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Formulation and Evaluation of Antiulcer Gel by Psidium Guajavaand Azadiracta Indicaleaves

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ABSTRACT
This study aimed to strengthen and determine the efficacy of an antiulcer gel formulated with extracts from *Psidium guajava* (guava) leaves and *Azadirachta indica* (neem) leaves. The antiulcer viable of these plant extracts is well-documented due to their wealthy phytochemical composition, along with flavonoids, tannins, and polyphenols, which possess antioxidant, anti-inflammatory, and antimicrobial properties.The gel components was prepared the usage of a appropriate gel base incorporating optimized concentrations of the plant extracts. Histopathological evaluation printed reduced ulcer severity and superior mucosal healing in handled with the gel.Overall, the developed antiulcer gel utilising*Psidium guajava* and *Azadirachta indica* leaves holds promise as a herbal and wonderful therapeutic choice for the management of peptic ulcers. The current study's investigation of *Psidium guajava*and*Azadirachta indica* leaf extract may increase drug penetration from the affected area, perhaps leading to a treatment that exhibits both antifungal and antibacterial action in the effective treatment of mouth ulcers. The created herbal composition proved more effective, safe, and stable in treating mouth ulcers than synthetic versions.The herbal gel is optimized by preparing 3 formulation (F1,F2,F3) Using the different concentration of extract *Psidium guajava*and*Azadirachtaindica*leavesextract.The prepared gel were evaluated for homogeneity, physical appearance, ph measurement, extrudability, viscosity, spredability and stability study.

Keywords: Antiulcer gel, *Pisidium guajava, Azadirachta indica,*Evaluation.

INTRODUCTION
Mouth Ulcer
An oral ulcer arises from erosion or loss of the upper mucosal layer. This is one of the most prevalent pathological conditions of the oral cavity. These sores usually hurt and are seen on the insides of the lips and cheeks most often. Mouth ulcers are suspected to occur for a variety of reasons, while their precise cause is unknown. Their development has been connected to a number of factors, including fungi, viruses, treponemal diseases, autoimmune diseases, hormonal changes, psychological stress, cancer, and others. The kind, location, duration, and frequency of mouth ulcers can all be affected by any underlying systemic issues (e.g., cyclic neutropenia, inflammatory bowel disease)[1,2].a nonkeratinized oral mucosa condition that is acutely and extremely painful is called RAS, or recurrent aphthous stomatitis. These ulcers are usually round, with an erythematous halo surrounding them and an edge that is just slightly raised. Ulcers can be classified into the following groups based on their size and quantity[3,5]

Types of Mouth ulcer

1] Minor Ulcer:

Minor ulcers are typically small, with a diameter of 2 to 8 mm, and they can heal in 10 to 14 days.

Fig. No1: Minor Ulcer

2] Major ulcers:

These are 1 cm or larger, deeper, and have elevated and wavy edges. Healing can take some weeks or months.

Fig. No2:Major Ulcer

3] Herpetiform ulcers:

These are a collection of tiny ulcers, each no larger than a pinhead. Very small ulcers, measuring 2-3 mm in diameter, can occur in huge, irregular lesions that can fuse together in numbers of 100 or more at once and remain for 7–10 days without leaving scars.[6-8]

Fig.No 3: Herpetiform ulcer

Factors responsible for the mouth ulcers

- Toothpastes and mouthwashes that contain sodium lauryl sulfate
- Emotional stress / Psychic stress
- Hormonal changes
- Nutritional deficiencies
- Mechanical trauma
- Viral infections
- Allergies and sensitivities
- Genetics
- Infectious agents (both bacterial and viral)
- Medical conditions

A mouth ulcer is a sore that develops on the soft tissue lining of the palate, lips, gums, inside cheeks, or tongue. These could hurt a lot and are frequently red or yellow. Other names for mouth ulcers are aphthous ulcers and canker sores.

Mouth ulcers are easy to recognize. They usually appear as sores on your lips, gums, tongue, inner cheeks, or roof of the mouth. Oral Ulcers frequently have a red border around the edges and a white, yellow, or grey center. One ulcer may occur, or you may develop several. Other signs and symptoms might be:

- Swelling around the ulcer.
- Increased soreness when brushing your teeth.
- Pain that worsens when eating spicy, Salty and sour food[9]

Causes

It is not known what causes mouth ulcers. However, these lesions might develop for a variety of reasons:

- Small tissue damage resulting from dental procedures, such filling a cavity.
- Biting your tongue or cheek by accident.
- Reaction to specific microorganisms causing allergies.

- Putting on retainers or braces for orthodontics.
- Deficits in vitamins.
- Applying toothpaste that is abrasive or harsh.
- Consuming a lot of acidic foods, like strawberries, oranges, and pineapples.
- Hormonal fluctuations during menstruationTension.
- Insufficient sleep.[9]

GEL

According to the I.P., gels are homogeneous, semisolid preparations that are frequently composed of solutions or dispersions of one or more drugs in suitable hydrophilic or hydrophobic bases. (2013) Vijay Kumar Singh and others.

A gel is defined by the U.S.P. as a semisolid system consisting of a dispersion of large organic molecules or small inorganic particles that are surrounded and in touch with liquid. The inorganic particles form a three-dimensional structure that resembles a "house of cards". [10]

CLASSIFICATION OF GELS:-

Gels can be classified based on colloidal phases, nature of solvent used, physical nature and rheological properties, etc.(GaireArjun et al, 2021)

1)Based on colloidal phases:-
They are classified into:
a)Inorganic (Two phase system)
b) organic (Single phase system

a)Inorganic (Two phase system)
When the partition size of the dispersed phase is fairly large and produces the three-dimensional structure throughout the gel, a system comprises floccules of small particles rather than larger molecules and a gel structure. The system is not always stable in this situation. They must be thixotropic, which means that they must form a semisolid state when not moved and turn liquid when disturbed.

b) Organic (Single phase system):
Large organic molecules scattered in a continuous phase make up this system. and can be found on twisted threads. These larger organic molecules—which can be polymers composed of synthetic or natural materials—are known as gel formers because of their propensity to randomly entangle or to be linked by van der Waals forces.

2)Based on the nature of solvent used:
a) Water-based hydrogels:
In hydrogels, water functions as a continuous liquid phase. For example, bentonite magma, gelatin, cellulosederivatives,andpoloxamergel.

b) Organic Gels (with a non-aqueous solvent):
These gels have a non-aqueous solvent in their continuous phase. Examples include low molecular weight polyethylene that has been dissolved in mineral oil and rapidly chilled, as well as metallic steel

dispersioninlubricants.

c)Xerogels:
Xerogels are solid gels that have a lower solvent concentration. When the solvent evaporates, leaving the gel structure behind when it comes into contact with fresh fluid, they are formed. Examples include acacia tears, polystyrene, dry cellulose, and tragacanth ribbons.[24]

4) Based on physical nature:

a) Elastic gels:
The fibrous molecules are held together at the junction by relatively weak interactions such as hydrogen bonds and dipole attraction. Agar gels, gum arabic, and alginates are a few examples.

b) Rigid gels:
These are gel macromolecules where a primary valence bond binds the structure together For instance:Si-O-Si-O bonds hold silica acid molecules together in silica gel, creating a polymer structure with a network of pores.[25]

5) Bases or gel forming polymers
a)Naturalpolymers:
These polymers are found in nature and can be created by living organisms. As an example, proteins like collagen, gelatin, etc., and polysaccharides like agar, tragacanth, pectin, and gum.

b)Semi-synthetic polymers:
These polymers are frequently made by reacting natural polymers chemically. Take cellulose derivatives like carboxymethyl cellulose, methylcellulose, and hydroxyethyl cellulose as an example.

c)Syntheticpolymers:
In vitro production is the method used to create synthetic polymers. Polyacrylamide, polyvinyl alcohol, copoxamer, carbomer, carbopol 940, and carbopol 934 are a few examples. (Arjun Gaire et al., 2021).

Characteristicsof Gels:

a) The gelling agent should ideally be safe, inert, and unable to react with other ingredients in the formulation.

b) When the gelling agent is stored, it should have a reasonable, solid-like consistency that breaks quickly when subjected to shear pressures generated by squeezing the tube, shaking the bottle, or applying topically.

c) An appropriate antimicrobial agent should be present.

d) The topical gel can't have any stickiness.

e) The eye gel needs to be sterile.

f) Every element of the system is continuous. (Hemendra Rathod, Sinh J, et al., 2015)

Uses of gel

a)Gels can be used as delivery mechanisms for medications taken orally.
b) For topical medications that are given straight to the eye, mucous membrane, or skin.
c) As long-acting medications that are implanted or injected intramuscularly.
d) As thickeners in oral liquid, suppository bases, protectingcollloids in suspensions, and binders in tablet granulation.
e) In cosmetics such as shampoos, dentifrices, fragrance products, and formulas for skin and hair care.
g) Catheter lubricant [11].

DRUG PROFILE

1] PISIDIUM GUAJAVA

Common Name : Guava , Yellow Guava , Apple Guava.

Biological Source : Guava is native to tropical and seems to have been growing from … MéxicotoperuPisidiumguajavaLinn belonging the familyMyrtaceae.

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Kingdom: Plantae

Order: Myrtales

Family: Myrtaceae

Subfamily: Myrtoideae

Genus: Psidium

Species: Guajava

Binomial name:*Psidium guajava* Linn

The guava plant (*Psidium guajava* L.) belongs to the Myrtaceae family. *Psidium guajava* is the most important fruit of the genus Psidium, which contains around 150 species. Guava is thought to have

originated from an area extending from southern Mexico to or widelyknown and cultivated throughout the world .[12]

Gauva leaves enriched with bioactive compounds have been gaining much attention in recant years due to their potential to lower the risk of the development of numerous chronic diseases. Seven pure compounds, quercetin, avicularin, apigenin, guaijaverin,such as antioxidant, antibacterial, and antitumor effects compared to unsulfated ones. Theuseful bioactivities of GL extract are presented in the following subsectionFlavonoids, triterpinoids, steroids, oils, lipids, carbohydrates, glycosides, alkaloids, tannins, and other constituents make up the chemical composition. Saponins. Utilized for its anti-inflammatory, antibacterial, antioxidant, and anti-cancer properties (Wang, 2014). Herbal medication is important for both medical and financial reasons. Although the use of herbal medicines has grown, industrialized and developing nations still place a high value on their safety, effectiveness, and quality. Patients are using herbal remedies more frequently because they don't have the common negative effects of allopathic medications.
It makes sense that 1.42 billion people, or one-fourth of the world's population, rely on traditional medicine to cure a variety of illnesses. Since the beginning of time, medicinal plants have been a key source of cures for illnesses affecting humans.

Chemical Composition of *Pisidium guajava* leaves

Guava leaves (GLs) are abundant in a variety of macro- and micronutrients that support good health as well as bioactive substances. 103 mg of ascorbic acid, 1717 mg of gallic acid equivalents (GAE)/g of total phenolic compounds, 18.53% protein, 12.74% carbs, 3.64% ash, 0.62% fat, and 82.47% moisture are all present in them [18].

Biological activitiesof*Pisidium guajava* leaves

1 Antioxidant Activity :

Aerobes depend on oxygen because it serves as a terminal electron acceptor during respiration, the process that produces the majority of their energy. On the other hand, a variety of illnesses in the human body, including inflammatory diseases, ischemic diseases, neurological disorders, hemochromatosis, emphysema, acquired immunodeficiency syndrome, and many more, are brought on by free radicals generated during metabolic processes [19]. The antioxidant functions of GLs are caused by the presence of phenolic chemicals, including ferulic acid, gallic acid, pyrocatechol, taxifolin, ellagic acid, and several others [20,21].

2 Antibacterial Activity :

Antibacterial qualities of guava extracts protect against both Gram-positive and Gram-negative bacteria. In vitro tests shown strong antibacterial activity of an aqueous mixture and a water-soluble methanol extract from guava leaves and bark against multidrug-resistant Vibrio cholera. They concluded that there is a possibility that this plant can lessen cholera epidemics.[23]

2]Azadirachta indica

Common Name :Neem,margasa ,nimtre or Indian lilac.

Biological source : Neem consists of the fresh ordried leaves and seed oil of Azadiracta I Indica J.Juss .Belonging the family Meliaceae.

Kingdom: Plantae

Order: Sapindales

Family: Meliaceae

Genus: Azadirachta
Species: Indica

Binomial name **:***Azadirachta indica*
The native and extensively grown Azadirachta indica, which is found throughout most of India and particularly in Bengal, is a member of the Meliaceae family of plants. Outside of India, it is referred to as neem, but the natives call it vembu. This plant is said to contain nimbidin, flavonoids, saponin, and phenolic compounds. The bitter taste of this plant isattributed to the alkaloid margosine. An oil that is yellow, bitter, and fixed makes up between 10 and 31 percent of the seeds. There are free and volatile fatty acids in the oil. The volatile fatty acids are composed of stearic and oleic acids, possibly with a little amount of lauric acid. [13]Azadirachta indica (neem) contains a number of phytochemicals, including gallic acid, epicatechin, catechin, margolone, nimbidin, nimbin, and nimbolide. Strong antibacterial qualities are shared by all of these substances. In the past, neem has been used to treat fever, skin diseases, infections, and inflammatory illnesses. Lahankar et al. used the herbs Curcuma longa, Azadirachta indica, Glycyrrhiza glabra, Sesamum indicum, and Nelumbo nucifera in a medicinal oil mixture known as "Haridradi Tail" to treat RAS. Treatment for roof of the mouth, palate, and lymph node development ulcers is found to be highly beneficial.[14]

Chemical compositionof*Azadirachta indica*

Terpenes and limonoids are two of neem's main chemical components. Azadirachtin, 1-tygloyl-3-acetyl-2-methoxyazadirachtin, 22,23-dihydro-23β-methoxyazadirachtin, nimbanal, 3-tigloylazadirachtol, 3-acetyl-salannoV nimbidio, margocin, margocinin, margocilin, and others are the main active ingredients in limonoids. Isombolazidine, nimbonone, nibonolone, methylgrevillate,

margosinone, and six nimbocinolides are terpenoids. Neem improves the liver's capacity to cleanse itself of chemical pollution by increasing the synthesis of glutathione-transferase.

Biological activities of*Azadirachta indica*

Anti-inflammatory activity:

Certain phytochemicals that are bioactive may have anti-inflammatory properties.A. indica's anti-inflammatory properties have been well researched and shown to work against both acute and chronic inflammation. Comparatively speaking, neem works better than non-steroidal anti-inflammatory medications like ibuprofen that are sold commercially. Neem has the remarkable ability to inhibit the release of tumor necrosis factor (TNF-α) and monocyte chemotactic protein-1 (MCP-1). While not as effective as aspirin, neem root also has anti-inflammatory properties.[23]

MATERIAL AND METHODES

Collection & Authentication of Plant Material:

The Plant leaves of *Pisidium guajava* and *azadiracta indica* collected from local area of PSGVPM College of Pharmacy , Shahada. Dist.-Nandurbar, Maharashtra. The herbariums of these plants were identified and authenticated by a botanist Dr. Sk. Tayade, Head Department (Caricaceae) of Botany, P.S.G.V.P Mandal's Arts, Science, Commerce College, Shahada, Dist-Nandurbar Carbopol 934, PEG 200, Methyl Paraben, Propyl Paraben,
Triethanolamine and Glycerine is of laboratory grade.

CHEMICALS

Ethanol ,Methnol, Carbopol940, Methyl paraben, Propyl paraben, Propyle glycol, Triethanolamine, Distilled water.

EQUIPMENTS

Digital balance ,ph meter ,Magnetic stirrer,Digital water bath

PREPARATION OF PLANT EXTRACT

After being cleaned of any dust particles with running tap water, the guava leaves and Azadirachta indicawere shade-dried for three to four weeks at room temperature. Using a mechanical grinder, the dried plant components were ground into a coarse powder and then sieved through a 40-mesh screen. To extract the powder's restorative extracts, ethanol, methanol, and water were used in a cold maceration process. In a separate conical flask, 500 ml of ethanol, methanol, and water were used to macerate 100 g of powdered dried guava leaves and 100 g of turmeric powder for 24 hours at room temperature with periodic shakingAfter a day, the mixture was filtered using a straightforward filtration technique, and the filtrate was gathered in several containers. A rotary vacuum evaporator operating at 45–50°C was used to extract the solvent from the filtrate under reduced pressure in order to produce the extract [15].

PREPARATION OF HERBAL GEL

Pour 15 milliliters of distilled water into a beaker, then evenly distribute the recommended dosage of carbopol 940 while stirring constantly. Set the beaker aside for 30 minutes to allow the carbopol to swell. Take 5 milliliters of distilled water and heat it on a water bath to add the necessary amount of methyl and propyl paraben. After the mixture has cooled, add Propylen glycol 400. The aforementioned combination was appropriately mixed with the Carbopol 940 gel while being continuously stirred, after an additional quantity of extract was added as needed. Finally, the formulation was volumetrically increased to 30 ml by adding the remaining distilled water, and

triethanolamine was added dropwise to get the necessary mouth skin pH (6.8–7) and to create the gel at required consistency. The same method was followed for preparation of control sample without adding any extract [16].

FORMULA FOR THE GEL

INGREDIENTS	F_1	F_2	F_3
Guava leaf extract	0.3		0.3
Azadirachta indica leaf extract		0.3	0.3
Carbopol 940 (1%)	0.3	0.3	0.3
Methyl paraben (0.2%)	0.05	0.05	0.05
Propyl paraben (0.1%)	0.03	0.03	0.03
Propylene glycol 400 (5%)	1.5	1.5	1.5
Triethanolamine (1.2%)	0.36	0.36	0.36
Glycerin (1.5%)	0.45	0.45	0.45
Distilled water	Upto 30 ml	Upto 30 ml	Upto 30 ml

EVALUTION PARAMETERS

1]

PhysicalEvalution

physical characteristics including color, scent, and Visual checks were made for uniformity.

Color:
The formulation's color was examined by visual examination

Consistency:
The formulation's consistency was verified by putting on skin.

Odor:
By combining the gel with water and smelling the result, the formulation's odor was evaluated.

2] Measurment of pH

A digital pH meter was used to measure the pH of herbal gel compositions. After weighing out one gram of gel, it was mixed with ten milliliters of distilled water and left for two hours.
Three measurements of the formulation's pH were made, and the average results are given. The gel formulation's pH was noted.

3] Homogeneity

After the gels were placed into the container, the homogeneity of each generated gel formulation was examined visually. They were examined to see if any aggregates were present and how they looked.

4] Spreadability

Spreadability is measured in terms of the number of seconds it takes for two slides to separate from a gel layer positioned in between them when subjected to a specific stress. The spreadability is better if it takes less time to separate two slides. Spreadability can be
computed using the following formula:

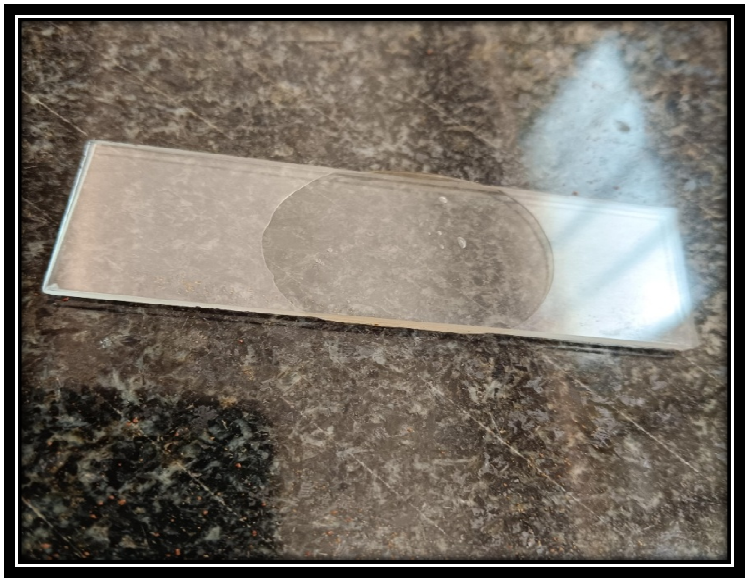

Fig.No 8 Spreadability of antiulcer gel

$S = M \times L / T$
Where
M = weight tied to upper slide
L = length of glass slides

T = time taken to separate the slides
Spreadabilty of gel formulations were reported in Table4

5] Viscosity

At 25°C, the viscosity of the prepared gel was measured using a Brookfield viscometer with spindle number 1. The gels were turned at three different speeds: 0.3, 0.6, and 1.5 revolutions per minute. The dial reading that corresponded to each speed was recorded. The produced gels' viscosity was then calculated by multiplying the dial reading by a value listed in the Brookfield Viscometer catalogs. Table 5 [17] provided information on the gel formulation's viscosity.

6] Extrudability

The gel formulations were filled in standard capped collapsible aluminum tubes and sealed to the end. The extrudability was determined by pressing of the thumb.

7] Antifungal activity

formulation and blank formulation—that is, formulation with (Zolout drug—was compared to commercially available antifungal formulation of cream). Two distinct bacterial cultures were employed, namely Aspargilious aureus and Candida albicans.
The agar well diffusion method was used to conduct the antifungal test. Prepared nutrients were provided, filled sterile Petri dishes, and allowed to cool and dry. Each bacterial culture was then dispersed using a micron wire loop after that. Drilling holes 4 mm deep was done with a sterile cork borer with a 6 mm diameter.0.5 gram of gel is added to these holes. After that, plates were incubated for 48 hours at 270 C Next, each batch Then,
for each fungal strength, the specific compound's zone of inhibition (diameter in mm) was
asses

Fig. No 9: Antiulcer activity of gel

RESULT

1] Physical Evaluation

Table No:1

Sr. no	Formulations	Color	Consistency	Odour
1	F1`	Yellowish green	Good	Characteristic
2	F2	Yellowish green	Good	Characteristic
3	F3	Yellowish green	Good	Characteristic

2] Evaluation of Measurement of pH

Table No: 2

Sr. no	Formulation	ph
1	F1	5
2	F2	5
3	F3	5

3] Evaluation of Homogeneity

Table No: 3

Sr. no	Formulation	Homogeneity
1	F1	Good
2	F2	Good
3	F3	Good

4] Evaluation of Spredability

Table No: 4

Sr.no	Formulation	Spreadability
1	F1	28.30
2	F2	28.50
3	F3	29.10

5] Evalution of Viscosity

Table No: 5

Sr.no	Formulation	Viscosity
1	F1	155030
2	F2	151730
3	F3	159040

6] Evaluation of Extrudability

Table No: 6

Sr.no	Formulation	Extrudability
1	F1	++
2	F2	++
3	F3	+++

7] Evaluation of Antifungal activity

Table No:7

Sr no	Formulation	Zone of inhibition
1	F1	12
2	F2	14
3	F3	17

CONCULSION

Natural remedies are increasingly widely accepted because of the belief that they are safer and have fewer side effects than manufactured pharmaceuticals. On the international market, there is currently a growing demand for herbal formulations. Making a herbal gel using extracts of holy basil and licorice is a really good idea. The investigation's findings demonstrated the herbal gel formulation F's significant therapeutic efficacy and suitability as a low-cost, highly promising drug delivery vehicle. As a result of the combination dosage form, the results showed that a new herbal gel formulation with potent antifungal and anti-inflammatory action had been produced. As a result, it is safe, stable, and effective for treating mouth ulcers.

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