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Formulation and Evaluation of Herbal Extract Sublingual tablet for Peanut allergy

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ABSTRACT

Rhinitis is characterised by nasal symptoms such as anterior or posterior rhinorrhoea, sneezing, nasal obstruction, and/or nose itching. Rhinitis is defined as an inflammation of the nose lining. Many days, these symptoms last for over an hour and happen for two or more days in a row. The clinical desensitisation produced by the specially formulated sublingual tablets containing peanut allergens provides a novel therapeutic alternative for the sensitive population. As of right now, there are no FDA-approved sublingual medications for food allergies, particularly peanut allergies. The clinical desensitisation produced by the specially formulated sublingual tablets containing peanut allergens provides a novel therapeutic alternative for the sensitive population. A meta-analysis demonstrated that for allergic illnesses, SLIT tablets were more effective than anti-allergic pharmacotherapies. The usage of SLIT pills was linked to remarkably low levels of daily inhaled corticosteroid use, asthma aggravation risk, and asthmatic symptoms.

KEY WORDS: Rhinitis, Inflammation, peanut allergies, Asthma

INTRODUCTION

Asthma has always been a mystery. Due in part to a rise in the number of afflicted people as well as a sharp rise in allergy awareness, allergic disorders and responses have been perceived as modern-day illnesses. Prior to the 20th century, reports of allergic response symptoms were sporadic and appeared to be caused by unidentified factors. Due to the enigmatic nature of allergies, ancient people thought that curses or bad spirits were responsible for reactions (Yazdanbakhsh, 2002). The same is true for many modern asthmatics and allergy patients as it is for many famous historical personalities. Both Seneca and Julius Caesar were known to have suffered from asthma.

Allergy

Allergy is the state of hypersensitivity to substances that are generally innocuous for most humans or animals in some cases. Allergy has been described by some as immunity "gone wrong". Von Pirquet coined the term "allergy" in 1906, and it meant "changed reactivity". "Understandable physiologic events mediated by a variety of different immunologic reactions" is the definition of allergy.A persistent overproduction of leukotrienes (lgE) in response to common environmental antigens such house dust mites, pollens, moulds, animal dander, and fungal spores is the main cause of atopic illnesses like allergic rhinitis and asthma. In order to defend oneself from future exposure, a human develops antibodies (Ab) against the pathogen or toxin upon coming into touch with it. This process is known as the immunological reaction. Allergy reaction mechanisms are not entirely understood. Ag most often localises in a specific tissue, like the cells lining the bronchial tubes or nasal passageways (Nakashima, 1990). The processes mostly mediated by Immunoglobulin E (IgE), a kind of ligand with distinct biologic features, make up this subset. 45 years later, Ishizaka and colleagues identified reagin as a new class of immunoglobulin called lgE, despite the fact that Prausnitz and Kustner had first shown the presence of serum "reagin" in allergic people in 1921 that could transfer the allergic Wheal-Flare reaction to a normal individual. The function of IgE in acute hypersensitivity syndromes has now been well studied.

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Allergic Rhinitis

Rhinitis is characterized by nasal symptoms such as anterior or posterior rhinorrhea, sneezing, nasal obstruction, and/or nose itching. Rhinitis is defined as an inflammation of the nose lining. Many days, these symptoms last for over an hour and happen for two or more days in a row (Merk et al., 1998). The most prevalent type of noninfectious rhinitis is allergic rhinitis, which is linked to a lgE-mediated immune response against allergens. It frequently manifests as ocular symptoms. Similar symptoms can be caused by a number of non-allergic disorders, including infections, hormonal imbalances, physical agents, anatomical abnormalities, and medication use. Allergy rhinitis symptoms that can be treated or resolved spontaneously include rhinorrhea, nasal blockage, nasal itching, and sneezing. When allergic rhinitis is present, postnasal drip mainly can happen either way—with extensive anterior rhinorrhea or without any noticeable anterior rhinorrhea in cases of chronic rhinosinusitis. It could just be a case of nasal blockage in preschoolers. On the other hand, nasal obstruction is extremely rarely connected to allergies when it is the only symptom. The symptoms of nonallergic rhinitis may resemble those of other patients. Two subtypes of allergic rhinitis exist: lAR and PER illness. There are two categories for allergic rhinitis severity: mild and moderate/severe.

Risk factors for allergic rhinitis include

- Family history of atopy
- Serum IgE > 100 IU/mL before age 6
- Higher socioeconomic class
- Exposure to indoor allergens such as animals hair, Aspergillus and dust mite

Classification of allergic rhinitis according to ARIA

1. Intermittent - means that the symptoms occur for 4 days a week or for 4 consecutive weeks
2. Continuous - means that the symptoms occur more than 4 days a week and for more than 4 weeks in a row
3 Mild - means that nothing happens: sleep disorders; disturbances in daily activities, leisure and/or sports;
4. Moderate/Severe - means that one or more of the following occur: sleep disturbances impairment of daily activities, leisure activities and/or sports; worsening of school or work problems

.

Occurs in up to 20% of the general population, Occurs in approximately 80% of asthmatics, AR patients have a 3-fold risk of developing asthma. It causes economic loss to the country which affects age group which decides the economy of innovation (Passalacqua, 2007). The slide break through modify the course of the disease. It is useful for contributing the economic growth of the country, physical well being of the country, population which in term will alter the physiological status promoting contributory potential.

Prevalence of the disease classification

- Severity of the disease which includes allergy rhinitis, Nas bronchitis, acute episode such as Asthmatic bronchitis
- Affected population and age wise which includes economical weaker classes, higher classes and middle class of both sexes
- Factors contributing to allergic rhinitis
- Working population, job insecurity, personal habit, obsessive with work
- Marital disharmony - A latest survey by a private press in Chennai city among IT field workers released a report stating that 60% of the married IT professionals were living single (due to work stress).

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Asthma

- Occurs in roughly 5% of the general population
- Occurs in up to 40% of AR patients.

Symptoms of Allergic rhinitis

The symptoms, which include frequent, severe, and persistent sneeze attacks, usually appear immediately or shortly after antigen exposure of the nose and palate. People who are allergic frequently have edematous nasal mucosa, which is typically pale or violet in color, as well as an abundance of clear mucus in their noses that frequently has a high concentration of eosinophils. The classic signs of a nasal allergy will appear with ongoing allergen contact. Individuals with persistent allergic rhinitis may exhibit a characteristic face appearance known as the "allergic facies". The bluish discoloration of the lower eyelids known as "allergic shiners" is caused by nasal blockage and venous congestion; the distinctive linear creases beneath the eyelid are called "Dennes lines"; and persistent nasal rubbing is indicative of the "allergic salute" and produces a prominent "nasal crease" across the nose. Sleep disturbances and "nasal speech" are brought on by persistent nasal obstruction.

Table 1. Principle Mediators Involved In Type I Hypersensitivity

Primary Mediators	**Effects**
Histamine	Increased vascular permeability; smooth muscle contraction
Serotonin	Increased vascular permeability; smooth muscle contraction
Eosinophil chemotactic factor (ECF-A)	Eosinophil chemotaxis

Secondary Mediators	**Effects**
Platelet-activating factor	Platelet aggregation and degranulation; contraction of pulmonary smooth muscles.
Leukotrienes(Slowreactive substances of anaphylaxis SRS-A)	Increased vascular permeability; contraction of pulmonary smooth muscles.
Prostaglandins	Vasodilatation; Contraction of pulmonary smooth muscles; Platelet aggregation.
Bradykinin	Increased vascular permeability; Smooth muscle contraction.

Immunomodulators.

Plant-based compounds have long been used as immunostimulants. But it wasn't until the 19th century that the isolation of the principals engaged became more prevalent. According to a 1990 research, 64% of people utilize herbal remedies to treat health issues. Nearly half of all synthetic medications on the market today are thought to have their origins in phytochemicals or be designed after them. Chemical synthesis is a defensive mechanism used by plants against infections (Golden, 2007). Numerous compounds that are efficient against microorganisms are

found in nature as anti-feedant and anti-infectant substances. For example, plants naturally produce flavonoids and hydroxylated phenols in response to infection. Because they are bitter, flavones and flavanones naturally have anti-feedant properties. The most prevalent metabolite in plants is alkaloids. It has been demonstrated that nicotine, an alkaloid derivative, possesses insecticidal properties.

Peanut induced allergy

One common food allergy that can cause life-threatening symptoms and anaphylactic reactions is peanut allergy. Clinical signs of peanut allergy can range from skin irritations to potentially fatal anaphylactic responses. The symptoms, which impact the respiratory, cardiovascular, and gastrointestinal systems, typically appear minutes after a relatively small amount of peanuts is consumed (Hafsa and Vidya, 2020). gastrointestinal systems, typically appear minutes after a relatively small amount of peanuts is consumed (Hafsa and Vidya, 2020). Additionally, in situations that are almost deadly, the upper and lower respiratory symptoms may get worse (Julie, 2019). Asthma, which ranks 28th among the main causes of the burden of diseases, is a prevalent chronic illness that affects both adults and children. One prevalent type of asthma is allergic asthma, which is brought on by allergens such as dust mites, pollen, or food items. One of the main allergens causing allergic asthma is classed as food allergies. The most common food allergies include milk, wheat, seafood, eggs, and peanuts or groundnuts. A variety of allergens found in the seeds of the Arachis hypogaea L peanut plant cause an immunological response mediated by immunoglobulin E (IgE). As of right now, sixteen peanut proteins, or Ara h proteins, are regarded as allergens to peanuts. The common consensus is that peanut allergies are caused by hypersensitivity reactions mediated by IgE(Palladino and Breiteneder, 2018).

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MATERIALS AND METHODS

Materials

The raw peanut (local market, Bhilai); Hydroxypropyl methyl cellulose (HPMC) and Mannitol (Rungta Institute of Phamaceutical Sciences Bhilai); Crospovidone, Croscarmellose Sodium and sodium hydroxide, Magnesium stearate Talc Ether, acetone and ethylenediamine tetraacetate (EDTA) Potassium dihydrogen orthophosphate ,Folin's reagent, Sodium carbonate ; Copper sulphate.

Preparation of allergen extract (Crude peanut extract)

After being purchased from the neighbourhood market, the raw peanuts underwent the following procedures: washing, cleaning, and processing (Fig. 1). Grinding: To create peanut powder, the dried crude peanuts were ground into a fine powder after drying. Defatting: In a conical flask, 50 g of peanut powder and acetone were added at a ratio of 1:3 (g: ml). After a few minutes of synchronous shaking at 4C, the upper oily layer of the conical flask was decanted. This procedure was carried out repeatedly until no colour remained. After that, it was freeze-dried, filtered through Whatman filter paper No. 1, and kept at 20 degrees Celsius in a plastic container. Extraction: To assess the impact of pH on the yield of the resultant product, a specified quantity of the defatted peanut powder was extracted in an Erlenmeyer flask with an equivalent amount of alkaline buffer in a pH range of 6.4 to 8.6. To facilitate the extraction process, protease inhibitors such ethylene diamine tetraacetate (EDTA) were also added to the buffer combination. After that, it was shaken constantly for eight to twenty hours at 4C (Koppelman, 2018). Centrifugation: To separate the soluble components, the extracted sample was centrifuged for approximately 30 minutes at

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10,000 rpm and 4C. Purification: Whatman filter paper was used to filter the centrifuged supernatant in order to remove any remaining product. Lyophilization: Using a freeze-dry system (Labconco's FreeZone 2.5 Litre), the produced crude peanut extract was lyophilized under vacuum at 50–100 microbars and stored between 60 and 70 degrees Celsius.

Standardization of the extract

Qualitative analysis

To standardise the crude peanut extract, several qualitative tests were conducted, including the Millon's test, the Xanthoproteic test, the Biuret test, and the Ninhydrin test. A UV-1700 Shimadzu double beam spectrophotometer (Kyoto, Japan) was used to measure the UV absorption. The samples were mixed evenly at 0.1 mg/mL in the appropriate extraction buffer, and at 25C, they were scanned from 240 nm to 600 nm. To determine the precise functional groups of the medication, Shimadzu (Kyoto, Japan) performed FT-IR analysis on the acquired crude peanut extract and all of the excipients.. 5.0 mL of the resulting peanut extract were injected onto a 0. 32150 mm Symmetry300 C18 5 mm particle size column (Waters, Bedford, MA) at a flow rate of 0.3 ml/min for LC (Agilent 1290 series, Agilent Technologies, Palo Alto, CA) analysis. For the separation, a gradient of 0.5% acetic acid and 0–50% acetonitrile was employed. Using a mass spectrometer (Agilent 6460 QQQ) in positive ionisation mode and a mass range scan of 200–2000 amu, mass peaks of the allergens were found. About 40 minutes is the run time.

Quantitative analysis

Using bovine serum albumin (BSA) as the standard, the protein quantification was carried out using the UV–Vis spectrophotometric approach and the conventional Lowry's method. As a blank, distilled water was utilised. 4.5 ml of Reagent A (50 ml of 2% sodium carbonate in 0.1 N sodium hydroxide + 1 ml of 0.5% copper sulphate solution) was added to the test tubes holding the various standard dilutions and sample extract, and the mixture was incubated for 15 minutes. After that, 0.5 ml of Reagent B (Folin's reagent with distilled water in a 1:2 ratio) was added, and the mixture was incubated for 30 minutes. 660 nm was used to quantify the absorbance, and the standard graph was used to estimate the protein content.

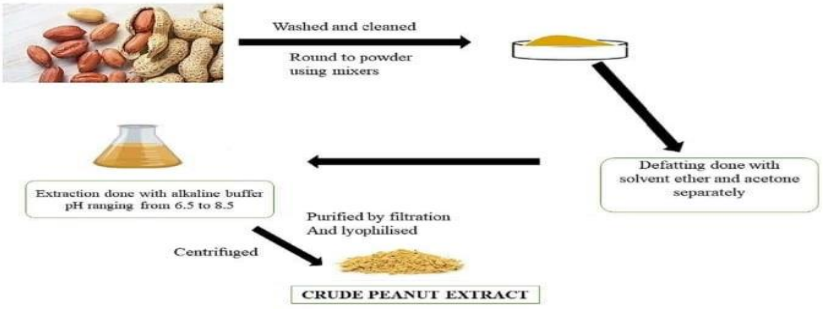

Fig.1 Method of preparation of Crude Peanut Extract

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Characterization of the extract

Evaluation Parameter

(a) Wettability

A weighed amount of powder (1 g) was kept on a glass slide, which was placed above distilled water in a small container at 25C. The powder was allowed to fall on the water surface by quickly removingthe glass slide. The time required for particles to wet was noted. The wettability was calculated as:

$w = m/t$

w is wettability in g s-1; m is the mass of sample in g; t: time in s.

(b) Hygroscopicity

The accurately weighed powder sample (±1 g) was transferred in to a container with sodium chloride saturated solution at 25C for a week, followed by further reweighing of the powder. Hygroscopicity was calculated as:

$H = A/(B*a) \times 100$

H is hygroscopicity in %; A is absorbed water mass in g; B is water content of the powder in g g-1; a is the mass of the sample in g.

(c) Apparent density

About 10 g of the peanut extract was transferred into a 10 ml measuring cylinder without tapping. Theapparent density was determined as,

$\rho a = M / Vt$

ρa is apparent density in g mL ; M is the mass of the solid in g; Vt is total volume in mL.

(d) Compact density

A 10 ml graduated cylinder was filled with a weighed mass of peanut extract. The graduated cylinder was tapped 50 times and the compact density was calculated as,

$\rho c = m / Vc$

ρc is compact density in g mL1 ; m is the mass of the solid in g; Vc is volume of the solid after compaction in mL.

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Table 1

Formulation of fast disintegrating SLIT tablets containing CPE.

INGREDIENTS	F1	F2	F3	F4	F5
DRUG	4.8	4.8	4.8	4.8	4.8
MANNITOL	127	137	147	157	167
HPMC	7.5	7.5	7.5	7.5	7.5
CROSPOVIDONE	7.5	7.5	3	-	3
MAGNESIUM STEARATE	1.5	1.5	1.5	1.5	1.5
TALC	3	3	3	3	3

Table 2

Physical characteristics of peanut extract

S. NO	ANALYSIS	OBTAINED
1	WETTABILITY (g/s)	0.006
2	HYGROSCOPICIY (%)	5.643
3	APPARENT DENSITY (g/ml)	0.362
4	COMPACT DENSITY (g/ml)	0.437

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RESULTS

Preparation of crude peanut extract

The crude peanut extract was made using a pH 8.6 buffer and a straightforward extraction technique. The yield of product produced with different pH buffers. 84.1% of the total yield of peanut extract was achieved.

Standardization of the extract

The creation of a violet-colored complex known as biuret was the outcome of peanut extract reacting with copper (II) ions. When some amino acids found in protein, including tyrosine and tryptophan, were nitrated, they formed xanthoproteic acid, which is why the peanut extract produced a yellow-colored material. When the reagent and peanut extract combined, a strong purple-blue complex was created. When the mixture boiled, its original appearance as a white precipitate turned brick red. It was discovered that the prepared peanut extract's kmax was 276.5 nm.The produced peanut extract's FT-IR spectrum revealed the presence of amide groups. The obtained peanut extract's amide functional groups attest to the existence of proteins.
Using Lowry's technique, the total protein content was estimated. It was discovered that the crude peanut extract (CPE) contained 208.86 lg of protein overall. Consequently, 20.8 mg of protein are present in 100 mg of CPE.

Characterization of the extract

The physical characterization of the prepared peanut (with skin) extract was performed, and data obtained after three replicates ± standard deviation

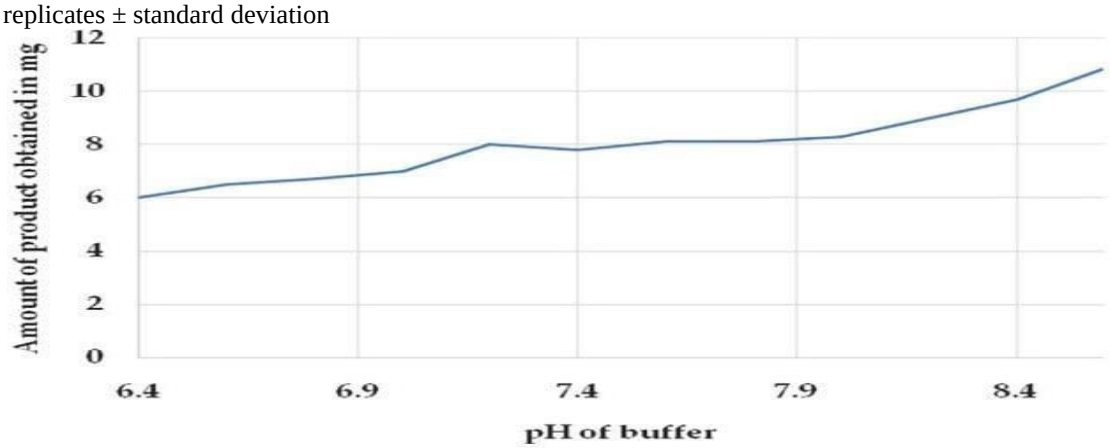

Fig. 1 Effect of pH on Product obtained

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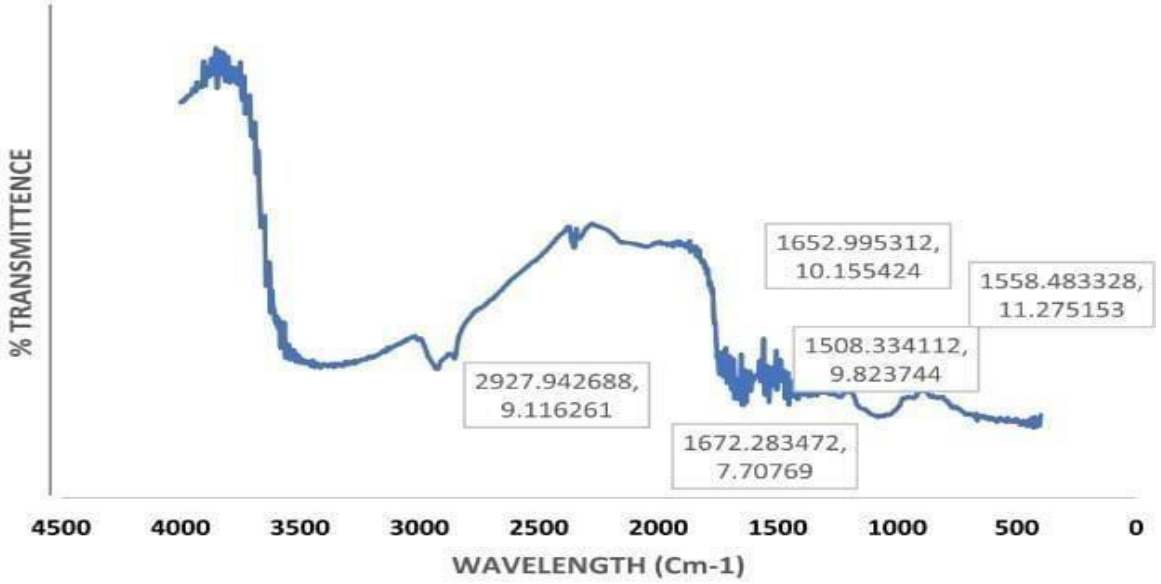
Fig.2 FT-IR of the prepared peanut extract



CONCLUSION

In western countries, around 1% of the general population and 25% of children suffer from peanut allergy. The current standard of care calls for a correct diagnosis, a strict diet free of allergens, and education for the patient and their family. There is an unmet need for additional therapeutic options because the available options for therapy are insufficient. As of right now, there are no FDA-approved sublingual medications for food allergies, particularly peanut allergies. The clinical desensitisation produced by the specially formulated sublingual tablets containing peanut allergens provides a novel therapeutic alternative for the sensitive population. A meta-analysis demonstrated that for allergic illnesses, SLIT tablets were more effective than anti-allergic pharmacotherapies. The usage of SLIT pills was linked to remarkably low levels of daily inhaled corticosteroid use, asthma aggravation risk, and asthmatic symptom. Mild oral reactions with a low risk of systemic allergic reactions are the most frequent side effects of SLIT. These data imply that SLIT pills may be used in addition to prescription medication to treat asthma. A bespoke design technique was used to optimise the SLIT tablet, which came in three doses and contained crude peanut extract. The approach examined the effects of different super disintegrant concentrations on disintegration time and dissolving. In order to identify any drug-excipient interactions, compatibility investigations using FT-IR and DSC were conducted; however, no interactions were found.

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