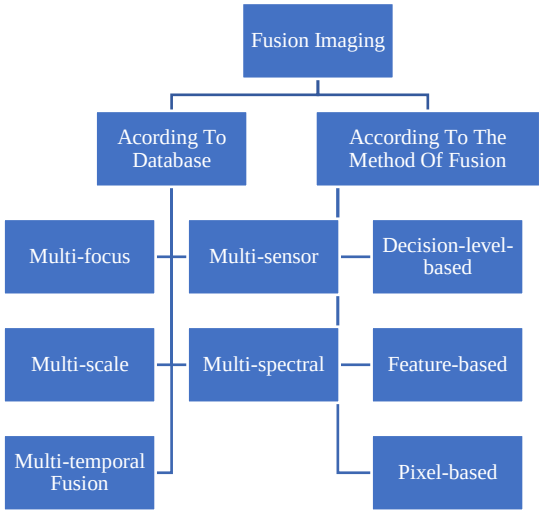
The classification of fusion imaging according to the dataset is.[11]

- Multi-focus method: This combines two or more source images to obtain a single image that is focused.[11]
- Multi-sensor: In this image of the same object is captured by multiple sensors, and they are fused to complement each other. [12]
- Multi-scale: Usually, high-resolution data can resolve pore structures up to the nanoscale, but the FOV will be small, and a larger FOV cannot capture the fine details. But by this method of fusion of multiscale data, high resolution and a larger FOV can be achieved.[13]
- Multi-spectral: This imaging fusion of multi-spectral images combines the image features of multi-spectral images to get a more comprehensive and clearer image using the spatiotemporal correlation and information on complementarity. [14]
- Multi-temporal fusion: In this method, the same source will be imaged at different times, and fusion imaging will help in knowing the progression.[11]

Further fusion imaging techniques are also classified as

1. Decision-level-based: This depends on the training of the dataset and performance fusion. In the dictionary learning fusion, the same decision-level technique is used. This method is application dependent.[15]
2. Feature-based: In these fusion images, they are usually combined in the region of interest for multiple input modalities. This information, such as edges, corners, texture parameters, and lines, can be extracted. Thus, this kind of method is usually robust to reduce noise and misregistration [16]
3. Pixel-based: The pixel-based medical image fusion techniques are further divided into the following: pre-processing, decomposition, fusion rules, and fusion performance evaluation. The advantages over feature-based and decision-based techniques are that Visual clarity is very informative in pixel intensity-based image fusion.[17,18]

Pictorial representation of the classification:



PET-CT:

Positron Emission Tomography is a type of functional radiography. In this type, accurate localization of the lesion is difficult because of the lower resolution. PET with a glucose analogue such as fluorine 18 fluorodeoxyglucose (FDG) is the most common addition for cancer detection. When used in combination with anatomical imaging methods like CT, they complement each other and provide an accurate location and nature of the lesion.[19,20]

A study done by Barton F. Branstetter et al. in 2005 at the University of Pittsburgh shows that combined PET/CT is more accurate than PET or CT alone. In this study, 65 patients with head-and-neck cancer were evaluated. The results show PET CT had a sensitivity of 98% and a specificity of 94%. [21]

SPECT-CT:

Single-photon emission computerized tomography (SPECT) uses radioactive materials and a specially designed camera to produce three-dimensional images of organs and tissues, mainly used for brain and neurological conditions, cardiac conditions, and bone disorders. In the traditional technique, ^{99m}Tc-labelled phosphonates are used.[22]

A retrospective study was conducted by Andreas M. Muret et al, analysing 201 patients who underwent 99mTc-hydroxymethane diphosphonate (HDP) SPECT/CT. The results showed a sensitivity and specificity of 96.5% and 96.2% for the detection of patellofemoral osteoarthritis.[23]

PET-MRI:

MRI plays an important role in cancer detection due to its excellent soft tissue contrast, which provides detailed anatomical information in a relatively small compartment.[24]

According to Shu-Hua Huang et al. who evaluated the diagnostic value of fused fluorodeoxyglucose positron emission tomography and magnetic resonance imaging (PET/MRI) compared with PET/computed tomography (CT), MRI, and CT in assessing surrounding tissue invasion of advanced buccal squamous cell carcinoma (BSCC), Fused PET/MRI was noted to be more reliable for focal invasion assessment and tumor size with sensitivity and specificity of 90.0% and 90.9%.[25]

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SPECT-MRI:
This imaging modality provides the functional as well as morphological measurement of the lesion more accurately. MRI gives high spatial resolution and good contrast. These techniques are mainly used in cardiology and neuroimaging [26]
SPECT can image ligands, like, peptides and antibodies, easily because of the longer half-life of the ^{99m}Tc, ^{111}In, or iodine isotopes (^{123}I, ^{125}I). The other advantage of SPECT over PET is that no cyclotron and associated infrastructure, and complex logistics are required on site, and that many tracers are readily available in the form of kits.[27]

Ultrasound, and MRI/CT:
These will give superior resolution to ultrasound, including its real-time imaging. This fusion method allows for more precise anatomy. It mainly helps in the ultrasound-guided biopsies in which the target area can be difficult to locate.[28]
In this type of image, fusion coupling of the images is carried out using an electromagnetic support and sensor placed on the probe. Analysis of the acquisition of previously loaded data into the ultrasound system. The synchronization is necessary so that the ultrasound and MRI visual site will be matched.[29]
In the field of abdominal imaging, interventional procedures, this method is very helpful.[30,31,32]

MRI-CT fusion:
CT provides excellent high-quality bone density information, and MRI provides high-resolution soft tissue detailing. This fusion will give a detailed orientation of the lesion and the surrounding area for the diagnosis and the treatment planning.[33]

Advantages and disadvantages of fusion imaging [34]
The structural and functional information of the lesion can be obtained together. Early detection and accurate identification of the margin can be obtained easily. This internally helps in the treatment planning, guidance of the biopsy, surgery, and radiation therapy. Importantly, metastatic tumours, in cases of occult primary tumours or smaller tumours that might not have been identified by CT or MRI, can also be detected.
In case of occult lesions, the detection of the primary site can be done easily. It also helps in increasing the self-confidence of the doctor in diagnosing and managing the lesion. The disadvantages of the technique include less clarity and decreased resolution of the image. The technique is expensive, time-consuming, and complex.

APPLICATIONS:
1. PET-CT/PET-MR is mainly used for the detection of osseous metastasis in the head and neck and all over the body. It gives added information regarding the occult primary, associated structures, and also information regarding the metastasis and metabolic activity of the tumor. This helps in the accurate staging and planning of the treatment. It helps in assessing the long-term prognosis of the disease. PET-MR is particularly helpful in differentiating between residual disease and infection. It mainly helps in defining the tumour margins in the oral and oropharyngeal areas.[35]
2. Gallium-68 (Ga-68) DOTA-1-NaI3-octreotide (DOTA-NOC) positron emission tomography (PET)/computed tomography (CT) is mainly used for neuroendocrine tumours (NETs), particularly in pancreatic NETs. The standardized uptake value (SUV) in these tumours is often very high, generally higher than in other NETs. [36]
3. F-18 fluorocholine-positron emission tomography/computed tomography (FCH-PET/CT) has emerged as a new diagnostic tool for the imaging of prostate cancer. F-18 overcomes some of the limitations of C-11, such as the short half-life, and provides more flexibility concerning imaging protocols and availability.[37]
4. Epilepsy and dementia imaging using neuroimaging CT and MRI helps in locating the lesion, but magnetic resonance spectroscopy and positron emission tomography (PET) give important information about the metabolic state and molecular events within the tumour.
5. Functional MRI and PET, in combination with electrophysiological methods like transcranial magnetic stimulation, are being used to delineate functionally important neuronal tissue, which has to be preserved from treatment-induced damage, as well as to gather information on tumour-induced brain plasticity.[38]
6. 18-F-fluoro-D-deoxyglucose positron emission tomography (FDG PET) has become an established imaging tool in clinical oncology, cardiology, and neurology and is now entering the field of clinical infectious diseases. FDG PET was noted to have an incremental value in the assessment of chronic osteomyelitis, especially in the axial skeleton, as well as in the diagnostic workup of fever of unknown origin and HIV complications.[39]
7. F18-angiography is commonly used in the detection of the neuro-vascularization of the tumors, similar to CT and MRI perfusion in the head and neck region
8. PET-MRI has applications mainly in the head and neck region in CNS tumours [40]

CONCLUSION:
Fusion imaging gives more relevant information than a single image. The results show more specificity and sensitivity in comparison with individual imaging modalities. The practical application of the technique is still limited because barriers like expense, the requirement of specialised equipment, a skilled/trained person, and the risk of toxicity delivered from the contrast agent exist.

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Chart-1: Different modalities of anatomical imaging

Imaging modality	
X-ray radiography	Electromagnetic waves are used Images formed are two-dimensional First line of routinely taken radiography
Computed tomography	X-ray beam is used to produce the image Gives a 3D representation view Commonly used to assess the musculoskeletal view
Magnetic Resonance Imaging (MRI)	In this, the image is acquired by the use of radio waves in a magnetic field Image formed depends on the tissue photon levels 3D view can be obtained Commonly used to assess the soft tissue abnormalities
Ultrasonography	Sound waves are used to form an image Gives the real-time imaging of the tissue. 3D view is possible in recent advances Widely used to detect soft tissue

Chart-2: Different modalities of molecular imaging with advantages and disadvantages [41]

Sr no	Technique	Advantages	Disadvantages
1.	Positron emission tomography	Transport of radiolabeled glucose into cells High sensitivity	Low resolution (better than SPECT) Cannot differentiate the inflammatory sites from neoplastic processes Chances of false positives (brown fat, infection, asymmetric muscle activity) and false negatives (small tumor, low glycolytic activity)
2.	Single-photon emission computed tomography (SPECT)	Nuclear medicine tomographic imaging using gamma-rays or characteristic X-rays	Poor resolution Time-consuming Underestimation is possible in deep tissues through the absorption of gamma-rays
3.	Proton MR spectroscopy	Detects the presence of specific metabolites (Elevated Cho/Cr levels suggest higher membrane turnover) in tissues	Low signal-to-noise ratio

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4.	Computed tomographic perfusion (CTP)	Continuous recording of X-ray attenuation over a fixed area of interest during the passage of a fast bolus of iodinated contrast medium through the region Evaluates blood volume, blood flow, and mean transit time, and the capillary permeability of a lesion Reproducible technique	Requires injection of contrast medium Large exposure to radiation
5.	Perfusion-weighted MRI	Blood flow dynamics at the microcirculation level Similar to CTP	Paramagnetic contrast medium injection Longer scan time Difficulty in optimization
6.	Diffusion-weighted imaging (DWI)	Tissues that are more compact at the molecular level (e.g., tissues with higher cellularity) tend to show relative reduction of water molecular motion expressed as lower ADC values Reproducible images in any MRI protocol	Lack of optimized threshold ADC values Susceptibility to dental fillings causes magnetic artifacts
7.	Diffusion tensor imaging (DTI) Form of DWI	Characterizes 3-D diffusion of water Tracks nerves from adjacent structures Characterizes microstructural changes	Nonspecific marker of neuropathology, thus imposing diagnostic or therapeutic challenges
8.	Hypoxia (optical-based, MRI-based, or PET imaging-based)	PET-based potential tumor hypoxia imaging agents include 18FFMISO and copper 60 (II)-diacetyl-bis (N4-methylthiosemicarbazone)	Suboptimal imaging Poor resolution
9.	Cell proliferation (PET-based)	Injected 3′-deoxy-3′-F-18-fluorothymidine becomes concentrated in nucleosides	Tumor vs. normal tissue contrast is low Less marrow uptake

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JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY: KARNATAKA STATE BRANCH

Complementary Alternative Medicine – An Ingenious Beneficial Approach for Oral Diseases

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ABSTRACT

As concerns continue to rise among patients about the adverse effects of conventional medicine, along with the increasing resistance of bacteria to antibiotics, and the difficulties faced by medical personnel in managing chronic diseases and their associated symptoms, it has become increasingly important for the health care professionals to have a thorough knowledge of complementary and alternative modalities for the treatment of such chronic ailments. Therefore, it is necessary for the dentists to be aware of complementary and alternative treatment modalities which are popular, safe, effective, and economical. Complementary medicine comprises of treatment modalities such as herbal medicines, traditional Chinese medicine, naturopathy, Ayurveda, aromatherapy, homeopathy, acupuncture, and ozone therapy.

INTRODUCTION:

There's no such thing as alternative medicine; if it works, it's just called medicine. —Ed Yong

With the growing concern among patients regarding the adverse effects of conventional medicines, increasing bacterial resistance to antibiotics, and difficulties faced by the medical personnel in managing chronic disease and their symptoms, it has become imperative for the health care professionals to have a sound knowledge of complementary and alternative modalities for the treatment of these chronic ailments. Many of these therapies have well-documented therapeutic benefits, have been used since ancient times, and are globally recognized for their effectiveness. [1,2]

Oral physicians and dental professionals encounter challenges in the management of certain dental conditions due to the resistance of oral microflora, and drug tolerance leading to persistence of symptoms and emergence of other side effects of conventional therapies. Hence, it becomes essential for dentists to be aware of complementary and alternative modalities that are popular, safe, effective, and economical.

Complementary and alternative medicine (CAM) refers to a wide range of medical and health care practices and products not typically considered as part of conventional medicine. It includes herbal medicine, traditional Chinese medicine, naturopathy, Ayurveda, aromatherapy, homeopathy, acupuncture, magnetic field therapy, ozone therapy, Mora therapy, and others. [1]

HERBAL MEDICINE:

Herbal medicine, also known as phytomedicine or botanical medicine, involves concentrated tinctures, herbal materials, preparations, and products. Herbs serve various therapeutic purposes, such as blood purification, warming of the body, enhancing surface circulation, promoting waste elimination, reducing inflammation, and relieving discomfort. They may be administered orally as tablets, syrups, or infusions, or used topically as plasters and ointments. [3]

THERAPEUTIC USES OF TULSI IN DENTISTRY:

Tulsi, often referred to as the "Elixir of Life," is recognized for its diverse pharmacological actions, including expectorant, analgesic, anticancer, antiasthmatic, antiemetic, diaphoretic, antidiabetic, antifertility, hepatoprotective, hypotensive, hypolipidemic, and antistress effects. [4]

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Table 1: Properties of various Herbs used in Dentistry

S.No	Herbs	Properties of various Herbs
a.	Aloe vera	Provides analgesia, has antibacterial effect, has antiviral effect, has antifungal effect, antioxidant and immune modulating, antiseptic properties, anti-inflammatory activities.
b.	Black Cohosh	It mainly has an anti-inflammatory effect.
c.	Bloodroot (Sanguinaria Canadensis)	It has antibacterial, anti-inflammatory, antifungal property.
d.	Ginger (Zingiber Officinalis)	It acts against bacteria, shows anti-inflammatory property, and has analgesic effect.
e.	Clove Oil (Syzygium Aromaticum)	It is an analgesic, with an antibacterial effect, it is also an antiviral drug, has actions against inflammation, It also has antioxidant property.
f.	Cranberry (Vaccinium Macrocarpon)	It has anticarcinogenic, antibacterial, antiviral, antifungal, and antioxidant properties.
g.	Green Tea (Camellia sinensis)	It works to reduce inflammation, has antibacterial action, and has antiviral action as well.
h.	Neem (Azadirachta Indica)	They act against viruses, fungi, microbes, bacteria, has antipyretic action, anti-inflammatory, antitumor, analgesic, helminths, acts against cariogenic agents, has antioxidant property.
i.	Peppermint (Mentha Piperita)	It is analgesic and also has muscle-relaxing action.
j.	Turmeric (Curcuma longa)	It is antimutagenic, acts against carcinogenic agents, has antioxidant action, and acts against bacteria's.
k.	Tulsi (Ocimum sanctum)	It acts against helminths, has analgesic property, antipyretic, immune stimulatory, antiulcer, antimicrobial, anti-inflammatory property.
l.	Triphala	It is not only an antioxidant but also acts against microbes.
m.	Garlic (Allium sativum)	Acts against bacteria , helminths , fungi and viruses and also has antiseptic effect.

Table 2: Manifestations of Herbs

No.	Name of the Herb	Toxicity	Indication
1.	Cranberry	Nephrolithiasis	Dietary supplement (Terris *et al.*, 2001)
2.	Willow Bark	Renal Dysfunction	Anti Rheumatic (Schmid *et al.*, 2001)
3.	Aconite , Monks Hood	Ventricular Arrhythmia	Pain (Sheth *et al.*, 2015)
4.	Black Cohosh	Acute hepatitis	Menopausal symptoms (Chow *et al.*, 2008)
5.	Kava kava	Acute liver failure	Tranquilizer (Gow *et al.*, 2003)
6.	Valerian	Liver toxicity	Sedative (Willey *et al.*, 1995)

At present the herbal products are often associated with safety, especially when compared to the synthetic pharmaceuticals that are regarded as less safe for both humans and the environment.[5] Properly dosed and timed herbal remedies are non-addictive and unlikely to cause allergic reactions, making them ideal for long-term use.

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Table 3: Uses of Different Herbs in Dentistry

Plant	Uses
Clove (*Syzygium aromaticum*)	Breath freshener reduces toothache in periodontitis, anesthetic, and treatment of bleeding gums
German chamomile	Gingivitis, periodontal disease, and cure oral ulcers in mouthwash form
Tea tree oil (*Melaleuca alternifolia*)	Breaks down the microorganisms in the oral cavity preceding the dental surgery, removes smear layer when used as a root canal irrigant, and relieves mouth soreness caused by dental procedures
Coconut water (*Cocos nucifera*)	Reduces inflammation, root canal irrigant (antiviral, antifungal, and antimicrobial properties) and storage media for avulsed tooth
Propolis	Dental caries, gingivitis, storage medium, intracanal medicament, dentinal hypersensitivity, stomatitis, halitosis, periodontal pocket/abscess, lichen planus, candidal infections, xerostomia, traumatic ulcers, pulp capping, and pericoronitis
Triphala	Dental caries, bleeding, and ulcerated gums
Turmeric (*Curcuma longa*)	Anticarcinogenic, antibacterial, halitosis, pit and fissure sealant, and dental plaque detection system. Massaging the aching teeth with roasted, ground turmeric eliminates pain and swelling
Aloe (*Aloe arborescens* Mill.)	Periodontal surgery, toothpick injuries, aphthous ulcers, gum abscesses, dry socket, lichen planus, benign pemphigus and gingival problems associated with AIDS, leukemia, migratory glossitis, geographic tongue and burning mouth syndrome, denture sore mouth, candidiasis, desquamative gingivitis, vesiculobullous diseases, acute monocytic leukemia, and xerostomia
Ashwagandha (*Withania somnifera*)	Antioxidative, antistress, and immunomodulatory
Casearia sylvestris Sw. (Gulkhair - Wild coffee)	Healing, antiseptic, antiulcerative, diuretic, tonic, stimulant, and antimicrobial. It is shown as an alternative intracanal medicament
Mustard tree (*Salvadora persica* Linn)	Sticks contain natural antibiotics, fluoride, and other anticavity components 15% of alcoholic extracts of it has maximum antimicrobial action. It can be used as a substitute for NaOCl and chlorhexidine as root canal irrigant
Curcuma longa	Inhibits growth and spread of various cancers such as lung, esophagus, liver, colon, prostate, head and neck, and skin
Neem (*Azadirachta indica*)	Anti-inflammatory and wound healing properties
Tamarind (*Tamarindus indica*)	A seed extract has antioxidant enzyme induction and cancer-related signal pathway blockage effect and anti-inflammatory effect
Tulsi (*Ocimum tenuiflorum* Linn)	Leaf extracts have antioxidant effect, wound healing property, antimicrobial effect, and anti-tumorigenic effect

"Mother Earth's medicine chest is full of healing herbs of incomparable worth." [6]

AYURVEDA:

Ayurveda is the oldest known medical system and is a science of life, prevention, and longevity. Originating in India over 5000 years ago, it contains extensive information on medicinal herbs to treat various diseases known to man. It was a fundamental part of the Santana dharma (universal religion), or Vedic religion. Ayurvedic concepts are a combination of these principles that are classified as follows: Vayu – Vata - Mayu or Pitta- Valasa – Kapha. Panchkarma treatment is a specialized tool in Ayurveda employed for elimination with five basic steps:

- Vamana- Emesis
- Virechana- Purgation
- Vasti – Enema
- Nasya- Nasal therapy
- Rakta Moksha- Bloodletting. [7]

THERAPEUTIC BENEFITS OF LIQUORICE IN DENTISTRY:

Liquorice, known as Gancao (sweet herb) in Chinese and as Jeshthamadh in India. The anti-carcinogenic properties of liquorice have been studied, with few studies published evaluating its role as an anticarcinogenic agent. It is used in the treatment of candidiasis, gingivitis, periodontitis & recurrent aphthous ulcer. [8]

UNANI :

The Unani system originated in Greece, and Aesculapius was said to be its originator. Hippocrates (460-377 BC), a Greek philosopher and physician, designed his theoretical framework. Unani medicine (or Unani Tibb), as its name suggests, owes its origin to ancient Greece (Yünän) and is popular by different names in other parts of the world.

It dates back to Mesopotamian civilization, which symbolizes the roots of the system. The homeostasis of the seven principles— elements, temperament, humors, organs, vital spirit, powers, and functions—delineates health as per this concept. [9]

EVIDENCE-BASED USAGE OF UNANI MEDICINAL HERBS USED FOR OROFACIAL AILMENTS:

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Table4

S No.	Name of herbal medicine	Botanical name	Uses in dentistry	Studies/ Clinical trials
1.	***Asgand***	*Withania somnifera*	Antistress adaptogenic activity both in humans and experimental animals, thus a potential assistance in treatment of patients with dental anxiety.	Bhattacharya and Muruganandam Rege et al.
2.	***Babul***	*Acacia arabica*	Clinical improvements in dental plaque and gingival indices by inhibiting suspected periodontal pathogens such as *Porphyromonas gingivalis* and *Prevotella intermedia*. Unlike other applicants, no discoloration of teeth was noted as a side-effect.	Pradeep et al. Clark et al.
3.	***Gul-e-Surkh***	*Rosa damascena Mill*	Various parts of rose contain active ingredients such as tannins and vitamin C which are proven to be effective as an astringent and antibacterial agents in various oral infections including gingival diseases and tonsillitis.	Kanwar et al. Ansari et al.
4.	***Haldi***	*Curcuma longa Linn*	Effectiveness in dental pain, periodontitis, in dental plaque detection, and as colorant in pit and fissure sealant. Inhibits/suppresses progression of melanoma cells. It has shown effectiveness in malignant oral mucosal lesions.	Chaturvedi Mehta et al. Kawamori et al.
5.	***Heel khurd***	*Elettaria cardamomum Maton*	The extracts strengthen the body against bacterial insults. It is indicated as a novel antibiotic for the treatment of oral infections.	Kaushik et al.
6.	***Katha***	*Acacia catechu Willd*	Antioxidant and astringent properties, thus being helpful in wound healing, gingivitis, dental caries, tonsillitis and halitosis. Particularly bactericidal in action against S*treptococcus* and *Lactobacillus* strains of cariogenic bacteria.	Stohs and Bagchi Lakshmi and Aravind Kumar
7.	***Kulanjan***	*Alpinia galanga*	Antibacterial, antifungal, anti-protozoal, anti-allergic, anti-tumor, anti-ulcer activities and is also used as halitosis remedy. The major compound responsible for these actions is myrcene.	Web source
8.	***Lehsun***	*Allium sativum L*	Fresh garlic juice has been found to be effective against *Streptococcus pyogenes* and *Corynebacterium diptheriae*. Active against strains of bacteria that are highly resistant to antibiotics.	Cavallito et al. Szyszkowska et al. Singh and Shukla
9.	***Majoon Suranjan***	*Colchicum autumnale Linn*	The disease modifying properties are responsible for its efficacy in various inflammatory conditions. It is a polyherbal formulation for toothache and arthritis.	Singh et al. Khan et al.
10.	***Maryamgoli***	*Salvia officinalis L*	Infusions are used for rinsing oral cavity and throat in cases of inflammations and purulent diseases, by virtue of having anti-inflammatory, antibacterial, antimycosal, astringent, antihydrotic and antilactative properties.	Szczyglewska et al.
11.	***Miswak***	*Salvadora persica*	Efficacy as a natural toothbrush. Comparison with ordinary toothpaste and brush showed that the risk of dental caries for each tooth in the control group was 9.35 times more than the case group. It significantly lowers the gingival index, plaque index and bleeding index. Inhibition of demineralization and promotion of remineralisation of tooth enamel.	Akhtar et al. Aldini et al. Kaur et al. Gazi et al.
12.	***Mur Makki***	*Commiphora myrrh Linn*	It possess nalgesic, antibacterial, astringent and anticancer properties. Oral application on inflamed and swollen gingiva, soreness, near loose teeth, canker sores and chapped lips is a common practice.	Web source

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Cicero, the great Roman orator, said, **"Not to know what has been transacted in former times is to continue always as a child. If no use is made of the labours of the past ages, the world must remain in the infancy of knowledge."** The herbal medicines, along with various other extracts from the plants, together with other therapies, have been practiced since time immemorial. The USM is credited by the World Health Organization (WHO) for being an alternative system to cater to the healthcare needs of the human population. [10]

HOMEOPATHY:

Homeopathy was developed by Samuel Hahnemann (1755-1843), a German physician. It is derived from the Greek words homio (like) and pathos (suffering). Homeopathic medicines treat illness by going with, rather than against, symptoms that are seen as the body's natural defences.

Rationale for homeopathy in dentistry is: [1]

1. Prevention of the development of diseases in the oral cavity.
2. Safe adjunct to conventional medicine.
3. Prevent, limit, or minimize complications of surgical intervention.
4. Reduce phobias and apprehensive anxieties of patients before a dental procedure.
5. Promotes rapid and gentle recovery from the trauma following surgical intervention.
6. Manage dental conditions with a holistic approach. [11]

ROLE OF HOMOEOPATHY IN TOOTH-RELATED PROBLEMS: [12]

Calcarea carbonica: Bleeding gums, delayed eruption of teeth, toothaches from hot/ cold exposures, bad breath.

Calcarea fluorica: Gumboil, jaw swelling, loose teeth with or without pain, toothache when food contacts them.

Magnesium carbonicum: Toothache, especially during pregnancy, that worsens at night, is aggravated by exposure to cold and rest, and is associated with crown decay and ailments resulting from the removal of wisdom teeth. Pain in the malar bone, which worsens during rest and at night. Swelling of the malar bone with pulsating pain, worsens on exposure to cold wind, and loosening of teeth with pain and extrusion from the socket.

Podophyllinum: Bruxism, intense desire to press the gums together (Phytol). Delayed eruption of dentition, large and moist tongue with burning sensation, foul, and putrid taste.

In children with behavioural difficulties, these remedies can be used with marginal success than oral midazolam in reducing anxiety during dental treatment. [4] Some studies reported improvement in appetite disorders, gum discomfort, and excess salivation using homeopathic medicines. One study showed a new gel with hyaluronic acid was more effective than an anaesthetic gel in improving signs and symptoms such as pain, gingival redness, and hampered sleep quality of patients. [13]

ACUPRESSURE:

Traditional Chinese medicine integrates acupuncture, acupressure, herbal remedies, diet, exercise, lifestyle changes, and others. It was documented in India even 5000 years ago. Aryans and currently China are dominating this field. This therapy was known to the Red Indians way back in the 16th century. [14]

Acupuncture involves inserting needles at specific acupoints in the body to trigger the body to release pain-relieving chemicals in the body called endorphins.

Acupuncture/Acupressure works to restore the balance of energy (Qi) by stimulating certain points on the body that affect the flow of Qi.

Some of the oral conditions for which acupuncture can be used safely and effectively include the following: [15]

1. Acute and postoperative dental pain
2. Dental anxiety
3. Nausea and gag reflex
4. Burning mouth syndrome (BMS)
5. Orofacial pain.

Acupuncture can be a useful adjunct in dentistry. There is a large body of scientific evidence supporting for safe use of acupuncture for pain, anxiety, and gagging. Dentists can help their patients and extend their practice contributions through education to incorporate acupuncture as an alternative aid in treatment. [16]

NATUROPATHY:

Naturopathy promotes healing through nature, focusing on the body's intrinsic ability to restore health. It emphasizes that within every human being, there is a healing energy, which includes our immune system in the complete sense of both the physical and the psyche, which is responsible for our wellness and our ability to heal and maintain health.

Naturopathic dentistry is distinguished by its proactive approach to oral healthcare, prioritizing comprehensive wellness over reactive treatment of isolated dental issues.

ADVANTAGES: [17]

Encouraging preventive care in Naturopathic Dentistry.

Integrating Natural Therapies into Naturopathic Dental Practice.

Advancing Minimally Invasive Approaches.

Empowering oral health through nutritional counselling.

Stress reduction in naturopathic dental care.

COLLABORATIVE CARE IN NATUROPATHIC DENTISTRY:

By embracing this holistic philosophy, naturopathic dentistry endeavours to delve deeper into the root causes of oral health concerns, recognizing them as manifestations of underlying imbalances in the body's overall equilibrium[18].

Naturopathic dentistry is distinguished by its proactive approach to oral healthcare, prioritizing comprehensive wellness over reactive treatment of isolated dental issues. By integrating preventive care, personalized treatment plans, and patient education, naturopathic dentistry aims to optimize oral health outcomes while enhancing overall quality of life[19].

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BACH FLOWER THERAPY:

Dr. Edward Bach (1886 – 1936) developed this system of Flower Remedy Therapy.

Dental treatments are no longer confined to the conventional modalities. We need to have a wider perspective and consider the multitude of fine interconnections and interrelations among the structures of the human body. The importance of this approach in dental medicine has its contribution towards obtaining a long-term favourable prognosis of maintaining the integrity of the dento-facial system, and of the whole human body[20].

It is the management of emotions, fear, and anxiety confronted by patients during dental appointments. Therefore, it is a must to manage such emotions to obtain a successful treatment

When talking about prevention or healing, the mind, the soul, and emotions are also to be concentrated, and this is the place where the first wave of disease as well as healing begins. Whenever a person is completely balanced, they have that constant sense of contentment and harmony, the mind has only positive thoughts, and they have that inner strength and love for all of creation. It is a gift from nature, and they are flowers of wild plants.

Although the Bach therapy action mechanism has not been scientifically completely investigated and demonstrated (as all other complementary and alternative therapies), floral remedies have been used for many years with notable results in all fields of medicine to improve the clinical signs of various diseases[21].

HYDROTHERAPY:[7]

The term hydrotherapy is synonymous with the term Water cure, and it was originally marketed by practitioners and promoters in the 1800s. Water cure has since come to have two opposing definitions, which can be confusing.

(a) A course of medical treatment by hydrotherapy.

(b) A form of torture in which a person is forced to drink large quantities of water.

Hydrotherapy in general encompasses a range of approaches and their definitions. These range from approaches and definitions which are either naturally distinct or made so for marketing purposes, to methods and descriptions which overlap meaningfully, and which can be difficult to extricate.

CHIROPRACTIC MEDICINE:

Chiropractic is a form of health care that focuses on the integrity of the spine and nervous system. As such, chiropractors can locate the correct areas of interference to the nervous system that could lead to many disease processes that occur in the body. Its integration with dentistry is promising in managing patients with temporomandibular disorders, migraines, trigeminal neuralgia, and facial myalgia by chiropractors and dentists is possible[22].

ENERGY THERAPIES: [23]

Energy therapies manipulate the body's energy fields and improve health using magnets and therapeutic touch. It is based on the concept of connection between the physical, emotional, mental, and spiritual dominions and uses focused healing energy to clear blocks that accumulate in the body, clogging the natural flow of physical, emotional, mental, and spiritual energy. This remedial focus promotes personal enablement, self-healing, and mystical growth.

EM has found its dentistry application in the managing of pain disorders such as chronic orofacial pain, atypical facial pain, trigeminal neuralgia, myofascial pain dysfunction syndrome, Horton's syndrome (cluster headache), inflammatory conditions, Temporomandibular joint and muscle disorders (TMJ) disorders, fractures, alleviation of dental anxiety and pain during and after dental procedures and in promoting faster healing of oral infections and wounds with reduced risk of their complications.

REIKI:

As stated by the International Centre for Reiki Training, it is a Japanese technique for stress reduction and relaxation that also promotes healing. It is administered by “laying on hands” and is based on the idea that an unseen “life force energy” flows through us and is what causes us to be alive [24]

It accesses the body's natural energy to speed healing while the practitioner hovers his or her hands over the patient's body, and the healing touch brings about a state of calm. A study evaluating the effect of Reiki on hospitalized subjects with heart disease showed that it was effective in bringing about an increase in happiness, relaxation, and a feeling of calm.

CONCLUSION:

Alternative medicine has been practiced in various countries like India and China, much before the development of present-day medical science. These include practices which may be based on traditional medicine, folk knowledge, spiritual beliefs, and newly conceived approaches to healing.

In India, various therapies like Ayurveda, meditation, and yoga have been used since ancient times to heal the body. While meditation provides relief from mental stress, yoga helps to regain mental as well as physical well-being.

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JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY: KARNATAKA STATE BRANCH

Radiation-Induced Mandibular Hypoplasia following Treatment for Rhabdomyosarcoma affecting the Left Eye: A Case Report

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ABSTRACT

Rhabdomyosarcoma is a rare soft tissue malignancy that primarily affects children, with treatment often involving a combination of surgery, chemotherapy, and radiation therapy. While these modalities have improved survival rates, they can also lead to long-term complications, including Radiation-Induced Mandibular Hypoplasia (RIMH). We present a case report of a patient who developed RIMH following treatment for rhabdomyosarcoma involving the left eye. Through this case study and literature review, we aim to highlight the clinical presentation, diagnostic challenges, treatment options, and long-term outcomes associated with RIMH in patients treated for head and neck malignancies.

INTRODUCTION:

Rhabdomyosarcoma is a malignant tumor originating from mesenchymal tissues, commonly occurring in the head and neck region in children, with an annual incidence of 4.3 per million below the age of 20 years[1]. The most common sites of involvement of RMS are the head and neck, genitourinary tract, retroperitoneum, and extremities. Treatment typically involves a multimodal approach, including surgery, chemotherapy, and radiation therapy. One of the major areas of deliberation is the harmful effects of Anti-Cancer Therapy (ACT) on the growth and development of childhood cancer survivors. Long-term complications associated with ACT in the orofacial region include Radiation-Induced Mandibular Hypoplasia (RIMH) and developmental dental anomalies, such as hypodontia, microdontia, root malformations, and enamel surface defects[3]. Most of these sequelae are permanent and require prosthetic or aesthetic rehabilitation. This manuscript aims to present a comprehensive overview of RIMH in the context of rhabdomyosarcoma affecting the left eye, emphasizing the importance of early recognition and multidisciplinary management.

CASE PRESENTATION:

A 9-year-old male patient reported to the Department of Oral Medicine and Radiology, Vydehi Institute of Dental Sciences, Bangalore, India, with a chief complaint of missing teeth in the upper and lower arches for the past 4 years. On eliciting the history of the present illness, the patient was diagnosed with embryonal rhabdomyosarcoma involving the left orbit, for which the patient underwent surgical resection and adjuvant chemotherapy at the age of 3 years, followed by localized radiation therapy to the left eye and orbit for 2 years. No History of recurrence. He revealed a history of lower left back tooth extraction, four years back. Following the treatment, the patient presented with progressive facial asymmetry and mandibular deviation.

On extraoral examination, facial asymmetry was noted on the left side of the face, reduced development of the lower 1/3rd of the face, giving a convex facial profile with a retruding chin, a deviated nasal septum towards the right side, and exophthalmos with scleral sclerosis in the left eye (with complete loss of vision) (Fig. 1). The maximum mouth opening was 20mm. The regional lymph nodes were not palpable. Intraoral hard tissue and soft examination revealed (Fig. 2) (a) reduced maxillary and mandibular arch size, retained deciduous teeth, and unerupted permanent teeth, a high-arched palate, (b) hypodontia, microdontia of present teeth, and (c) macroglossia.

Radiographic examination revealed (Fig 3a) (i) severe left mandibular hypoplasia (ii) deep left sigmoid notch (iii) reduced vertical height of ramus (iv) incomplete root formation/stunted roots (v) absence of tooth buds, (Fig 3b) (i) bilateral hypoplasia of both coronoid and condyle (Fig 3c) (i) retrognathic maxilla and mandible (ii) reduced facial height.

Based on clinical and radiographic findings, a final diagnosis of radiation-induced mandibular hypoplasia with micrognathia was considered.

DISCUSSION:

Radiation-induced mandibular hypoplasia in cases of rhabdomyosarcoma treatment is indeed a significant concern. Rhabdomyosarcoma, being a soft tissue sarcoma that often occurs in children, may require aggressive treatment modalities

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such as surgery, chemotherapy, and radiation therapy. While these treatments aim to eradicate the cancerous cells, they can inadvertently affect surrounding healthy tissues, leading to various complications, including mandibular hypoplasia.

Mandibular hypoplasia refers to the underdevelopment or incomplete growth of the mandible, which can result in functional and aesthetic issues for the patient. Radiation therapy, in particular, can cause damage to the developing bones of the jaw, leading to impaired growth and development. In the context of rhabdomyosarcoma treatment, the radiation-induced mandibular hypoplasia can pose several challenges. First, it can impact the patient's ability to chew, speak, and swallow effectively, affecting their quality of life. Second, aesthetic concerns may arise due to the asymmetry or deformity of the jaw, potentially impacting the patient's self-esteem and psychosocial well-being.

Managing radiation-induced mandibular hypoplasia requires a multidisciplinary approach involving oncologists, radiation oncologists, maxillofacial surgeons, and dentists. Treatment options may include orthodontic interventions, surgical reconstruction, and prosthetic devices to restore function and appearance.

Furthermore, close monitoring of the patient's growth and development is essential, as mandibular hypoplasia can continue to evolve, especially in pediatric patients. Regular follow-ups and interventions may be necessary to address any emerging issues and optimize the patient's long-term outcome

CONCLUSION:

RIMH is a significant long-term complication of radiation therapy in patients treated for rhabdomyosarcoma involving the head and neck region, particularly the orbit. Awareness of this potential adverse effect, coupled with early detection and appropriate management, is essential for optimizing outcomes and enhancing the quality of life for affected individuals. Further research is needed to elucidate the underlying mechanisms of RIMH and develop targeted preventive and therapeutic strategies in this vulnerable patient population.

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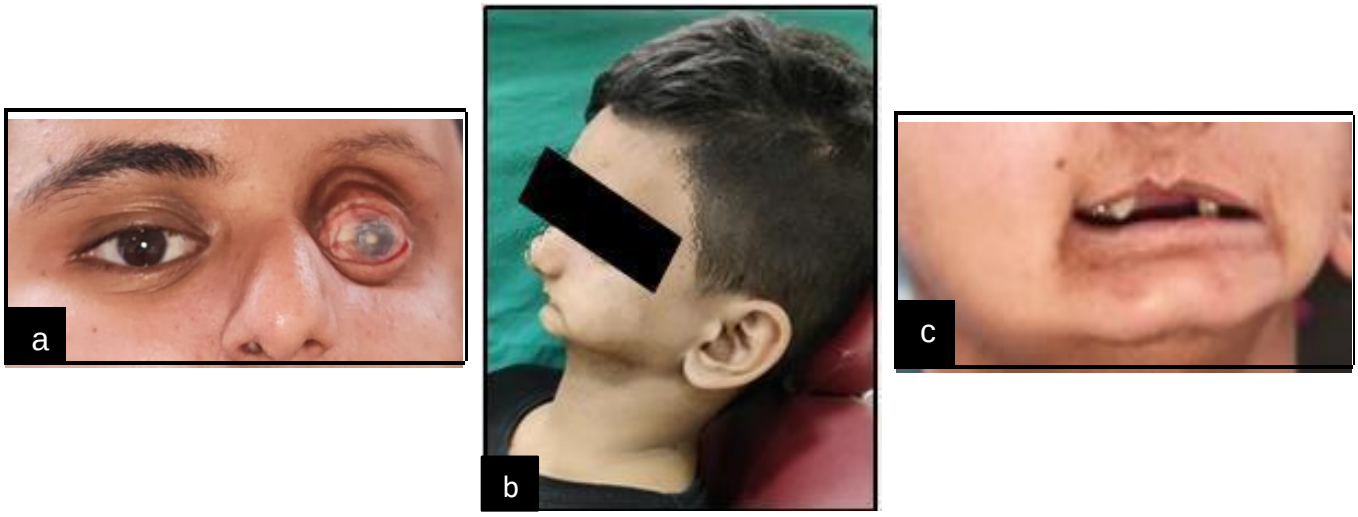

Fig 1: Extraoral examination features (a) deviated nasal septum towards the right side and exophthalmic sclerotic left eye (b) convex facial profile (c) reduced mouth opening

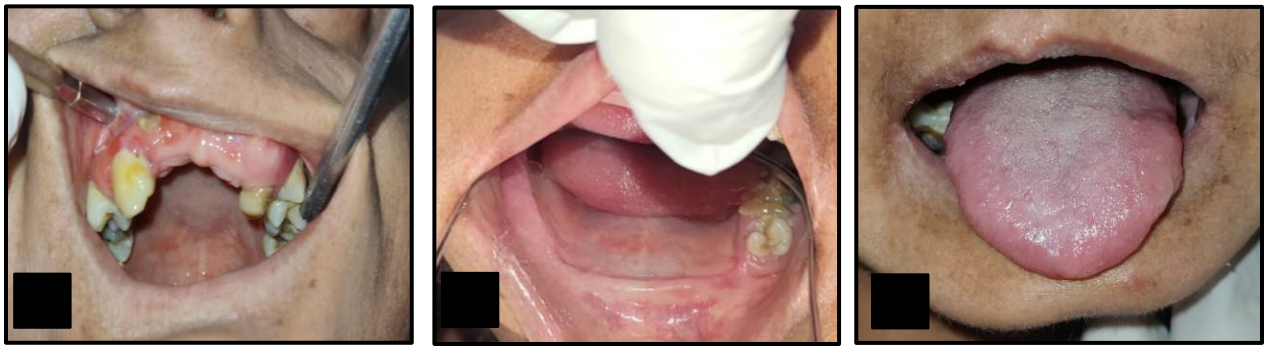

Fig 2: (a) reduced maxillary and mandibular arch size, retained deciduous teeth and unerupted permanent teeth, high arched palate (b) hypodontia, microdontia of teeth present (c) macroglossia

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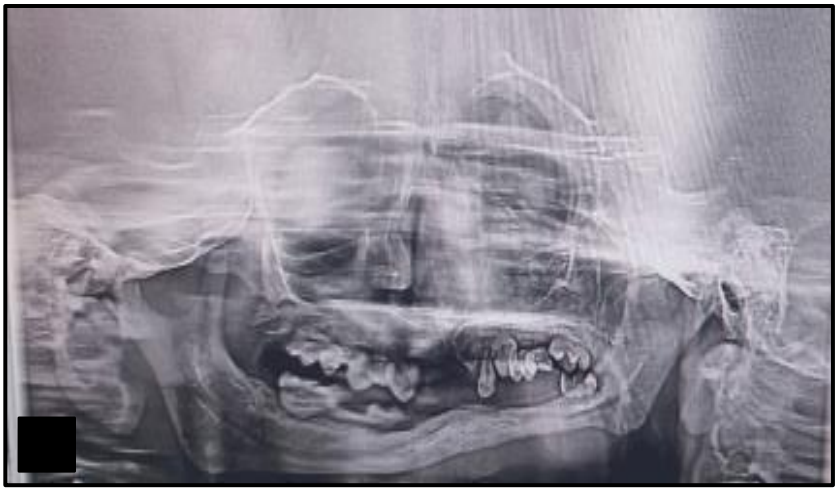

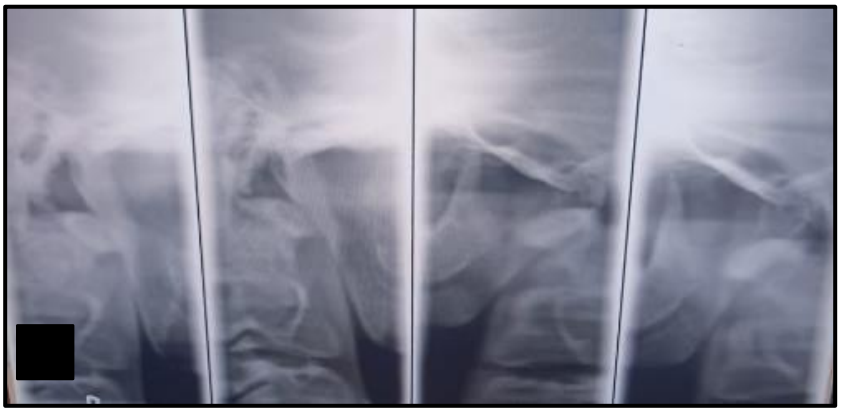

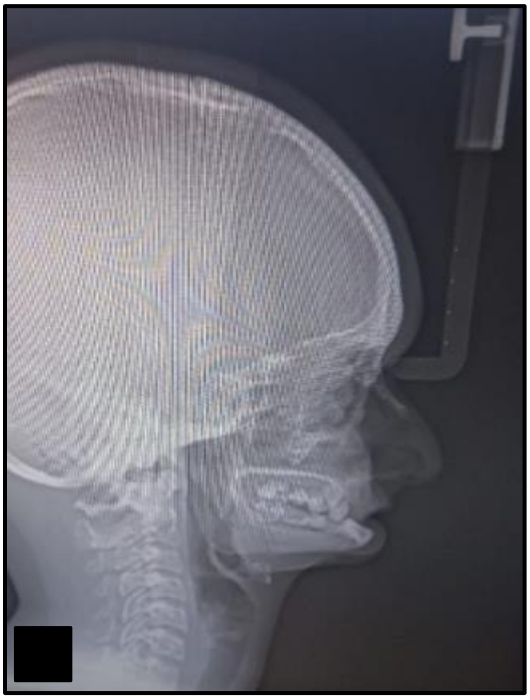

Fig 3a: (i) Severe left mandibular hypoplasia (ii) deep left sigmoid notch (iii) reduced vertical height of ramus (iv) incomplete root formation/stunted roots (v) absence of tooth buds. Fig 3b: (i) bilateral hypoplasia of both coronoid and condyle. Fig 3c: (i) retrognathic maxilla and mandible, (ii) reduced facial height.

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JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY: KARNATAKA STATE BRANCH

CRISPR/CAS9 Technology: A Revolutionizing Treatment for Oral Squamous Cell Carcinoma

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ABSTRACT

Cancer is one of the most common diseases one would come across affecting huge number of population each year worldwide. It is a disease in which few body cells grow uncontrollably and spread to other parts of the body. Unlike normal cells, which follow a regulated life cycle, cancer cells divide continuously, often forming tumors or infiltrating healthy tissues. Early detection is important for a better prognosis. Surgery is the primary treatment while others include radiotherapy, chemotherapy, immunotherapy, targeted therapy, combination therapy, etc. The existing treatment plans used from decades cause a lot of discomfort and disfigurement of the affected areas. Hence, newer, and emerging technologies are being explored and one such treatment is CRISPR/Cas9. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) are repetitive DNA sequences found in genomes of bacteria that contain DNA segments from past viral infections, serving as molecular memory of previous encounters. Cas9 enzyme has ability to cut DNA at specific locations guided by RNA. Therefore, this review enlightens about the therapeutic potential of CRISPR/Cas9 technology.

INTRODUCTION:

Cancer has become a major global threat to public health and the leading cause of human deaths worldwide due to the high incidence and mortality rates. Previous studies have demonstrated the significant correlation between the onset, advancement, management, and prognosis of malignant tumors and genetic variations and mutations.[1]

CRISPR-Cas9 is a revolutionary gene editing tool derived from a bacterial immune system that can correct errors, turn on and off genes, and thereby alter their expression. Research on cellular and animal models has indicated promising outcomes for the utilization of the CRISPR/Cas9 technique in cancer treatment.[2] CRISPR/Cas9 can target tumor suppressor genes like TP53, Rb, and CDKN2A, which are mutated in the cancer cells and inhibit tumor growth.[3] Other potential applications of CRISPR/Cas9 include treatment of infectious diseases, genetic disorders, immunotherapy and regenerative medicine, and crop and livestock improvement.[3] This review provides an in-depth study of CRISPR/Cas9, focusing on its mechanism of action and applications, including cancer treatment. Additionally, it addresses the challenges, clinical studies, and ethical debates surrounding this innovative technology.

DISCUSSION:

The choice of treatment depends on the stage of cancer, location, and size of the tumor, patient's health, and preference. Surgery is the primary treatment, along with other options which include chemotherapy, radiotherapy, immunotherapy, targeted therapy, and a combination of several therapies.[4] Whereas Gene therapy is the emerging trend and is being explored for the treatment of cancer.

In recent years, gene editing tools such as zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have greatly enhanced the ability to make precise modifications to the genome, but they still come with certain limitations.[5] Clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR-associated protein 9 (Cas9) genome editing system have gained popularity as a versatile tool for precisely targeting genes and inducing mutations. This includes the ability to insert or delete genes, replace segments of DNA, and even convert single base pairs with high accuracy.[6] The CRISPR/Cas9 systems are categorized into two classes, each further divided into six types and 33 subtypes, each characterized by unique signature Cas genes.[7] The type II CRISPR/Cas9 system is mainly used in gene editing owing to its simplicity and ease of use. [5,8]

HISTORY:

Clustered regularly interspaced short palindromic repeats were first discovered in the DNA sequences of *Escherichia coli* in 1987 by Ishino at Osaka University in Japan. [9,10] In the Journal of Bacteriology, Ishino documented that the gene seemed to contain repeating sequences of 29 base pairs, separated by unique sections of DNA. Despite noting these findings, he chose not to pursue a deeper understanding of their function at that time. [10,11] His paper concluded with the statement, *"So far, no sequence homologous to these has been found elsewhere in prokaryotes, and the biological significance of these sequences is not known."* [11] In 1995, Francisco Mojica, a student at the

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University of Alicante in Spain, studying archaea, also observed the repetitive sections of DNA. The presence of these repeating sequences in two distinct organisms, *E. coli* and archaea, led Mojica to conclude that these organisms likely have biological relevance.[11] In 2002, scientists in the Netherlands identified these repeating patterns in 40 microbial species and named them SPacers Interspersed Direct Repeats (SPIDR). But it was Mojica who introduced the term that stuck: CRISPR, short form for Clustered Regularly Interspaced Short Palindromic Repeats.[11] In 2005, the role of CRISPR loci in prokaryotes against foreign genetic information was proposed. 2002 also marked the first description of the Cas9.[10] In 2007, French food scientists Rodolphe Barrangou and Philippe Horvath conducted pioneering studies on yogurt bacteria (*Streptococcus thermophilus*) for the company Danisco, providing the first insights into the mechanism of action of the CRISPR system.[10] Two RNA molecules, crRNA and tracrRNA, were discovered as part of the guide RNA complex in 2007 and 2011, respectively.[10]

In 2011, Professors Jennifer Doudna from the University of California and Emmanuelle Charpentier from the University of Vienna started their investigation on a CRISPR-associated enzyme called Cas9. They discovered that Cas9 is guided by two types of RNA: crRNA, which carries sequences from viral DNA and directs Cas9 to viral RNA targets, and tracrRNA, which helps bind crRNA to Cas9 and activates the enzyme complex. [10,11] In 2020, the Nobel Prize in Chemistry was awarded for the development of a genome editing method using CRISPR–Cas9 technology. This recognition came less than a decade after the discovery of all essential molecular components of the system. For the first time, the Nobel Prize was awarded jointly to two women, Emmanuelle Charpentier and Jennifer Doudna, for their pivotal contributions to DNA manipulation with the CRISPR–Cas9 system, often referred to as "genetic scissors."[10]

MECHANISM OF ACTION:

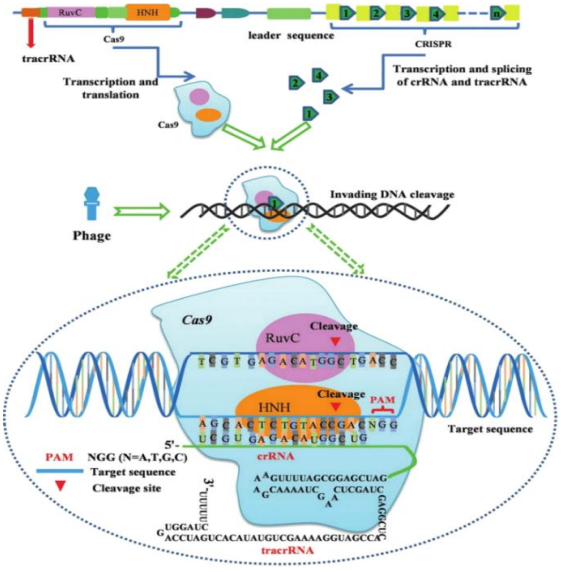

Fig. 1 Molecular mechanism of CRISPR/Cas9-mediated DNA cleavage. Courtesy of Xianwang Wang, School of Medicine, Yangtze University from the review article-

CRISPR/Cas9 genome editing technology significantly accelerated herpes simplex virus research.

When a virus infects bacteria, special enzymes called CRISPR-associated proteins (Cas) cut out a piece of viral DNA called a protospacer, which is saved in the bacterial genome in a section known as CRISPR. If the same virus attacks again, the bacteria use these saved sequences. The stored viral DNA pieces are transcribed and turned into short sections of RNA. These RNA segments then join with CRISPR-associated enzymes to search the bacteria for viral DNA or RNA that matches the stored sequence. When the CRISPR RNA-Cas complex finds a match from an invading virus, it cuts the viral DNA or RNA, stopping the virus from causing harm.[11] The CRISPR/Cas9 system consists of two fundamental components: a guide RNA (gRNA) that targets the gene of interest, and a Cas9 protein complex that contains a nuclease, which together act as molecular scissors to achieve double-stranded DNA cleavage.[12] Guide RNA is composed of 2 parts: a CRISPR RNA (crRNA) sequence, which is complementary to the target DNA sequence, and a trans-activating CRISPR RNA (tracrRNA), which interacts with the Cas9 protein. (Fig.1) CRISPR/Cas-9 genome editing mechanism can be summarized in 4 steps: 1. Recognition: The gRNA binds to the Cas9 protein, forming a Cas9-gRNA complex. The gRNA then guides the Cas9 protein to the target DNA sequence. 2. Binding: The Cas9-gRNA complex binds to the target DNA sequence via complementary base pairing between the crRNA and the DNA. 3. Cleavage: Once bound to the target DNA, Cas9 creates a double-strand break (DSB) in the DNA at a specific position called the Protospacer adjacent motif (PAM). PAM is a short, specific DNA pattern that helps Cas-9 find its target. 4. Repair: After the DNA is cut, the cell's natural DNA repair machinery comes into play.[12]

There are two primary DNA repair pathways: non-homologous end joining (NHEJ) and homology-directed repair (HDR). (Fig.2) NHEJ leads to the repair of DSBs by directly joining DNA fragments facilitated by enzymes in the absence of homologous DNA. It is the primary DNA repair mechanism, but also an error-prone process that may result in small random insertions or deletions called indels at the site of the break. HDR is a highly precise pathway of DNA repair that utilizes a homologous DNA template to execute gene insertion, deletion, or replacement at specific locations in the genome. [12,13]

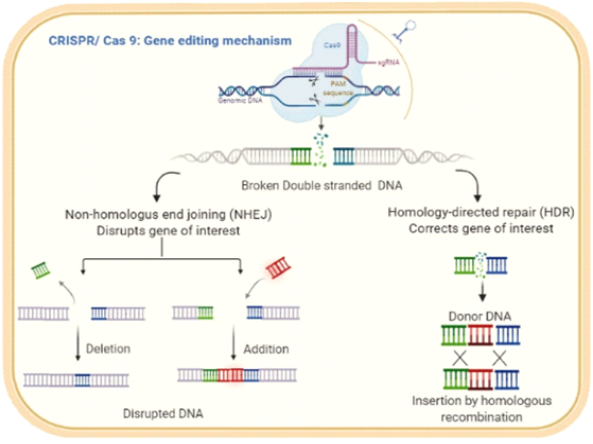

Fig 2. CRISPR/Cas9 repair mechanism involving non-homologous end joining and homology-directed repair. Courtesy of Bharathkumar Nagaraj, Department of

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Microbiology, ICMR National Institute of Virology, from review article- CRISPR/Cas9 Based Modifications for Therapeutic Applications: A Review

APPLICATIONS OF CRISPR/CAS9:

Advancements in genome sequencing have led to the identification of numerous mutated proto-oncogenes and tumor suppressor genes associated with oral cancer. The CRISPR/Cas9 system's efficient gene editing capabilities now provide a promising approach to specifically target these mutated genes, mainly directly in vivo, revolutionizing oral cancer treatment strategies. [1,3] It enables precise modification of DNA, allowing scientists to target and correct genetic mutations associated with cancer. In oral cancer, CRISPR-Cas9 can be used to inactivate oncogenes such as TP53 and PIK3CA or restore the function of tumor suppressor genes to inhibit tumor growth. In HPV-associated oral cancers, it can target viral oncogenes like E6 and E7, which are responsible for disabling key tumor suppressors like p53 and Rb. Additionally, CRISPR can help overcome drug resistance by editing genes like ABCB1, which are involved in chemotherapy resistance. It also holds promise in enhancing cancer immunotherapy by modifying immune-related genes to boost the body's defence against cancer cells. Despite its potential, challenges such as off-target effects, ethical concerns, and effective delivery systems need to be addressed. Overall, even though not many studies have been reported on the use of CRISPR-Cas9 in the treatment of oral cancer, it represents a promising approach in the evolving landscape of oral cancer therapy. [1,3]

CRISPR/Cas-9 gene editing holds potential for curing most of the known genetic diseases, such as sickle cell disease, β-thalassemia, cystic fibrosis, and muscular dystrophy.[12] Sickle cell disease (SCD) is a genetic disorder affecting red blood cells, caused by a mutation in the β-globin gene that leads to the production of abnormal haemoglobin (HbS). When oxygen levels are low, HbS molecules can clump together, causing the red blood cells to become rigid and sickle-shaped, leading to various health problems, including severe anaemia. CRISPR/Cas-9 gene editing offers two main approaches to treat SCD. One method involves directly fixing the gene responsible for HbS production. The other approach boosts the production of foetal haemoglobin (HbF), which can prevent the formation of sickle-shaped cells. In clinical trials, researchers typically disable a gene called BCL11A in bone marrow cells using CRISPR/Cas-9. BCL11A normally turns off the production of foetal haemoglobin. The edited cells are then infused back into the patient's body to potentially lessen the symptoms of SCD. CRISPR/Cas-9 has successfully corrected Duchenne muscular dystrophy (DMD), a condition caused by a mutation in the dystrophin gene that results in muscle weakness. This correction was achieved in the patient by inducing pluripotent stem cells. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene reduce the structural stability and functionality of the CFTR protein, resulting in cystic fibrosis that can be corrected using CRISPR.[12] CRISPR has been applied in mutation-causing β-thalassemia in humans by inducing pluripotent stem cells ex vivo. [13]

Another potential clinical application of CRISPR/Cas9 is the treatment of infectious diseases, such as HIV. Hu *et al* demonstrated that the CRISPR/Cas9 system could be used to target HIV-1 genome activity. This inactivated HIV gene expression and replication in a variety of cells that can be latently infected with HIV, without any toxic effects. [13] Oncogenic viruses are highly related to carcinogenesis, including Human papillomavirus (HPV), which could cause cervical cancer; Epstein-Barr virus (EBV), which causes nasopharyngeal carcinoma; and hepatitis B virus, which triggers liver cancer. CRISPR-Cas9 was first used to cleave HBV genomes. It has previously been reported that the production of the HBV core can be decreased through the HBV expression vector. These advancements highlight ongoing efforts to explore CRISPR-Cas9 as a potential tool for combating viral-induced cancers.[12]

CRISPR-Cas9 is used in crop improvement to increase disease resistance, improve yield, improve nutrition, etc. The fertility of crops is severely affected by the invasion of plant viruses. CRISPR-Cas9 has been utilized to knock out the mitogen-activated protein kinase-5 (OsMPK5) gene, aiming to improve disease resistance in rice. For instance, lycopene, an antioxidant-rich plant nutrient abundant in tomatoes, offers beneficial therapeutic properties. With successful efforts to increase lycopene levels in tomatoes, CRISPR-Cas9 technology plays an important role in boosting the micronutrient content of various plants. CRISPR-Cas9 has not only increased animal product yields but has also significantly advanced biomedicine through the creation of transgenic and cloned animals. CRISPR-Cas9 proves to be invaluable in immunology and vaccine development due to its minimal risk to human health, potentially preventing viral transmission.[3]

CRISPR technology has significant potential in both immunotherapy and regenerative medicine due to its precision in genome editing. In immunotherapy, CRISPR can be used to enhance immune cells like T cells to target and destroy cancer cells. This approach, known as CAR-T therapy, has shown promising results in clinical trials.[3] In regenerative medicine, CRISPR can be used to edit genes in stem cells to correct genetic disorders before these cells are used to regenerate damaged tissues or organs. Additionally, CRISPR has enabled researchers to create animal models of human diseases more accurately, facilitating drug development and research into genetic diseases. CRISPR/Cas9 can be used to recreate mutations in vivo and observe the development and progression of carcinogenesis in animal models.[14]

ADVANTAGES:

Overcoming drug resistance: Drug resistance remains a significant obstacle in effective cancer treatment. Recently, genome wide CRISPR/Cas9 screening has proven to be crucial in pinpointing genes involved in drug resistance mechanisms of cancer cells.[2]

Reduced Side Effects: CRISPR targets specific genetic sequences hence, it can potentially reduce the severe side effects commonly associated with conventional treatment options like chemotherapy (such as nausea, hair loss, and immune suppression) and radiotherapy (such as tissue damage and radiation toxicity) which are caused due indiscriminate killing of healthy cells along with cancer cells.

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Cost-effective: CRISPR-Cas9 offers significant cost-effectiveness compared to other gene editing methods like ZFNs and TALENs, which involve complex protein engineering. The simplicity of CRISPR-Cas9, which primarily relies on two molecules for inducing edits, and the flexibility in designing sgRNAs to target multiple sites, enables researchers to initiate editing swiftly and adjust experiments effortlessly. [15]

Ease of use: CRISPR-Cas9 editing is relatively easy to use as compared to previous gene-editing techniques, which were more complex and time-consuming. In addition, it is widely available, making it accessible to researchers with limited resources.[15]

Versatility: It can be used to edit genes in a wide range of organisms, including plants, animals, and microbes, making it a versatile tool. CRISPR is highly customizable and capable of editing virtually any segment of DNA within the 3 billion letters of the human genome and other organisms. Moreover, it is more precise than other DNA-editing tools.

Efficiency and Precision targeting: CRISPR-Cas9 enables highly precise modifications to the genome, allowing only targeted changes. It allows scientists to edit genomes with utmost efficiency and accuracy, paving the way for advancements in therapeutics, medicine, agriculture, and various other fields.

CHALLENGES:

Off-target effects: Off-target mutations are a significant limitation of CRISPR/Cas9 gene editing. While this method typically targets specific DNA sequences, there are instances where the sgRNA can induce mutations in unintended regions that resemble the target sequence. These off-target mutations may disrupt normal gene function and lead to genetic instability, with reported frequencies exceeding 50%. Addressing this challenge is crucial for advancing CRISPR/Cas9 towards clinical applications. To counter off-target effects, sgRNA design plays a critical role. Tools like CHOPCHOP, E-CRISP, and CRISPR-ERA help in designing sgRNAs that are more specific and suitable. Additionally, using the D10A-mutated Cas9 variant, which creates single-strand breaks instead of double-strand breaks, can significantly reduce off-target effects when paired with a dual sgRNA approach. Single-strand breaks are repairable by local enzymes, thereby minimizing unintended mutations.[2]

Immune response: An unpredicted immune response in CRISPR-Cas9 can occur due to off-target edits, delivery methods, immunogenic properties of the Cas9 protein, genetic variations influencing immune reactions, and differing immune responses based on tissue type. These factors must be carefully monitored to ensure the safety and efficacy of CRISPR-Cas9 therapies.[1]

Ethical concerns: Ethical concerns in CRISPR-Cas9 focus on issues such as the ethical implications of germline editing, informed consent for experimental treatments, equitable access to therapies, and potential off-target effects.

In 2018, the "Gene-edited Infant" incident sparked significant controversy regarding the use of CRISPR technology at the clinical level, in direct violation of the international scientific community's regulations. CRISPR/Cas9 technology was not permitted for making heritable changes to humans until further advancements and widespread acceptance were found. This event raised critical questions about whether individuals should have the right to choose their genetic traits for future generations and whether genetically modified individuals should enjoy the same rights as unmodified humans. Thus, improving the ethical review system for activities involving human genome editing is of utmost importance [1]

Long-term effects: When treating malignancies, nonspecific cuts may have a dominant-negative effect on the function of oncogenes and tumor suppressor genes, leading to either gain-of-function or loss-of-function mutations.[14]

Delivery challenges: The CRISPR/Cas9 system also poses delivery challenges. AAV vectors are the most common delivery systems used currently. However, its limitations include stimulating an immune response and increased off-target mutations. To counter these challenges, nonviral vectors such as nanoparticles have been suggested. In vivo delivery also has limitations, such as degradation by certain enzymes and immune cells, which appear to be a major drawback of CRISPR.[2]

CLINICAL STUDIES:

Notable clinical studies and trials using CRISPR/Cas9 are as follows:

Sr. No.	Study	Year	Review
1.	FDA Approves Casgevy (Exagamglogene autotemcel) CRISPR/Cas9 Genome-Edited Cell Therapy for the Treatment of Sickle Cell Disease	2024	Casgevy marks a significant milestone as the first FDA-approved treatment using CRISPR/Cas9 technology for sickle cell disease. This represents a breakthrough in genetic medicine, offering new hope for patients with this challenging condition.[16]
2.	A Safety and Efficacy Study of Transcription Activator-like Effector Nucleases and Clustered Regularly Interspaced Short Palindromic Repeat/Cas9 in the Treatment of HPV-related Cervical Intraepithelial Neoplasia	2022	This study demonstrated that targeting the E6 and E7 oncogenes of human papillomavirus (HPV) effectively suppressed tumor growth associated with cervical cancer. This approach highlights promising developments in combating HPV-related malignancies.[17]
3.	Phase 1, Open Label Study of CRISPR-CAR Genome	2020	CRISPR/Cas9 CAR-T cell therapy was employed for treating

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	Edited T Cells (PBLTT52CAR19) in Relapsed /Refractory B Cell Acute Lymphoblastic Leukaemia		relapsed/refractory B-cell acute lymphoblastic leukemia. In CAR (Chimeric Antigen Receptor)-T cell therapy, CRISPR/Cas9 technology has been utilized to extend the persistence of CAR-T cells, counteract exhaustion, and boost their anti-tumor effectiveness.[18]
4.	CRISPR-Edited Stem Cells in a Patient with HIV and Acute Lymphocytic Leukemia	2019	A trial was conducted successfully where CRISPR/Cas9 was used via non-viral delivery system to induce indels (insertion or deletion in the genome) in the CCR5 gene related to HIV infection in donor-derived hematopoietic stem and progenitor cells (CD34 + cells).[19]
5.	Efficacy and long-term safety of CRISPR/Cas9 genome editing in the *SOD1*-linked mouse models of ALS	2017	Amyotrophic lateral sclerosis (ALS) is associated with mutations in SOD1, C9orf72, FUS, ATXN2, etc genes. Mutations in Superoxide Dimutase 1(SOD1) are linked to familial ALS (fALS), which is a form of ALS that runs in families. Since 2017, CRISPR systems have been employed to disrupt SOD1 gene expression in efforts to potentially modify its impact on ALS. By targeting specific genetic mutations associated with ALS using CRISPR technology, researchers hope to develop new therapeutic strategies that could ultimately benefit patients affected by this neurodegenerative disease.[20]
6.	CRISPR-Cas9 mediated efficient PD-1 disruption on human primary T cells from cancer patients-	2016	This study demonstrated that targeting Programmed Cell Death-1 Protein (PD-1) in the T cells of patients with melanoma and gastric cancer resulted in the improvement of cytotoxicity of T cells. This enhanced cytotoxicity resulted in the killing of tumor cells, highlighting the potential therapeutic benefit of PD-1 targeting in these cancers.[21]
7.	A Phase I Clinical Trial of PD-1 Knockout Engineered T Cells Treating Patients with Advanced Non-small Cell Lung Cancer	2016	The first human phase I clinical trial of CRISPR was conducted in China for treating metastatic non-small cell lung cancer (NSCLC) patients who had not responded to chemotherapy, radiotherapy, and other conventional therapies.[22]

CONCLUSION:

The prospects of CRISPR-Cas9 in the treatment of cancer, particularly oral cancer, look promising. CRISPR-Cas9 technology holds the potential for targeted gene editing, which could lead to advancements in understanding the genetic basis of oral cancer, identifying therapeutic targets, and potentially developing more effective treatments. The CRISPR/Cas9 technique faces challenges such as off-target effects, ethical concerns, which require effective solutions to overcome these limitations. While significant work is needed before this technology can be widely implemented, CRISPR/Cas9 stands as a revolutionary development in the field of oncology and beyond.

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Contemporary advances in Oral mucoadhesive drug delivery for oro-mucosal lesions - A conspectus

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ABSTRACT

Oral health influences general health and quality of life. The majority of oral diseases require high topical doses applied over the lesions of the oral mucosa. The oral medicine specialists face several challenges in finding an ideal drug delivery system that offers sustained drug release to target the oro mucosal lesion. Disadvantages of topical therapy are when used in an aqueous environment of saliva, which may cause the drug to be washed off and repeated dosing to obtain a therapeutic dose. For topical therapy in the oral cavity, mucoadhesion can increase retention at the application site, resulting in a reduced total dose for target delivery. This review focuses on the recent developments in the mucoadhesion drug delivery for various oro mucosal lesions.

INTRODUCTION:

Oral health negligence can affect general health and quality of life. The majority of oral diseases require high topical doses applied over the lesions of the oral mucosa. The oral medicine specialists face several challenges in finding an ideal drug delivery system that offers sustained drug release to target the oro mucosal lesion.

Disadvantages of topical therapy are when used in an aqueous environment of saliva, which may cause the drug to be washed off and repeated dosing to obtain a therapeutic dose. For topical therapy in the oral cavity, mucoadhesion can increase retention at the application site, resulting in a reduced total dose for target delivery. As a result, the creation of mucoadhesive delivery systems explicitly designed for the oral mucosa, capable of providing sustained release, could offer significant benefits in managing lesions in the oral mucosa.

Only a small number of topical formulations have been tailored explicitly for diseases affecting the oral mucosa. The predominant topical treatments in current use are those intended for addressing dermatological conditions. While certain localized topical treatment modalities utilizing gels or creams are presently available, a significant portion of these exhibit only temporary therapeutic efficacy owing to restricted drug retention on the afflicted mucosa. This underscores a substantial gap in clinical care, as there are presently no commercially viable drug delivery systems effectively addressing these challenges. Hence this review focuses on the recent developments in the mucoadhesion drug delivery for various oro mucosal lesions.

HISTORY AND DEVELOPMENT OF DISEASE/ LESION SPECIFIC MUCOADHESIVE DRUG:

Bioadhesion refers to the state in which two materials, at least one of which is biological in nature, are maintained together for an extended time-period through the interfacial forces. This concept began to be applied to drug delivery systems in the 1980s. Essentially, it involves incorporating adhesive molecules into pharmaceutical formulation designed to maintain close contact with the absorption tissue, allowing the release of the drug near the action site, thereby increasing its bioavailability and promoting local or systemic effects.

A mucoadhesive drug delivery system has the potential to prolong the residence time at the absorption site, enabling extended contact with the epithelial barrier. However, the adhesion of preparations onto mucous membranes can be impaired by the mucociliary clearance system. This is a natural defense mechanism of the body against the deposition of impurities onto the mucous membrane, and can also remove the preparation. Thus, by using bioadhesive molecules, it is possible to retain the preparation at the action site and to direct the drug to a specific site or tissue. Other features associated with the development of controlled drug delivery systems using bioadhesive molecules include a decrease in drug administration frequency and an increase in patient compliance with the therapy. Therefore, a bioadhesive system controlling drug release could improve the treatment of diseases, helping to maintain an effective concentration of the drug at the action site.[16]

MECHANISM OF ACTION OF MUCOADHESION:

The process of mucoadhesion generally occurs in two steps, the initial contact stage and the consolidation stage. The contact stage is characterized by the contact between the mucoadhesive and the mucous membrane, with the spreading and swelling of the formulation, initiating its deep contact with the mucus layer.[1]

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ADVANTAGES AND DISADVANTAGES OF ORAL MUCOSAL DRUG DELIVERY FOR OROMUCOSAL LESIONS:

Advantages	Disadvantages
• Easily accessible • Capable of self-administration • Rapid oral mucosa repair • Variation in permeability across different oral cavity regions • A moist environment facilitates drug dissolution • Feasibility of sustained delivery • Potential mitigation of systemic side effects	• The permeability barrier presented by the oral mucosa • Drug clearance by saliva • Consideration of taste as significant • Presence of high enzyme activity • Limited surface area in relative terms

CONTEMPORARY ADVANCES IN ORAL MUCOADHESIVE DRUG DELIVERY FOR ORO-MUCOSAL LESIONS:

In their study, Yarden Shtenberg et al. evaluated three hybrid alginate/liposome drug delivery systems: a hybrid paste, which presented excellent adhesive capabilities, yet fast burst release of 90% after 2 hr; a hybrid hydrogel, demonstrating controllable release rates of 5%, 30% or 60% after 2 hr but poor mucoadhesive properties. These findings led to the development of a hybrid crosslinked paste. Polymer retention studies demonstrated that 80% of the crosslinked paste was retained on tongue tissue compared to 50% retention of the non-crosslinked pastes, verifying its superior mucoadhesion. The hybrid cross-linked paste presented a controllable release rate of 20% after 2 hr. Moreover, alginate paste containing doxorubicin-loaded liposomes exhibited similar release patterns and effectively induced cancer cell death. Thus, it was an innovative formulation, including both the desired characteristics of mucoadhesion and sustained liposome release.[2]

H.E. Colley et al. in their study, electrospun polymeric mucoadhesive patches were produced and characterized for their physical properties and cytotoxicity before evaluation of residence time and acceptability in a human feasibility study. Clobetasol-17-propionate incorporated into the patches showed sustained release in both tissue-engineered oral mucosa and ex vivo porcine mucosa. Further, in vivo studies demonstrated prolonged adhesion and drug release at therapeutic-relevant doses and time points. The results indicated that electro-spun patches adhere effectively to mucosal surfaces without causing tissue damage while successfully delivering clinically active drugs.[3]

Mona G. Arafa et al. studied the use of oromucoadhesive films for buccal delivery of Propolis extract (PPE) entrapped in niosomes to treat recurrent aphthous ulcers (RAU). The films containing niosomal PPE were evaluated for swelling, mucoadhesion, and elasticity. 24 patients suffering from RAU were divided equally into medicated and placebo groups and participated in this study to examine the onset of ulcer size reduction, complete healing, and pain relief. Clinical results revealed the duration of film adherence from 2–4 h in the two groups. These oromucosadhesive films, which offer controlled and targeted drug delivery, can be proposed as a new therapeutic strategy in the treatment of oral recurrent aphthous ulcers.[4]

B.N. Matos et al. formulated mucoadhesive chitosan nanoparticles carrying the chemotherapeutic oxaliplatin (OXPt) and evaluated their ex vivo penetration in porcine mucosa under both passive and iontophoretic topical treatments. These nanoparticles displayed an initial “burst effect” followed by a longer-term controlled release. When applied to the oral mucosa, the chitosan nanoparticles increased 3-fold drug penetration, and were maintained even when the mucosa was "washed" with a buffer to mimic salivation, suggesting the feasibility of topical therapy with chitosan nanoparticles, potentialized by the application of iontophoresis, to treat oral tumors.[5]

J.H. Ryu et al. developed an adhesive polysaccharide oral patch called ‘Chitoral’ that utilizes chemical principles shown in wet-resistant mussel adhesion. Upon contact with saliva and mucosal layer, the Chitoral instantly dissolves and then forms an insoluble adhesion layer with mucins at the Chitoral/mucous interface nearly immediate actions. Chitoral gradually converts into adhesive hydrogels by the cooperative actions of covalent crosslinking and physical entanglement. The instant, robust muco-adhesion properties of Chitoral provide long-lasting therapeutic effects of drugs, resulting in enhanced healing of oral ulcers.[6]

Thais F. R. Alves et al. study focused on films for target drug delivery with respect to the treatment of the diseases of the oral mucosa, specifically mucositis. The results of a single clinical study as a pre-experimental design were performed and followed up to the outcome until 30 days. The polymeric film was prepared in a mucoadhesive bilayer structure: the basal layer with lidocaine HCl had a faster release than the apical layer with benzydamine HCl and N-acetylcysteine. The cell viability and cytotoxicity were evaluated in the MCF7 cell line. The mucoadhesive bilayer film was biologically safe and stimulated cellular proliferation.[7]

Tingting Lia et al. developed a mucoadhesive in situ forming gel to deliver a novel drug molecule, Bupivacaine γ-linoleate (Bup-γL), for prolonged and more potent oral mucositis pain control. The formulation is sprayable at room temperature and forms a mucoadhesive gel on contact with the oral mucosa. Pluronic® F127 and F68 were used to achieve in situ forming properties. Either Carbopol® or Noveon® was included as a mucoadhesion enhancer. Both Carbopol® and Noveon® significantly improved mucoadhesion without compromising the other main properties of the system (such as gelation temperature and drug content). Moreover, a promising platform for the mucoadhesive in situ gels that allows high loading of hydrophobic drugs has been developed.[8]

Lucas Garcia Camargo et al studied the immunomodulatory agent imiquimod (IQ) that was incorporated in chitosan (Ch) and alginate (A) films, aiming at developing a biomaterial to topically treat oral mucosal squamous cell carcinomas. IQ was

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directly added to either the suspension of the isolated polysaccharides or the polyelectrolyte complexes formed by their mixture before film casting. In conclusion, the films may have high potential as oral cancer therapeutic tools, replacing usual topical gels and creams, which are susceptible to leaching.[9]

Ana Ortega et al.'s study proposed the development of a thermosensitive hydrogel containing curcumin-loaded lipid-core nanocapsules coated with chitosan to increase mucoadhesion, circumventing several limitations of this route of administration. Hydroxy propyl methyl cellulose and Poloxamer® 407 were incorporated for hydrogel production. Tensile analysis and washability test on porcine buccal mucosa indicated higher mucoadhesion for hydrogels in comparison to the nanocapsules in suspension, remaining on the mucous membrane for up to 8 h. The findings demonstrated that the proposed nano system is mucoadhesive and has the potential to deliver buccal treatments.[10]

Molania et al.'s study investigated the effect of atorvastatin mucoadhesive tablets as a topical treatment on the reduction of symptoms and duration of recurrent aphthous stomatitis. Patients were divided into two groups: atorvastatin and placebo; each of the patients received three mucoadhesive tablets daily in the morning, noon, and night. Finally, the patients were examined on days 0 (baseline), 3, 5, and 7 to determine the diameter of the inflammatory halo.

In conclusion, Atorvastatin mucoadhesive tablets effectively reduced the pain of patients with minor recurrent aphthous stomatitis and reduced the size and healing time of the lesions.[11]

Divyambika Catakapatri Venugopal et al. developed a silymarin-based mucoadhesive gel for prolonged release in oral mucosa and evaluated the same by using in vitro drug release kinetic models and ex vivo methods for drug permeation using chicken buccal mucosa, proving that the gel can permeate through the oral mucosal membrane and its potential use in various oral diseases.[12]

Duy Toan Pham et al. developed and characterized the hydroxypropyl microparticles for the local administration and disease treatments in the oral cavity. Ibuprofen was used as a model drug. HPMC microparticles showed a sustained release pattern with a maximum release amount of nearly 100%. The particles also possessed high mucoadhesive properties in the ex vivo test using the buccal mucosa.[13]

Gergely Kali et al. designed a novel thiolated-carrageenan (-CA-SH) and evaluated its potential as an excipient for the design of mucoadhesive drug delivery systems. Native -carrageenan (-CA) was thiolated with phosphorus pentasulfide in sulfolane. Tensile and mucosal residence time studies were performed on buccal and small intestinal mucosa. Thiolated -CA shows a slow release of positively charged active pharmaceutical ingredients and enhanced mucoadhesive properties; it might be a promising excipient for local drug delivery in the oral cavity.[14]

Ting Liu et al. studied pullulan, which was used to prepare mucoadhesive spray-dried microparticles for delivering benzydamine hydrochloride (BZH) to the oral mucosa. Pullulan markedly extended drug-release time to >180 min, ~9 times greater than the duration (i.e., 20 min) reportedly achieved by chitosan. [15]

SUMMARY TABLE FOR THE STUDIES DISCUSSED:

Sl.No	Study	Year	Objective	Methodology	Key Findings
1	Hagerstrom et al.	2003	Study compatibility between pharmaceutical gels and mucous tissue using dielectric spectroscopy.	Low-frequency dielectric spectroscopy.	Found that dielectric spectroscopy is useful for evaluating gel-tissue interactions.
2	Shtenberg et al.	2018	Develop mucoadhesive alginate pastes with liposomes for local oral drug delivery.	Embedded liposomes in alginate pastes.	The formulation showed enhanced mucoadhesion and drug retention.
3	Colley et al.	2018	Preclinical evaluation of mucoadhesive bilayer patches for clobetasol-17-propionate delivery.	Developed bilayer patches, tested in vitro and ex vivo.	Improved drug delivery to the oral mucosa.
4	Arafa et al.	2018	Develop propolis-based niosomes as Oro mucoadhesive films for aphthous ulcer treatment.	Randomized clinical trial.	Effective in reducing ulcer healing time.
5	Matos et al.	2020	Develop chitosan nanoparticles for oxaliplatin delivery in oral tumours.	Iontophoresis-enhanced mucoadhesive delivery.	Enhanced penetration and retention in mucosal tissue.

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6	Ryu et al.	2020	Develop chitosan oral patches inspired by mussel adhesion.	Bio-inspired chitosan patches.	Strong mucoadhesion and prolonged drug release.
7	Alves et al.	2020	Develop a bilayer mucoadhesive buccal film for mucosal ulcer treatment.	Single-study case, film characterization.	Effective localized treatment with controlled drug release.
8	Li et al.	2020	Develop mucoadhesive in situ forming gel for oral mucositis pain control.	Gel formulation with in vitro and in vivo testing.	Improved pain relief and adhesion to mucosal tissue.
9	Camargo et al.	2021	Develop bio-adhesive polysaccharide-based films for imiquimod delivery.	Polysaccharide-based film formulation.	Improved topical drug delivery for oral mucosa lesions.
10	Ortega et al.	2023	Develop thermosensitive hydrogel with curcumin-loaded lipid-core nano capsules for oral cancer treatment.	Chitosan-coated hydrogel system.	Enhanced mucoadhesion and anticancer efficacy.
11	Molania et al.	2023	Evaluate atorvastatin mucoadhesive tablets for recurrent aphthous stomatitis.	Randomized clinical study.	Significant reduction in ulcer severity and recurrence.
12	Venugopal et al.	2023	Develop silymarin gel as a novel topical mucoadhesive formulation.	Formulation and characterization of silymarin gel.	Potential for treating oral pathologies with enhanced retention.
13	Pham et al.	2023	Develop swellable hydroxypropyl methylcellulose microparticles incorporating ibuprofen.	Mucoadhesive microparticle formulation.	Improved local retention and anti-inflammatory effect.
14	Kali et al.	2023	Study thiolated κ-carrageenan as a mucoadhesive excipient for intraoral drug delivery.	Development of highly thiolated κ-carrageenan formulation.	Increased mucoadhesive properties and prolonged drug residence time.
15	Liu et al.	2024	Develop pullulan-based spray-dried mucoadhesive microparticles for sustained Oro mucosal drug delivery.	Spray drying method for microparticle formulation.	Prolonged drug release with enhanced mucoadhesion.
16	Carvalho et al.	2010	Review of mucoadhesive drug delivery systems.	Literature review.	Summarized advancements in mucoadhesive drug delivery.

CONCLUSION:

As a summary to this review, numerous recent studies have contributed to the mucoadhesive drug delivery domain for the treatment of Oro mucosal lesions, mucoadhesive carriers enlisted as follows, hybrid crosslinked alginate pastes, electro spun polymeric mucoadhesive patches, niosomal oromuco-adhesive films, mucoadhesive chitosan nanoparticles, adhesive polysaccharide oral patch called 'Chitoral' that utilizes chemical principles of wet-resistant mussel adhesion, mucoadhesive bilayer polymeric film, Carbopol® or Noveon® as mucoadhesion enhancer, lipid-core nanocapsules coated with chitosan, silymarin-based mucoadhesive gel, hydroxypropyl microparticles, Native -carrageenan (-CA) was thiolated with phosphorous pentasulfide in sulfolane, pullulan to prepare mucoadhesive spray-dried microparticles.

Additional research is required to fully harness the potential of topical delivery systems in oral medicine, aiming to enhance treatment outcomes in this specific domain. Numerous obstacles in drug delivery involve surmounting the permeability barrier, shielding drugs from enzymatic degradation, and

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intended target in therapeutic concentrations. These challenges are currently under investigation through innovative formulations and technologies. Continued progress in mucobuccal adhesive technology, along with sustained local drug release and targeted delivery, could bring about substantial transformation in the treatment of oral mucosal diseases by precisely targeting the therapy to the affected area.

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JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY: KARNATAKA STATE BRANCH

Subacute Thyroiditis co-occurring with Mumps: A rare case report.

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ARTICLE INFO

Keywords:
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Hypothyroidism

ABSTRACT

The occurrence of subacute (transient) thyroiditis concomitant with mumps infection is rare, with limited case reports in the medical literature. One such rare case of a 23-year-old female patient presented with extraoral swelling below the ear lobule, extending along the angle of the mandible on the right side, was noted with other symptoms such as fever, headache, and difficulty in swallowing, leading to severe discomfort while performing day-to-day activities. Mild enlargement of the thyroid gland was also visibly appreciable. The patient was subjected to high-resolution ultrasound of the neck. Lab investigations for T3, T4, and TSH levels were checked, which depicted elevated TSH levels suggestive of hypothyroidism. The patient was managed by asking to increase the intake of fluids with conservative supportive care and medications. The TSH levels were re-evaluated after a month.

Hence, this case underscores the importance of considering thyroid complications in patients with mumps. The patient is under medication for hypothyroidism, further investigations, and patient evaluation are to be followed at regular intervals until the patient is euthyroid. This case report aims to provide insights into clinical cases, diagnostics, and management strategies of this pathology.

BACKGROUND:

Mumps is an acute viral infection caused by rubulavirus of the paramyxoviridae family of RNA viruses, most prevalent during the late winter and early spring. The incubation period is 12-24 days, with the virus commonly affecting the parotid glands. Affected individuals can present with salivary gland swelling, fever, and fatigue.[1]

Subacute Thyroiditis is a condition characterized by inflammation of the thyroid gland, leading to damage to thyroid follicular cells. Affected individuals can present with swelling of the thyroid gland, loss of appetite, and muscle aches, with signs and symptoms of hyperthyroidism/hypothyroidism.[2]

CASE PRESENTATION:

A 23-year-old female patient presented to the Department of Oral Medicine and Radiology with pain and swelling on the right side of the face. The swelling has progressively increased in size over time.

The patient reports a history of fever, headache, and swallowing difficulties, with a dental history of extraction two years ago, followed by orthodontic treatment, which is ongoing. No significant medical history is present.

Upon systemic examination, her body temperature was 38.9 degrees Celsius and normal blood pressure of 121/81 mmHg.

Extraoral examination of her revealed swelling extending along the angle of the mandible, below the ear lobule. Slight enlargement. Of thyroid gland was also appreciable. On palpation, the swelling was tender. No abnormal findings were detected intraorally.

Clinical findings demonstrate swelling and tenderness of the parotid gland, and the thyroid gland, fever, headache, fatigue, difficulty in swallowing, muscle ache, and loss of appetite, with no signs of hyperthyroidism/hypothyroidism.

INVESTIGATIONS:

High-resolution ultrasound of the neck and Blood investigations were carried out. Ultrasound of the neck revealed right parotid and submandibular gland enlargement with edema and increased vascularity.

The thyroid gland was normal, showing echogenic septations with mild diffuse increased vascularity.

Blood investigations showed her haemoglobin count of 12.9 g/dl with normal hemogram & Serum T3 0.76 ng/mL, Serum T4 5.91 µg/dL with highly elevated TSH levels of 28.0004 µlU/mL. (Reference interval- 0.35-4,94). Serological investigations were not performed.

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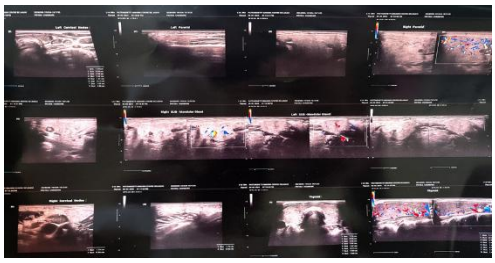

Courtesy: Pattanshetti Imaging Center, Belagavi, Karnataka, 590 001

DIAGNOSIS:

This case was diagnosed as Acute right parotid and submandibular sialadenitis & Subacute thyroiditis (Hypothyroid phase). Differential diagnosis was given as bacterial parotitis, mumps, lymphadenitis, sialolithiasis, and Sjogren syndrome.

TREATMENT:

The patient is advised to take rest, intake more fluids, and stay hydrated. Medications prescribed are Tab. Clindamycin 300mg (1-0-1) x 5 days, Tab. Metrogyl 400mg (1-1-1) x 5 days, Tab. PCT 500mg (1-1-1) x 5 days, Tab. Seratid 10mg (1-1-1) x 5 days.

Since Subacute thyroiditis is a transient condition, the case was monitored, and no treatment was administered for elevated TSH levels.[3]

Blood investigations were assessed one month later, showing Serum T3 1.13 ng/mL, and Serum T4 8.08 µg/dL with TSH levels of 8.1232 µlU/mL, significantly lower than the previous reports but higher than the reference interval.

Subacute thyroiditis occurs in three phases, namely Hyperthyroid, Hypothyroid & Euthyroid.[3] Hence, treatment for Subacute thyroiditis (Hypothyroid phase) was administered. Tab. Thyrox 75mcg (1-0-0), treatment is continued till the patient is in an euthyroid state again.

PROGNOSIS & OUTCOME:

Mumps, a viral infection, presents with fever, headache, fatigue, and swollen salivary glands, particularly the parotid gland [1], whereas subacute thyroiditis presents with symptoms such as neck pain, thyroid tenderness, fatigue, and fever.

In terms of the diagnostic process, imaging techniques such as ultrasound, Scintigraphy, MRI, Ultrasonography & laboratory investigations may be necessary. Testing for the mumps virus through serological tests/PCR can confirm the diagnosis. For SAT, T3, T4, TSH, and inflammatory C-reactive protein, it may aid in diagnosis.[4,5]

The mechanism of co-occurrence of SAT in viral infection is most commonly associated with HLA-B35. It has been noted that follicular thyroid cells share structural similarities with viral antigens, as well as a compromised immune system, stress, lack of vaccination, and exposure to infectious agents [6]

Association between SAT and HLA-B35 is noted in ethnic groups and tested. A decrease in serum C3, IgM, and alpha-1 acid glycoprotein is seen along with normal IgA, and decreased alpha-2 macroglobulin in HLA-positive patients, suggesting that major histocompatibility complex (MHC) plays a role in the pathogenesis of SAT.[7]

Familial occurrence of SAT [8] and recurrence during the course of time[9] is associated with HLA-B35. Onset is genetically influenced, and SAT might occur through susceptibility to viral infection in genetically predisposed individuals.

The correlation of HLA-B35 with other viral infections including chronic active hepatitis with rapid progression of AIDS and T-lymphocyte responses against Human parvovirus B19, is noted.[10]

In histologic and immunohistochemical studies, SAT presents with non-caseous granulomatous inflammation, small lymphocytes, neutrophils, macrophages, and giant cells. Small lymphocytes in granuloma are CD3+, CD8+, CD45RO, and cytotoxic T-cells. Giant cells are CD68+, thyroglobulin, and cytokeratin. This depicts thyroid injury in SAT as a result of cytolytic T-cell recognition of viral and cell antigens present in an appropriate complex [10, 11]

A high prevalence of thyroid antibodies is found in patients with follow-up over 3-4 years and patients with illness in low titers. Damage to the thyroid in SAT might release normally sequestered antigen-inducing an immune response. A study conducted for 1697 patients with SAT showed that antibodies were found positive in 2% of patients, but hyperthyroidism was not always present. Therefore, SAT could trigger autoreactive B-cells to produce TSH receptor antibodies. [12, 13]

The occurrence of SAT concomitant with mumps is very rare. Recent studies have shown that the incidence of SAT is 12% cases per 100,000/yr. However, to date, only 1 case has been reported by RC Parmar et. al in June 2001 of a 9-year-old boy where Parotitis/mumps occurred 12 days after the onset of thyroiditis.[14]

Supportive care for both conditions are necessary and may include rest, hydration, and pain relief with NSAIDs. Prednisone can be used in the management of SAT, but steroids suppress the immune response and prolong viral shedding.[15]

It is important to carefully monitor thyroid function as it can cause hypothyroidism, which may become permanent. Antibiotics are administered to prevent secondary infection.

CONCLUSION:

The presentation of SAT with mumps highlights the importance of considering rare simultaneous occurrences in clinical practice. This case underscores the necessity for comprehensive diagnostic evaluation and multidisciplinary management. Further research is warranted to elucidate the mechanism underlying the co-occurrence of the condition necessitating clinical assessment and therapeutic interventions.

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JOURNAL OF INDIAN ACADEMY OF ORAL MEDICINE AND RADIOLOGY: KARNATAKA STATE BRANCH

Microneedles and Nanotechnology: Transforming Oral Disease Treatment

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ARTICLE INFO

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ABSTRACT

In recent years, the field of dentistry and oral healthcare has observed remarkable advancements in drug delivery technologies. Among these, micro-needling and nano patch-based drug delivery systems have gained importance in the therapeutics of many oral diseases. The conventional methods of drug delivery require repeated doses in the oral cavity due to the presence of saliva, as its continuous flow can wash away the applied drug. Microneedles involve the use of tiny needles that penetrate the skin or mucous membrane. The microneedles can be fabricated according to the design and function required for drug delivery. Nano patches are miniature patches loaded with nanoparticles of the drug that aid in the controlled release of the drug and healing. Micro needling and nano patches together have found their applications in the treatment of oral lesions like oral ulcers, mucositis, biofilm disruption, periodontal regeneration, local anaesthesia, tissue healing, extraction of fluids for local and systemic effects, etc. In addition, these devices can also be used as an aid in the diagnosis and therapy of oral cancers, delivering anti-carcinogenic and anti-plaque agents. It provides solutions to many problems or difficulties patients face by being less invasive, painless, or less painful, and thus aims at targeted, sustained, and enhanced drug delivery with increased efficacy. Also, it can be self-applicable, reducing patient discomfort. The limitations include limiting drug dosing capacity, limited application sites, infection risk, and depth of penetration. Continued research and development in this area may lead to further innovations in dental care.

INTRODUCTION:

Local drug delivery in dentistry involves the targeted administration of medications or therapeutic agents directly to the oral cavity or surrounding tissues. Its applications include treatment of oral lesions, local anaesthesia, periodontal diseases, dental caries in the form of fibres, films, gels, strips, vesicles, etc. It offers several advantages, including targeted drug delivery, reduced systemic side effects, enhanced therapeutic outcomes, and improved patient comfort during dental procedures. [1] But a continuous flow of saliva can cause a problem as it washes away the topically applied medications. Hence, requiring multiple applications. Also, orally administered drugs undergo metabolism, requiring a higher dose of the drug.[2] Micro needling and Nano patches are advanced techniques in local drug delivery, offering several advantages over traditional methods. Hence, the following article gives a brief review of the literature on micro needling and nano-patch-based drug delivery systems.

DISCUSSION:

Micro needling is a device with fine needles that creates tiny punctures in the skin. This controlled injury stimulates the body's natural healing process, promoting collagen and elastin production. After micro needling, nano patches are applied to the treated area. These patches contain active ingredients such as peptides, vitamins, or growth factors, encapsulated in the nanoparticles. The micro needling creates channels that allow these ingredients to penetrate deeper into the skin**.**

In 1995, Orentreich and Orentreich used micro needling for the first time to treat wrinkles and scars with hypodermic needles. In 2006, Dr. Desmond Fernandes developed the first MN product, which became the modern-day Derma roller. Micro needling is a minimally invasive mechanical procedure that creates micro-injuries in the skin's surface using fine needles and primarily focuses on stimulating collagen production. It is an alternative to conventional needles and other injection methods. [3] Microneedle (MN) array consists of 12-24 rows of submillimetre-sized needles (up to 1500µm in length) that penetrate the stratum corneum and deliver the drug. The MN system limits itself to the epidermis and does not interfere with the dermal layer, where the nerve fibres and blood vessels are located. Thus, the medication is administered in a pain-free manner [4]. Microneedles typically have a tapered, sharp tip. Length ranges from 800-1500 µm, and the **s**pace between MNs is between 600-1100 µm**.** The width varies between 50 to 250 µm, and the tip thickness is typically between 1 to 25 µm. The depth can range from 0.25mm to 2.5mm. [5]

TYPES AND MECHANISM:

Microneedles are first applied to the skin or mucous membrane and then used for drug delivery.

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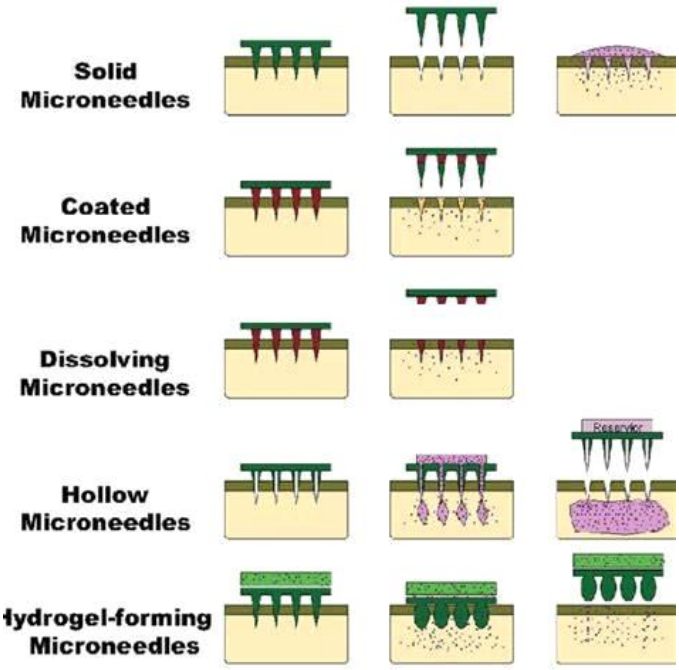

Fig 1: Courtesy: Zahra Faraj Rad, Advanced Science News

i. Solid microneedles: Solid microneedles work on the principle of poke and patch. It creates micron-scale pores in the skin, and the drug is applied on the surface of the skin through which the drug can slowly diffuse into the body. [6]

ii. Coated Microneedles: Coated microneedles follow the coat and poke approach. A water-soluble formulation can be coated on the microneedle. After insertion, the drug coating dissolves into the skin, and then the microneedles can be removed. [6]

iii. Dissolving microneedles: These needles follow a poke and dissolve approach. The microneedles can be made out of biodegradable or water-soluble polymer, which dissolves completely when it comes in contact with the interstitial tissue fluid and releases the encapsulated drug formulation, leaving behind zero waste. [7]

iv. Hollow microneedles: This type follows the poke and flow approach and can be used to infuse liquid formulations of the drug. Hollow microneedles can also be used to withdraw liquids from tissues. [8]

v. Hydrogel-forming Microneedles: Polyvinyl alcohol (PVA) and polyvinyl pyrrolidone are commonly employed polymers for fabrication. Upon insertion, these microneedles penetrate the skin and swell up, securing attachment and enabling sustainable release of the drug. [9]

MATERIALS AND METHODS:

Silicon- Flexible enough to manufacture desirable shapes and sizes. Silicon has been used for the manufacture of solid, coated, and hollow MNs

Metal-Good biocompatibility and mechanical properties. It also has high fracture toughness and is strong and hard to break.

Ceramic possesses superior chemical and compression resistance. Alumina and calcium sulfate dihydrate have been utilized for the fabrication of microneedles.

Polymer- has excellent biocompatibility, low toxicity, and low cost, but possesses low strength [10,11]

Micro needling has its application in various conditions and can be employed as a potential diagnostic and treatment modality. Dermatologically variety of MN products have been developed to treat scarring and wrinkles, enable skin rejuvenation, and improve skin appearance. Clinical trials have been practiced inducing hair restoration, treating hyperhidrosis, and disorders of pigmentation.[12]

Dental applications-

a. Enhanced wound healing: Microneedles loaded with antibacterial agents, growth factors like platelet-derived growth factor (PDGF), transforming growth factor -alpha and beta (TGF) can be administered to accelerate healing; therefore, a useful adjunct to periodontal surgery. [14]

b. Improving gingival biotype: The use of microneedles independently or with a grafting procedure could potentially improve the areas with a thin gingival biotype. [15]

c. Gingival Depigmentation: Currently used methods for treating gingival depigmentation, such as scalpel surgery, laser ablation, bur abrasion, and electrocautery, often lead to complications such as postoperative pain, bleeding, discomfort, and delayed wound healing. Microneedles could be a minimally invasive, painless, and cost-effective treatment modality for gingival depigmentation. [15]

d. Collecting oral diagnostic fluid: Microneedle patches could be used to collect oral diagnostic fluids such as Gingival Crevicular Fluid (GCF), saliva, and peri-implant fluid, which could be used to identify various biomarkers. [16]

e. Administering antiplaque agents: In medically compromised patients, post-surgical cases, orthodontic patients, paediatric patients, etc, efficient mechanical plaque control is difficult. Microneedle patches loaded with antiplaque agents could be applied on the oral mucosa and gingiva, aiding in maintaining oral hygiene. [17]

f. Adjunct in cancer chemotherapy: Mucositis and xerostomia are common adverse effects associated with the treatment of cancers. Microneedles could be used to deliver drugs such as transforming growth factor beta-3 (TGF-b3) or supersaturated calcium phosphate to treat and protect the mucosa.[15]

g. Deliver anticariogenic agents: Microneedles could be used in paediatric or adult patients with low compliance to oral hygiene procedures for sustained release of fluoride or other remineralizing agents such as Casein phosphopeptide–amorphous calcium phosphate (CPP–ACP) for prevention of caries. [15]

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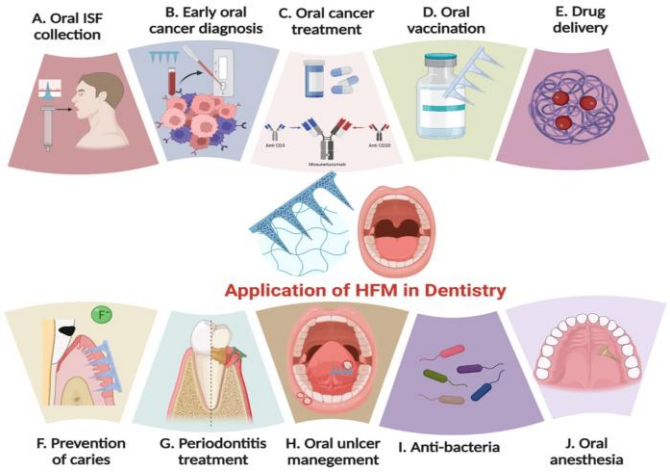

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CLINICAL AND EXPERIMENTAL DENTAL RESEARCH:

i. In a study conducted by Diana Mostafa and Razan Alarawi to analyse the effectiveness of micro needling technique using coconut and sesame oils on the severity of gingival inflammation and plaque accumulation, twenty-four patients with clinically diagnosed plaque- induced gingivitis were selected and randomly assigned to one of three groups; group A consisted of eight participants who were treated with derma pen and topical coconut oil, group B had eight participants who were treated with derma pen and topical sesame oil, and group C involved eight patients who only received periodontal mechanical treatment. At weeks 1,2, and 4 postintervention gingival and plaque status for all subjects were assessed using a modified average gingival index and a plaque index. Groups A and B experienced highly significant reductions in gingival indices, while group C showed reduced scores but was not significantly notable, and when compared altogether, there was no significant difference in the reduction of plaque indices. Therefore, this study demonstrates an effective technique that revealed a noticeable improvement in the gingival status with reduced average gingival index and plaque index. [18]

ii. In another study, gingival depigmentation using the Micro needling technique with topical Vitamin C was performed. 16 participants were enrolled in this study according to the inclusion and exclusion criteria. Using the Derma pen instrument, micro needling was performed, which was followed by applying ascorbic acid on the pigmented gingiva topically. Variations in the Dummett oral pigmentation index (DOPI) and Hedin melanin index (HMI) scores were considered for each patient, and a one-month follow-up was conducted on all patients. There was noticeable improvement in all the reported cases at the end of the sessions. Moreover, seven patients showed complete depigmentation of the gingiva. The study concludes that micro needling combined with topical ascorbic acid is a novel, non-invasive dental technique that can effectively treat gingival hyperpigmentation. [19]

Benefits: Micro needling offers improved delivery and sustainable release of the therapeutic agents, causing better absorption. This method is less invasive than hypodermic needles, causing minimal pain and discomfort to the patient. By delivering the drugs locally rather than systemically, micro-needling reduces the risk of systemic side effects and drug interactions. Moreover, micro needling can be used for a wide range of drugs, including small molecules, peptides, proteins, and vaccines. As a result, it can be considered the best choice for people who have needle phobia. [15]

Drawbacks -The use of a microneedle for transdermal drug delivery introduces disadvantages such as extended application time, multiple patches within a given area, the requirement of specific mechanical strength, and a good biocompatible material.

NANOTECHNOLOGY AND NANOPATCHES:

Nanotechnology in drug delivery involves the use of nanoscale materials and devices to enhance the delivery of therapeutic agents. Nano patches use nanotechnology to create miniature patches containing drug-loaded nanoparticles. Due to their small size and large surface area, nanoparticles (NPs) can deliver drugs across the stratum corneum (SC) without disrupting the skin barrier. These patches adhere to skin or mucosal surfaces and facilitate controlled release of medications [20]. Nanotechnologies exhibit significant potential in the field of medicine, which includes imaging techniques and diagnostic tools, drug delivery systems, implants, and pharmaceutical therapeutics, and have advanced treatments of several diseases, including cardiovascular diseases, cancer, musculoskeletal conditions, psychiatric and neurodegenerative diseases, bacterial and viral infections, and diabetes.[20] In Gene Therapy, Nanoparticles can deliver genetic material to specific cells, offering potential treatments for genetic disorders.[20]

Cancer Therapy: Nanoparticles can target cancer cells specifically, delivering chemotherapeutic agents directly to the tumor while sparing healthy tissue.[21]

Infectious Diseases: Nanocarriers can enhance the delivery of antimicrobial agents, overcoming issues like drug resistance.[22]

Neurological Disorders: Nanoparticles can efficiently cross the blood-brain barrier, maintaining a high drug bioavailability in neural parenchyma, which is a significant challenge in treating brain diseases.[23]

TYPES OF NANOPARTICLES:

A micelle is defined as a collection of amphiphilic surfactant molecules that spontaneously aggregate in water into a spherical vesicle. The centre of the micelle is hydrophobic and therefore can sequester hydrophobic drugs.[20]

Carbon nanotubes are cylindrical molecules that consist of rolled-up sheets of a single layer of carbon atoms (graphene). They can be single or multi-walled, or several concentrically interlinked nanotubes. Due to their high external surface area, carbon nanotubes can achieve considerably high loading capacities as drug carriers.[24]

Liposomes are spherical vesicles composed of one or more phospholipid bilayers and can encapsulate a variety of drugs, both hydrophilic and hydrophobic. Their structure closely resembles cell membranes, which makes them biocompatible and able to fuse with cell membranes to deliver their contents[24]

Dendrimers- Dendrimers are macromolecules characterized by their branched, tree-like structures, expanding from a central

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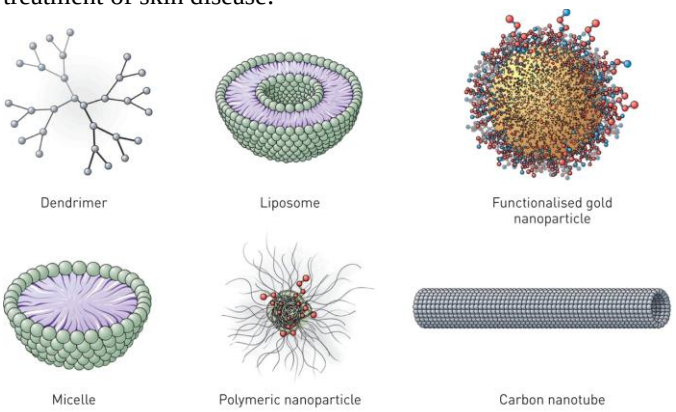
core and consisting of exterior functional groups. These functional groups can be anionic, neutral, or cationic terminals. Therapeutic agents can be encapsulated within the interior space of dendrimers or attached to the surface groups.[20]

Inorganic NPs and carbon nanomaterials, such as superparamagnetic iron oxides (SPIONs), titanium dioxide (TiO2), zinc oxide (ZnO), gold (AuNPs), silver (AgNPs), graphene oxide (GO), carbon nanofibers (CNFs), and fullerenes have been recently applied in TDD, and also in the diagnosis or treatment of skin disease.[20]



Courtesy: https://radiationdangers.com/2020/10/09/explosive-information-5g-vaccination-nanoparticles-and-the-genocide-of-humanity/

APPLICATIONS OF MICRONEEDLE-ASSISTED NANOPARTICLE DELIVERY IN DENTISTRY:

Localized Drug Delivery: Microneedles can deliver drugs directly to specific sites within the oral cavity, such as gums or dental pulp, ensuring higher local drug concentrations and reducing systemic side effects.

Pain Management: Microneedles can be used to deliver anaesthetics directly to the required area, providing faster and more effective pain relief for dental procedures compared to traditional injections.

Enhanced Treatment of Periodontal Disease: Microneedles can deliver antimicrobial nanoparticles directly into periodontal pockets, improving the management of periodontal infections and promoting faster healing.

Regenerative Dentistry: Microneedles can deliver growth factors and other regenerative agents encapsulated in nanoparticles directly to damaged tissues, promoting tissue regeneration and repair in conditions like periodontitis or after dental surgeries.

Improved Delivery of Fluorides and Other Preventive Agents: Microneedles can be used to deliver fluoride or other remineralizing agents directly to the teeth, enhancing their effectiveness in preventing dental caries.

Targeted Treatment of Oral Cancer: For patients with oral cancer, microneedles can deliver chemotherapeutic drugs or therapeutic nanoparticles directly to the tumor site, potentially improving treatment outcomes and reducing systemic toxicity.

Topical Anaesthetics: Microneedles can provide rapid and effective delivery of local anaesthetics for pain-free dental procedures.

Antibiotic Delivery: Targeted delivery of antibiotics to treat infections, such as dental abscesses or post-surgical infections, can be enhanced using microneedles.

Advantages- Transdermal drug delivery through microneedle-assisted nanoparticle delivery offers several benefits, such as

Minimally Invasive Delivery: Microneedles penetrate the outer layer of the skin without reaching the pain receptors, making the delivery process less painful and more acceptable for patients compared to traditional needles.

Enhanced Penetration and Absorption: Microneedles create microchannels in the skin, which can enhance the penetration and absorption of nanoparticles. These nanoparticles can be loaded with chemotherapeutic agents, allowing for controlled and targeted drug release.

Targeted Therapy: By modifying the surface of nanoparticles, it is possible to target specific cancer cells, reducing the impact on healthy cells and minimizing side effects.

Improved Bioavailability: The direct delivery of drugs through microneedles can bypass the gastrointestinal tract and first-pass metabolism, leading to improved bioavailability of the chemotherapeutic agents.

Controlled Release: Nanoparticles can be engineered to release their payload in a controlled manner, ensuring a sustained release of the drug over time and potentially reducing the frequency of dosing.

Potential for Combination Therapies: Nanoparticles can be designed to carry multiple drugs or therapeutic agents, enabling combination therapies that can be more effective than single-drug treatments.

CHALLENGES:

Manufacturing and Scalability: Producing microneedles with consistent quality at scale can be challenging.

Regulatory Hurdles: Ensuring safety and efficacy through rigorous clinical trials and obtaining regulatory approvals is a lengthy and expensive process.

Patient Acceptance: Despite being less painful, the concept of microneedles might still be met with resistance by some patients.

CONCLUSION AND FUTURE PERSPECTIVES:

A combination of MNs and NPs has shown multiple benefits over conventional systems, such as the improved skin penetration of NPs, prolonged and controlled drug release, and the possibility of new add-on therapeutics (e.g., Photodynamic therapy and Photothermal therapy). However, factors such as the dosage and location, permeability, and the structure of the targeted tissues are key factors in determining their success. Moreover, these combined systems have been especially explored for vaccination, immunotherapy, and gene delivery. Therefore, they can revolutionize treatment delivery in the field of dentistry, but further studies are required to exploit the diagnostic and therapeutic potentials of smart MNs.

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From Wave to Wellness: A Look into Trans-magnetic Stimulation for Trigeminal Neuralgia

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ABSTRACT

Trigeminal Neuralgia is a chronic disorder characterised by severe pain in the regions supplied by the Trigeminal Nerve (CN V). It is usually bilateral, sudden in onset which may precipitates on normal day to day activities like brushing, chewing, shaving etc. The pathophysiology of Trigeminal Neuralgia is not known but it is caused due to compression of the trigeminal nerve, trauma, infections etc. The current treatment of trigeminal neuralgia includes drugs like Carbamazepine which is the drug of choice. Surgical treatments include peripheral neurectomy, microvascular decompression, anaesthesia injections and others. However, these treatments have their own side effects so if used in moderation and along with adjunctive therapies can produce significant results

One of such adjunctive therapies are Trans-magnetic Stimulation (TMS). Trans-magnetic stimulation is a non-invasive therapy where it uses magnetic fields to bring about alterations in the neural activity in the nerves. TMS is used in various medical applications and has shown excellent results and is a breakthrough in the management of Trigeminal Neuralgia.

Advancements in technology has brought about numerous innovations in the field of medicine and TMS is one of them. This review aims at understanding Trans-magnetic Stimulation and its application for management of Trigeminal Neuralgia.

INTRODUCTION:

The Trigeminal Nerve is the fifth cranial nerve, which supplies the face and muscles of mastication. It has 3 divisions: Ophthalmic branch V1, Maxillary branch V2, and Mandibular branch V3. [1] Trigeminal neuralgia (TN) is a typical type of facial pain characterized by sudden, electric shock-like episodes that are recurrent. It is triggered by basic daily tasks such as brushing, eating, drinking, and shaving, often leading to poor life quality. TN is usually seen in females more than men and is bilateral; however, cases of bilateral TN have been reported.[2]

Trigeminal neuralgia can be broadly classified as

- Classical TN, where it is usually due to vascular compression of the nerve.
- Secondary TN: it is caused by underlying reasons like cysts, tumours, etc
- Idiopathic TN: where is cause is unknown. [1]

The causes of trigeminal neuralgia, like tumours, vascular malformations that compress the nerve, can be identified by the use of magnetic resonance imaging (MRI), angiography, and neurophysiological tests. These causes can then be eliminated by surgical intervention. The surgical therapies, like peripheral neurectomy, radiosurgery, microvascular compression, and others, are some of the other treatment methods used for TN. [3] The drug of choice for trigeminal neuralgia is carbamazepine, a voltage-gated sodium channel blocker. Other drugs like oxcarbazepine, gabapentin, botulinum toxin, etc, are also used for the management of trigeminal neuralgia. [3] However, the use of these drugs provides symptomatic relief and a short-term solution for the recurrent episodes of TN. Hence, newer treatment modalities need to be identified and implemented to provide better patient care, one of which is Magnetic Stimulation (TMS).

TRANSMAGNETIC STIMULATION

Trans-magnetic stimulation, or TMS, was first introduced by Anthony Barker and his colleagues in the year 1985. Its first use caused twitching of certain muscles of the hand, and was used in a female suffering from epilepsy, who was not responding to medication. TMS was first approved by the FDA in 2008 for the treatment of major depressive disorder and was later approved for various other disorders in the subsequent years.[4] TMS is one of the newer treatment modalities that can be used for the treatment of trigeminal neuralgia. TMS is a technology where electromagnetic waves are used to manage and treat TN effectively with minimal risks of complications. TMS uses electromagnetic waves produced by a coil, which stimulates the brain, leading to a change in the activity of the neurons, leading

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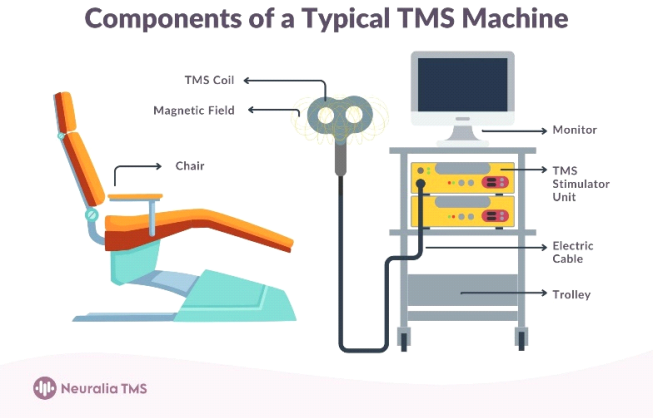
to reduced excitability of the nerves. TMS is used for neuropsychiatric disorders like Parkinson's, depression, schizophrenia, [5] and also for tobacco addiction.

TMS Machine:

A typical TMS machine mainly consists of 2 components: a capacitor, which stores electrical charge from a power source and produces it when in use, and a coil, which converts the electrical charge into electromagnetic waves.[6] The coils of the TMS machine are available in various types, such as circular, butterfly, double D, figure of eight coils, etc. The figure of eight coil is the most commonly used coil in trans-magnetic stimulation. [7]



Components of a typical TMS machine. Courtesy: Neuralia TMS

Figure of eight coil. Courtesy: MagVenture

WORKING OF TMS IN TRIGEMINAL NEURALGIA:

The exact pathophysiology of trigeminal neuralgia is not known, but it is attributed to demyelination of the nerves due to secondary causes.[8] It is also believed that due to the nerve demyelination or nerve damage, there are bursts of stimuli in the cluster of neurons in the trigeminal ganglion, causing hyperexcitability of the neurons, leading to episodes of pain in patients.[9]

Another theory suggests that the pain produced is due to the imbalance of inhibitory components that work on the neurons in the somatosensory system. [10]

When patients with TN are subjected to TMS sessions, the electromagnetic waves cause repolarisation of the nerve signals in the brain and in the trigeminal ganglion, which causes a reduction in the episodes of pain as seen in TN. The protocol of TMS for management of trigeminal neuralgia is not fixed, but various studies have shown that 10-20Hz of electromagnetic waves, when used for 5 -35 sessions, depending on the severity of episodes and 1000-3000 pulsations per session [10] has helped in significantly reducing the intensity and recurrence of trigeminal neuralgia. Though the results were satisfactory, the long-term therapeutic effect of TMS on trigeminal neuralgia is yet to be studied and evaluated. [11]

MEDICAL CONSIDERATIONS:

Heating of metal implants:

TMS causes minimal to no heating of titanium implants; hence, it is safe to use, but metals like silver and gold, which have high conductivity, tend to heat and can cause serious damage if used for long periods. [12]

Implanted devices:

TMS has the potential to interfere with the electrical conduction of implanted devices like cochlear implants, devices for deep brain stimulation, vagus nerve stimulation, etc. Hence use of TMS to be taken into consideration with patients with such devices. [13]

Epilepsy:

TMS is known to induce seizures in patients with epilepsy or any other neurological disease.[14] Hence use of TMS in such patients should be avoided, or close monitoring of such patients to be done.

TMS can cause transient hearing disturbance, but it has not shown any serious effects in patients. TMS is safe to use in children and pregnant women, and also with medically compromised individuals. [15] So, proper recording of the medical history of the patients has to be done to avoid complications.

STUDIES:

Studies have been done on various orofacial pain which are listed in **Table 1.**

Table 1.

Sl. No	Title of study	Year	Results
1.	Repetitive Transcranial Magnetic Stimulation at Different Frequencies for Postherpetic Neuralgia: A Double-Blind, Sham-	2019	Sixty patients were treated in three groups, where two groups were subjected to 5 Hz and 10 Hz of TMS, and one group served as

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	Controlled, Randomized Trial. Qian Pei et al [16]		the sham group. When compared to the sham group, the groups subjected to TMS showed better results in various parameters like sleep quality, quality of life, and self-rating depression scales.
2.	Analgesic effects of navigated motor cortex rTMS in patients with chronic neuropathic pain Ayache SS et al [17]	2016	Sixty-six patients were subjected to 10Hz TMS for a single session in three groups, where one group served as the sham group and the other two groups were navigated and non-navigated groups receiving real TMS. As a result, patients experienced pain relief in the real groups, whereas the sham group did not experience any relief. Also, the navigated group showed better results when compared to the non-navigated group.
3.	High-Frequency Repetitive Transcranial Magnetic Stimulation Reduces Pain in Postherpetic Neuralgia Ma SM et al [18]	2015	A total of 40 patients randomly received Sham TMS or Real TMS of 10Hz for 10 sessions. As a result, the patients receiving real TMS showed reduced VAS compared to the Sham group, hence suggesting that TMS is effective for postherpetic neuralgia.
4.	One-Year rTMS Treatment for Refractory Trigeminal Neuralgia Soroush Zaghi et al [19]	2009	A 62-year-old patient with Trigeminal neuralgia was treated with rTMS over one year, with four interval periods and 35 individual sessions. It showed a significant reduction in the pain with individual rTMS, but the effects were limited to 2-4 weeks post-stimulation.

CONCLUSION:

Trans-magnetic stimulation holds great potential in the management of Trigeminal neuralgia, especially in patients with complex medical conditions where conventional therapy is contraindicated. TMS can also be used as an adjunct with conventional therapies to provide better care to the patients. More research on the long-term advantages of TMS for the management of TN and other orofacial pain should be done. TMS is a well-tolerated treatment modality with minimal side effects. Proper protocol has to be formulated for the management, which will lead to a good prognosis and reduce complications. However, patient selection, proper case history recording, and thorough knowledge of the technology and the mechanism behind it are of utmost importance.

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