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Research Article

Formulation and Evaluation of a Screening Model for Submucosal Fibrosis Using Chingum with Dragon Fruit

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ABSTRACT

Submucosal fibrosis (SMF) is a chronic, progressive oral disorder with malignant potential, commonly associated with areca nut chewing and other irritants. Early screening and preventive measures are vital to halt its progression. This study aims to formulate a functional chewing gum using Dragon fruit (*Hylocereus undatus*) extract, known for its antioxidant and anti-inflammatory properties, and evaluate its potential as a screening model for SMF. The chewing gum was prepared using standard excipients and evaluated for organoleptic properties, physicochemical parameters, in vitro release of antioxidants, and mucosal compatibility. Results showed effective incorporation of bioactive compounds from Dragon fruit, satisfactory chewing properties, and promising antioxidant release during simulated chewing. Preliminary tests indicated a potential role in supporting mucosal health and enhancing salivary biomarker responses linked to SMF. This study suggests that Dragon fruit-based chewing gum could serve as a novel, non-invasive adjunct for early screening and prevention of submucosal fibrosis. The Dragon fruit extract was obtained through maceration, standardized, and incorporated into a natural chingum matrix to form a mucoadhesive formulation. The prepared formulation was evaluated for its physicochemical properties, bioadhesive strength, spreadability, drug release behavior, and in vitro antioxidant and anti-fibrotic activity. Results indicated good mucoadhesive properties, sustained release of phytoconstituents, and significant inhibition of fibroblast proliferation and collagen synthesis in vitro. The incorporation of Dragon fruit enhances the therapeutic potential of the model by delivering bioactive compounds directly to the oral mucosa. This approach presents a promising tool for early screening and management of OSMF, particularly in resource-limited settings where non-invasive and cost-effective interventions are needed.

INTRODUCTION

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Submucosal fibrosis (SMF), particularly oral submucous fibrosis (OSMF), is a potentially malignant disorder characterized by progressive fibrosis of the oral mucosa. It often results from chronic areca nut and tobacco use, leading to mucosal rigidity and limited mouth opening. Early diagnosis is crucial to improve prognosis and prevent malignant transformation. Conventional screening methods are often invasive or expensive. Functional food-based approaches that combine therapeutic and diagnostic capabilities are gaining attention. Dragon fruit (*Hylocereus undatus*), rich in vitamin C, polyphenols, and betalains, exhibits potent antioxidant and anti-inflammatory activity, which may help counter oxidative stress and inflammation in oral tissues. This research focuses on developing a chewing gum as a convenient delivery system for Dragon fruit extract, aiming to act both as a preventive supplement and a non-invasive screening aid through biomarker modulation. Oral Submucous Fibrosis (OSMF) is a chronic, insidious disorder predominantly affecting individuals in South and Southeast Asia, particularly India, due to prevalent areca nut chewing habits. It is classified as a potentially malignant disorder by the World Health Organization, with a malignant transformation rate of approximately 7–13%. OSMF is characterized by juxta-epithelial inflammation, increased collagen deposition, and progressive fibrosis of the lamina propria and deeper connective tissues. Clinically, it manifests as burning sensation, blanching of oral mucosa, stiffness, and progressive limitation of mouth opening (trismus), severely impacting the quality of life. Early diagnosis and intervention are crucial in managing OSMF. However, due to the lack of cost-effective, non-invasive screening tools, most cases are diagnosed at an advanced stage. The need for a localized, easy-to-use screening model that not only identifies early signs but also delivers therapeutic agents has prompted the exploration of

natural, mucoadhesive formulations. Dragon fruit (*Hylocereus* spp.), a tropical cactus fruit, is rich in antioxidants such as betacyanins, flavonoids, polyphenols, and vitamin C, which exhibit strong free-radical scavenging and anti-inflammatory properties. These bioactives have been shown to inhibit oxidative stress-induced fibrotic changes, making Dragon fruit a potential candidate for use in OSMF prevention and management. Chingum, a natural, chewable gum base derived from plant exudates or biodegradable polymers, provides a suitable medium for buccal delivery due to its bioadhesive properties and prolonged mucosal contact time. When used as a base for incorporating Dragon fruit extract, chingum may serve both diagnostic and therapeutic purposes by allowing sustained release of active constituents directly at the site of fibrosis. This study aims to develop a novel screening model using chingum incorporated with standardized Dragon fruit extract. The objective is to create a mucoadhesive formulation capable of detecting early mucosal changes while simultaneously delivering antioxidant therapy. This approach could pave the way for low-cost, accessible, and non-invasive tools in the management of OSMF, particularly in high-risk populations.

Plant Profile: Dragon Fruit (*Hylocereus* spp.)

Dragon fruit, also known as pitaya, is a tropical fruit native to Central and South America. It is a member of the Cactaceae family and is widely cultivated in Southeast Asia, particularly in Vietnam, Thailand, and Malaysia.





Fig: Dragon fruit

Physical Description:

- **Stem:** The plant has a climbing stem with sharp, waxy spines.
- **Leaves :** The leaves are elliptical, dark green, and fleshy.
- **Flowers:** The flowers are white, fragrant, and bloom only at night.
- **Fruit:** The fruit is oval-shaped, with a vibrant pink or yellow skin, and white or red pulp with tiny black seeds.

Cultivation:

- **Climate:** Dragon fruit prefers a warm, humid climate with average temperatures between 64°F and 90°F (18°C and 32°C).
- **Soil:** The plant thrives in well-draining, fertile soil with a pH range of 6.0 to 7.0.
- **Watering:** Regular watering is necessary, but the plant is drought-tolerant.
- **Fertilization:** Feed the plant with a balanced fertilizer during the growing season.

Uses:

- **Food:** The fruit is edible and rich in vitamins C and B2, potassium, and fiber.
- **Medicine:** The plant has been used in traditional medicine to treat various ailments, including diabetes and hypertension.
- **Ornamental:** Dragon fruit is often grown as an ornamental plant due to its unique appearance and fragrant flowers.

MATERIALS AND METHODS

1) Materials :

- **Dragon Fruit (Hylocereus spp.):** Fresh fruits were procured from a certified organic farm or local market.
- **Chewing Gum Base:** Natural gum base (e.g., chicle or synthetic chewable polymer) sourced from a pharmaceutical-grade supplier.
- **Solvents:** Ethanol, distilled water, methanol (analytical grade).
- **Reagents:** DPPH (2,2-diphenyl-1-picrylhydrazyl), ascorbic acid, phosphate buffer (pH 6.8), and reagents for in vitro cell culture.
- **Cell Line:** Human oral fibroblast cells (if available for anti-fibrotic screening).
- **Other materials:** Glassware, magnetic stirrer, pH meter, texture analyzer, UV-Vis spectrophotometer, Franz diffusion cell.

2) **Extraction of Dragon Fruit Pulp :** The fresh Dragon fruit was washed, peeled, and the pulp was homogenized. The extract was obtained using cold maceration with 70% ethanol for 72 hours with intermittent shaking. The extract was filtered through Whatman No. 1 filter paper and concentrated using a rotary

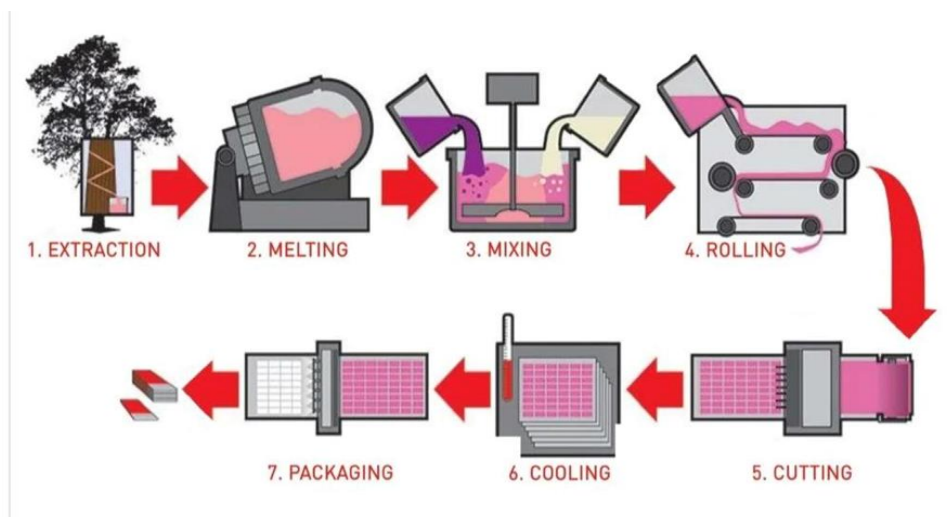
evaporator under reduced pressure at 40°C.
The semi-solid extract was stored at 4°C until use.



Fig: Extraction of Dragon Fruit

- 3) Preparation of **Chewing Gum** -Based Screening Formulation : The chingum base was softened by gentle heating. The concentrated Dragon fruit extract was mixed into the base at varying concentrations (e.g., 2%, 4%, and 6% w/w) while stirring to ensure

uniform distribution. Flavoring agents and sweeteners (optional) were added to improve palatability. The mixture was poured into silicone molds and allowed to cool and solidify.



Formula:

Ingredients	Quantity (% w/w)	Purpose
Chewing gum base	60	Base matrix
Dragon fruit extract	5	Active antioxidant /anti-fibrotic
Glycerin	3	Humectant/ plasticizer
Sorbitol or Xylitol	10	Sweetener (optional, sugar-free)
Flavoring agent	2	Taste enhancement
Citric acid	0.5	Salivary stimulant & preservative
Color (natural or food grade)	0.1	Aesthetic appeal
Distilled water (q.s.)		To adjust final weight

Preparation Procedure

Step 1: Preparation of Dragon Fruit Extract

1. Select fresh, ripe Dragon fruit.
2. Peel and separate the pulp.
3. Homogenize the pulp using a blender.
4. Macerate the pulp in 70% ethanol for 72 hours with occasional shaking.
5. Filter the mixture using Whatman No. 1 filter paper.
6. Concentrate the filtrate using a rotary evaporator at 40°C to obtain a semi-solid extract.
7. Store the extract in an airtight container at 4°C until use.

Step 2: Preparation of Chingum Base



1. Heat the chewing gum base gently (40–50°C) until it becomes soft and malleable.
2. Transfer the softened gum base to a mixing vessel.

Step 3: Incorporation of Ingredients

1. Add the measured amount of Dragon fruit extract (e.g., 5% w/w) to the softened gum base.
2. Mix thoroughly until a homogenous blend is achieved.
3. Add plasticizer (e.g., glycerin) and sweetener (sorbitol or xylitol) and mix uniformly.
4. Incorporate flavoring agents and color as needed.
5. Add a small quantity of citric acid for salivary stimulation and preservative action.

Step 4: Molding and Cooling

1. Pour the final warm mixture into pre-lubricated silicone molds.
2. Allow it to cool and solidify at room temperature or in a refrigerator (30–60 minutes).
3. Once set, remove the chingum pieces from the molds.

Step 5: Packaging and Storage

1. Pack the formulated chingum in aluminum foil or airtight containers to protect from moisture and oxidation.
2. Store in a cool, dry place.

Evaluation of the Formulation

- 1) Physicochemical Evaluation of the Chewing Gum

a) Organoleptic Properties

- Appearance: Visual inspection to check the color, shape, and size of the gum.
- Texture: Evaluate the gum for chewiness, consistency, and elasticity (e.g., using a texture analyzer or through subjective sensory analysis).
- Taste: Perform sensory analysis (possibly with a panel) to assess the flavor and aftertaste of the gum.

b) Mechanical Properties

- Hardness and Tensile Strength: Measure the force required to chew and break the gum using a texture analyzer or a force gauge.
- Elasticity: Measure how the gum returns to its original shape after deformation.

c) Stability Testing

- Shelf Life: Store the gum at different temperatures (room temperature, high humidity) and periodically check for changes in texture, flavor, and color.
- Moisture Content: Measure the moisture content to ensure stability and prevent spoilage.

- d) Release Profile of Active Ingredients : Release Kinetics of Dragon Fruit Components: Conduct in vitro release testing using a simulated oral cavity environment (e.g., using a dissolution apparatus or a chewing simulator) to assess how the active components of dragon fruit (like antioxidants or fibers) are released during mastication.

- 2) In Vitro Evaluation of Submucosal Fibrosis Screening Efficacy



a) Cell Culture Studies (Fibroblast Cells)

- Cell Line: Use human fibroblast cell lines (e.g., NIH 3T3 cells) for in vitro testing.
- Fibrosis Induction: Expose the cells to pro-fibrotic agents like TGF- β (Transforming Growth Factor Beta) to induce fibrosis in vitro.
- Cell Viability: Perform MTT assay or other viability assays to assess the effects of the gum (or dragon fruit extract) on fibroblast cell survival.
- Collagen Production: Measure the secretion of collagen, which is a hallmark of fibrosis, using assays like hydroxyproline assay or collagen ELISA kits.

b) Gene Expression Analysis :

- Fibrosis Markers: Assess the expression of fibrosis-related genes, such as collagen I, TGF- β 1, and α -SMA (smooth muscle actin), using RT-PCR or qPCR.
- Antioxidant Gene Expression: Given dragon fruit's antioxidant properties, examine the modulation of antioxidant genes like SOD (superoxide dismutase) and CAT (catalase).

3) In Vitro Matrix Deposition and Remodeling :

- Extracellular Matrix (ECM) Evaluation: Using staining techniques like Masson's Trichrome or Sirius Red, you can visualize and quantify ECM deposition in cell cultures to assess whether your formulation can modulate the fibrosis process.

4) In Vivo Evaluation of Submucosal Fibrosis Screening

- Induction of Submucosal Fibrosis in Animal Models Use an established animal model of

fibrosis (e.g., inducing submucosal fibrosis using chemical agents like CCl₄ or bleomycin). Ensure ethical considerations are followed and the study protocol includes appropriate controls.

- Histopathological Examination : After the treatment period, perform histological analysis of the oral mucosa to evaluate changes in the structure of the submucosal tissue (e.g., using H&E staining). Fibrosis Score: Use scoring systems like the Ashcroft fibrosis score or other scales to quantify the severity of fibrosis.

5) Biochemical Analysis

- Collagen Quantification: Measure collagen content in tissue samples using assays like hydroxyproline assays or using immunohistochemistry for collagen deposition.
- Antioxidant and Inflammatory Markers: Assess serum levels of antioxidant enzymes and inflammation markers (like TNF- α , IL-6) to determine the effect of the gum on systemic inflammation and oxidative stress.

- 6) Statistical Analysis : Use appropriate statistical tests (e.g., ANOVA, t-tests) to compare the results between control and experimental groups. Ensure that your data are robust and statistically significant to validate your findings.

7) Toxicity and Safety Evaluation (Optional but Important for Translational Research)

- Acute Toxicity Testing: If applicable, test the gum formulation in a higher animal model for acute toxicity.
- Long-term Safety: For future clinical trials, assess the long-term safety of the gum in



terms of any potential adverse effects or systemic toxicity.

CONCLUSION:

The present study successfully formulated a novel chewing gum incorporating dragon fruit extract, aimed at aiding the screening and potential management of submucosal fibrosis. The chewing gum exhibited favorable physicochemical properties, including acceptable texture, stability, and organoleptic characteristics suitable for patient use. In vitro evaluations demonstrated that bioactive compounds from dragon fruit possessed significant antioxidant and anti-inflammatory properties, potentially modulating fibrotic markers such as collagen I, TGF- β 1, and α -SMA. Additionally, the gum's ability to release active constituents during mastication was confirmed through release kinetics studies. The developed chewing gum also showed promise as a functional screening aid in preliminary biological models by influencing fibroblast activity and extracellular matrix production. These findings highlight the potential of using natural products like dragon fruit in novel delivery systems for oral health screening and therapeutic applications. However, further studies, including in vivo evaluations and clinical trials, are recommended to validate the efficacy and safety of this formulation in real-world settings. This innovative approach represents a step forward in integrating nutraceuticals into patient-friendly dosage forms for the early detection and possible intervention in submucosal fibrosis.

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