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Original Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF LOZENGES CONTAINING POLYHERBAL EXTRACT OF *CINNAMOMUM TAMALA* AND *SPILANTHES ACMELLA*

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Abstract In recent year, the growing demand of herbal has lead to a quantum jump in a volume of plant material traded within and across the country. *Cinnamomum Tamala* and *Spilanthes Acmella* is an important medicinal plant, commonly known as Tejpatta (*Cinnamomum Tamala*) and Akarkara (*Spilanthes Acmella*) which rich source of therapeutic constituent. The aim of this research to develop of modern dosage form such as lozenges associated with an extended period of local remedy with beneficial therapeutic effect. The combination of *Cinnamomum Tamala* leaves and *Spilanthes Acmella* flowers extract exhibit antimicrobial property against the selected microorganism *(staphylococcus aureus, streptococcus mutans and Escherichia coli)*. The qualitative Phytochemical screening of ethanol, methanol and petroleum ether extracts of both *Cinnamomum Tamala* leaves and *Spilanthes Acmella* flowers extract was performed and confirmed the presence of many phytochemicals like alkaloids, flavonoids, glycosides and triterpenes .
From the result obtained it can be concluded that the optimized formula F3 was selected for the formulation of tablet lozenges and was prepared by direct compression method which exhibit optimum friability, weight uniformity, hardness and disintegration time.

Keyword:- *Cinnamomum Tamala* and *Spilanthes Acmella* extract, antimicrobial evaluation, Phytochemical screening, lozenges, evaluation parameter.

Introduction: Herbal Medicine is as ancient as the history of mankind with well researched record. Today many consumers believe that herbal medicines are safe because they are more natural than prescription drug.

Cinnamomum Tamala ***which*** is an evergreen tree up to 8 m in height is also cultivated. Natural habitat is in the tropical and subtropical Himalayas at altitudes of 900-2500 m.[1] The essential oil from leaves of the tree is known as Tejpat oil. This essential oil is used in the

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flavouring and formulation of liquors and confections. Medicinal uses of the oil are primarily as a carminative, antiflatulent, diuretic and in cardiac diseases.[2] The leaves yield an essential oil with lemon yellow colour and clove like peppery odour. Essential oil of cinnamomum leaves has excellent inhibitory effect on bacteria.[3]

Spilanthus acmella commonly known as 'akarkara' is an annual hairy herb, up to 40-60 cm. tall with numerous stems of marigold yellow flowers. Stems are glandular and hairy with pungent taste. The whole plant is acrid in taste. Spilanthol was first isolated in 1945 from the flower head ethanol (EtOH) extract of *S.* acmella.[4] *Spilanthes Acmella* Murr. (Compositae) has been used as a traditional medicine for toothache, rheumatism and fever. Its extracts had been shown to exhibit vasorelaxant and antioxidant activities. Herein, its antimicrobial, antioxidant and cytotoxic activities were evaluated. A number of constituents had been isolated from the S. acmella, for example, spilanthol, isobutyl amid and triterpenoids.[5]

lozenges are solid unit drug delivery of one or more medicaments, usually in a flavored, sweetened base and that are intended to dissolve or disintegrate slowly in the mouth or pharynx and they have local effect.[6] Lozenges can be used as an alternative dosage form to tablets and capsules when patients are unable to swallow. Lozenges historically have been used for the relief of minor sore throat pain and irritation and have been used extensively to deliver topical anaesthetics and antibacterial. Today they are used for analgesics, anesthetises, antimicrobials, antiseptics, antitussives, aromatics, astringents, corticosteroids, decongestants, demulcents and other classes and combinations of drug.[7] The lozenges are designed not to disintegrate in the mouth but to dissolve or slowly erode over a period of perhaps 30 min or less it also depend on the patient, as patient control the rate of dissolution & absorption by sucking on lozenges until it dissolves. [8]

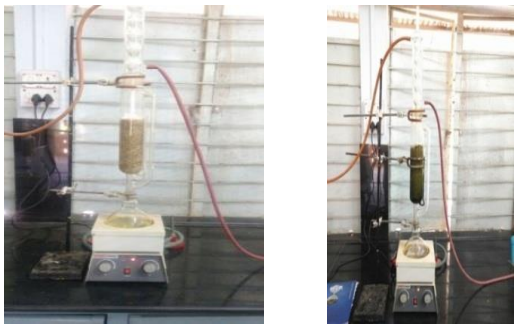
In this study for the first time we prepared lozenges dosage form containing combination of *Cinnamomum Tamala* and *Spilanthes Acmella* extract for cure the Toothache and sore throat.

Material and methods

Material: Avicel® pH 101, Polyvinyl Pyrrolidone (PVP), was purchased from Sigma Aldrich, Talc Lactose purchased from Loba Chemie Mumbai, Magnesium Stearate Fine chemical Ltd., Mumbai. *Cinnamomum Tamala* leaves & *Spilanthes Acmella* flower were purchased from the local supplier. Nutrient agar and Nutrient broth were purchased from Hi-Media Laboratories Pvt. Ltd., Mumbai. All other ingredient was of laboratory grade.

Preparation of *Cinnamomum Tamala* and *Spilanthes Acmella* extract: The *Cinnamomum Tamala* leaves & *Spilanthes Acmella* flower were collected for preparation of extract. The fresh dried plant leaves (*Cinnamomum Tamala*) and flower (*Spilanthes Acmella*) was crush & carried out with Ethanol, Methanol & Petroleum ether using soxhlet apparatus. Place it on heating mantle & heated to reflux for about 24hr. The solvent was filtered & collected in a beaker was subsequently concentrated to dryness in a room temperature to obtained extract. The dried extract was weighed & store in an air tight container for further experiment.

Fig.1. Extraction by soxhlet apparatus (a) *Cinnamomum Tamala*,(b) *Spilanthes Acmella*.



(a) **(b)**

Phytochemical screening

Detection of alkaloids: Extract were dissolved individually in dilute hydrochloric acid and filtered.

Mayer's Test: Filtrates were treated with Mayer's reagent (Potassium mercuric Iodide). Formation of a yellow colored precipitate indicates the presence of alkaloids.

Wagner's Test: Filtrates were treated with Wagner's reagents (Iodine in Potassium Iodide) Formation of brown /reddish precipitates indicates the presence of alkaloids.

Dragendroff's Test: Filtrates were treated with dragendroff's reagent (Solution of potassium Bismuth Iodide).Formation of red precipitate indicates the presence of alkaloids.

Hager's Test: Filtrates were treated with Hager's reagents (saturated Picric acid solution). Presence of alkaloids confirmed by the formation of yellow colored precipitate.

Detection of Glycosides Extract were hydrolyzed with dil. HCl, and then subjected to test for glycosides.

Modified Born trager's test: Extracts were treated with Ferric chloride solution and immersed in boiling water for about 5min.The mixture was cooled and extracted with equal volumes of benzene. The benzene layer was separated and treated with ammonia solution. Formation of rose-pink color in the ammonical layer indicates the presence of anthraquenol glycosides.

Legal's Test: Extracts were treated with sodium nitropruside in pyridine and sodium hydroxide. Formation of pink to blood red color indicates the presence of cardiac glycoside.

Detection of saponins

Froth Test: Extract was diluted with water to 20 ml and this was shaken in graduated cylinder for 15 minutes. Formation of 1 cm layer of foam indicates the presence of saponins.

Foam Test: 0.5 gmof extract was shaken with 2 ml of water. If foam produce persists of 10 minutes it indicates the presence of saponins.

Detection of phenol

Ferric chloride test: Extracts were treated with 3-4 drops of ferric chloride solution. Formation of bluish black color indicates the presence of phenols.

Detection of tannins

Gelatin test: To the Extracts, 1%gelatin solution containing sodium chloride was added. Formation of white precipitate indicates the presence of tannins.

Detection of flavonoids

Alkaline reagent test: Extracts were treated with few drops of sodium hydroxide solution. Formation of intense yellow color, which becomes colorless on addition of dilute acid, indicates the presence of flavonoids.

Lead acetate Test

Extracts were treated with few drops of lead acetate solution. Formation of yellow color precipitate indicates the presence of flavonoids.

Detection of protein and amino acids

Xanthoproteic Test: The extract were treated with few drops of conc. Nitric acid formation of yellow color indicates the presence of protein.

Ninhydrin Test: To the extract, 0.25% ninhydrin reagent was added and boiled for few minutes. Formation of blue color indicates the presence of amino acid.

Detection of Diterpenes

Copper acetate Test: Extracts were dissolved in water and treated with 3-4 drops of copper acetate solution. Formation of emerald green color indicates the presence of Diterpenes.

Isolation of *Cinnamomum Tamala* and *Spilanthes Acmella* extract by TLC method

A small amount of Cinnamomum. Tamala and *Spilanthes Acmella* extract taken & dissolve in methanol. A sample was spotted on TLC plate & place in a beaker consisting N-Hexane: Ethyl acetate (2:1) as mobile phase for *Cinnamomum Tamala* and Benzene: Ethyl acetate (9.5:0.5) as mobile phase for *Spilanthes Acmella*. It was run till $3/4^{th}$ of the plate, and then placed in iodine chamber. It gives color spots.

$$Rf = \frac{\text{Distance traveled by the compound}}{\text{Distance traveled by the solvent front}}$$

Antimicrobial evaluation of *Cinnamomum Tamala* and *Spilanthes Acmella* extract

Selection of Antibiotics and Microbial strains

The different classes of antibiotics are divided according to the part of the bacterium that is targeted. For example, all antibiotics in the penicillin class (tetracycline, ampicillin etc.) block the formation of the external waxy layer of some bacteria. Other classes of antibiotics target other essential parts of the bacteria, including components necessary for its structure, cell division, & protein synthesis. Bacteria were divided into two types, depending on their external structure. Gram-positive bacteria have thick waxy layer, whereas Gram-negative bacteria have an extra fatty layer that can act as a barrier against some antibiotics which is important to understand the structures to determine which antibiotic can pass through the barrier. Some classes of antibiotics can pass through the barrier. Some classes of antibiotics can also target this external structure, damaging them enough to either stop their growth or to kill them.

In the present study the selected bacterial strains were of gram positive bacteria Staphylococcus aureus, Streptococcus mutan & gram negative bacteria Escherichia coli. The tetracycline antibiotic was selected for comparing antimicrobial activity of prepared extract of *Cinnamomum Tamala* & *Spilanthes Acmella*.

Culture media preparation: The microbiological media prepared as standard instruction provided by the HI-MEDIAL laboratories Pvt. Ltd., Mumbai. The medium used for antibacterial activity were Nutrient Agar and Nutrient Broth. They were prepared by suspend 1.3gm in 100ml of distilled water. Heat if necessary to dissolve the medium completely. Sterilized at 121ºC at 15 psi for15-30 minutes in autoclave.

Preparation of standard and extract: The stock solution of *Cinnamomum Tamala* , *Spilanthes Acmella*, combination of both extract & std. drug (tetracycline) was prepared by dissolving DSMO for study with the conc. 0.1%.

Determination Zone of Inhibition: Zone of inhibition was determined using Agar-well diffusion method. Sterile petri plates were aseptically inoculated with 0.1ml of suspension of the test organism E.Coli, S. aureus and *S.Mutans* in a petri dish and 20ml of the culture media poured into it under aseptic condition using laminar air flow. The mixture was swirled gently to mix and allowed to solidify.

Using the sterile flamed cork-borer, well were bored on the seeded agar plates, discarding the removed agar rings into the disinfectant solution, the wells were aseptically filled with the extracts of S. Acmella, C.tamala t& combination of both. The plates were allowed to stay for 30 min. in refrigerator for diffusion & then incubation to allow for diffusion of the micro-organisms. The plates were incubated at 37^0C for 24 hours. After 24hr. the diameter of clear zone of inhibition produced around the well or holes were measured & compared with standard drug.

Formulation of Compressed tablet lozenges: The tablet technique employed is direct compression. The following excipients were employed: *Cinnamomum Tamala* & *Spilanthes Acmella* extract as active ingredient, Avicel(R) as disintegrant, polyvinyl pyrrolidone (PVP) as binder, magnesium stearate as lubricant, talc as anti-adherent and glidant, and lactose as bulking agent. The formula for each batch, percentage composition and weight of ingredients for each batch is as shown in Table.1. The required quantities of the ingredients were weighed and mixed thoroughly for 5 minutes. Each resultant batch was exposed to heat (40^0C) for 30 minutes to reduce the moisture content.

Table 1. Formulation of *Cinnamomum Tamala* & *Spilanthes Acmella* compressed tablet lozenges.

Batch	Extract	Avicel ®	Polyvinyl Pyrrolidone	Magnesium stearate	Talc	Lactose
F1	0	50	15	5	5	415
F2	100	60	25	5	5	305
F3	100	50	25	5	5	315
F4	100	40	40	5	5	310
F5	100	60	40	5	5	290

Unit weight of tablet 500mg

Evaluation parameter

Pre-compression study

Angle of repose:

Angle of repose was measures the resistance to particle flow, was determine by a fixed funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the heap of the blend. Accurately weighted powder were allowed to pass through the funnel freely on to the surface. The height & diameter of the powder cone was measured & angle of repose was calculated using the following equation:

$$\theta = \tan^{-1} h/r$$

Where, h/r is the surface area of the free standing height of the powder heap that is form on a graph paper after making the powder flow from the glass funnel.

Bulk density and Tapped density: A quantity of 2 gm. of power blend form each formula, was introduced in to 10ml measuring cylinder. After that the initial volume was noted & the cylinder was kept in a tapped density apparatus. Tapping was continuous until no further change in volume was noted. Bulk density & tapped density were calculated using the following equation as follow,

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Bulk volume of powder}}$$

$$\text{Tapped density} = \frac{\text{mass of power}}{\text{Tapped volume of power}}$$

Compressibility Index: The compressibility index of the powder blend was determining by Carr's compressibility index. It is a simple test to evaluate the bulk density & tapped density of a powder & the rate at which it packed down. The formula for Carr's index is as below:

$$\text{Carr's index} = \frac{\text{TD-BD}}{\text{TD}} \times 100$$

Hausner'sratio (HR): This was calculated as the ratio of tapped density to bulk density of the sample

$$\text{Hausner's ratio (HR)} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Post compression study:

Hardness test: The hardness test on the compact was carried out using a Monsanto Tablet Hardness tester to measure the force required to break a tablet when a force generated by a coiled spring is applied diametrically.

Friability test: The friability test was conducted using Roche Friabilator, using 6 tablets for each batch with 100 revolutions (i.e. 25 revolutions per minute for 4 minutes). The tablets were dedusted, weighed together (W0) and friabilated. The friabilated tablets were re-weighed (W1).

Friability was calculated as follows:

F = {Wo-W1/W0} x 100%

Thickness: The thickness of each tablet was measured using micrometer screw gauge and expressed in mm.

Weight uniformity tests: A quantity of 10 tablets was randomly selected from each batch. 10 tablet of the formulation were weighed using an electronic balance & the test was performed

according to the USP. A quantity of 10 tablets was randomly selected from each batch weighted individually to determine weight variation.

$$\text{Percent deviation} = \frac{W_{avg} - W_{initial}}{W_{avg}} \times 100$$

Where,

$\mathbf{W_{avg}}$ = Average weight

$\mathbf{W_{initial}}$ = Initial weight

Disintegration time test: The disintegration time of the tablet was determined in distilled water at 37 + 0.5 ºC. A tablet was placed on the wire mesh just above the surface of the distilled water in the test tube and the unit was switched on simultaneously with a stop clock. The time taken for the tablet to disintegrate and all particles to pass through the wire mesh was recorded as the disintegration time.

Results and Discussion

Observation of *Cinnamomum Tamala* and *Spilanthes Acmella* extract for Phytochemical screening: The data pertaining to the various constituent present in extract of plant material are shown in the table.2 and 3.

1. Petroleum ether extract of *Cinnamomum Tamala* showed presence of proteins & *Spilanthes Acmella* showed absence of any constituent.
2. Methanolic extract of *Cinnamomum Tamala* showed presence of alkaloid, flavonoids, triterpenes & *Spilanthes Acmella* showed presence of alkaloid, glycoside, flavonoids, triterpenes.
3. Ethanolic extract of *Cinnamomum Tamala* showed presence of alkaloid, flavonoids, triterpenes, & *Spilanthes Acmella* showed presence of alkaloid, glycoside, flavonoids, triterpenes.

Evaluation by TLC method

Evaluation of *Cinnamomum Tamala* :

Stationary phase : - Silica gel G
Mobile phase : - N-Hexane: Ethyl acetate(2:1)
Spraying agent : - vanillin-sulphuric acid reagent

Evaluation by TLC in *Spilanthes Acmella*:

Stationary phase : - Silica gel G
Mobile phase : - Benzene: Ethyl acetate (9.5 : 0.5)
Spraying agent : - vanillin-sulphuric acid Reagent

Table 2. Preliminary phytochemicals screening with various extract of *Cinnamomum Tamala* leaves

Constituents	Pet. ether	Methanol	Ethanol
Alkaloids	-	+	+
Glycosides	-	-	-
Flavonoids	-	+	+
Phenolic group	-	-	-
Proteins	+	-	-
Tannins	-	-	-
Triterpenes	-	+	+
Saponines	-	-	-

+ Present, - Absent

Table 3: Preliminary phytochemicals screening with various extracts of *Spilanthes Acmella* flowers

Constituents	Petroleum ether	methanol	Ethanol
Alkaloid	-	+	+
Glycosides	-	+	+
Flavonoids	-	+	+
Phenolic group	-	-	-
Proteins	-	-	-
Tannins	-	-	-
Tirterpenes	-	+	+
Saponins	-	-	-

+ Present, - Absent

Table 4. Isolation of *Cinnamomum Tamala* and *Spilanthes Acmella* extract

Extract	Color of spot after elution	Rf value standard	Observed value
Cinnamomum Tamala	Light-purple	0.5	0. 4
Spilanthes Acmella	Red-Pink	0.57	0.48

In TLC studies different spot are observed in *Cinnamomum Tamala* & *Spilanthes Acmella* extract. The *Cinnamomum Tamala* were found at 0.4 showing light-purple color & *Spilanthes Acmella* were found at 0.48 showing Red-pink color. It was observed that the spot at 0.4 was found to be of Eugenol & spot at 0.48 was of Spilanthol & were found to be well separated.

Antimicrobial activity of extract

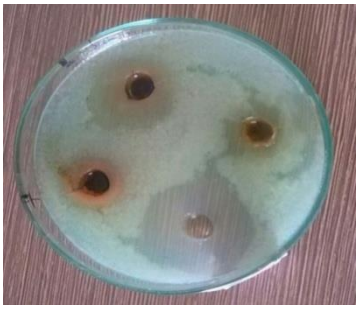
The alcoholic extract of *Cinnamomum Tamala* & *Spilanthes Acmella* were screened for antimicrobial activity.

Table 5. Antimicrobial activity of *Cinnamomum Tamala* & *Spilanthes Acmella* extract

Diameter Zone of inhibition in mm			
Extract (0.l %)	S. aureus	E. coli	S. mutans
Cinnamomum Tamala	19	18	17
Spilanthes Acmella	21	19	19
Combination of C. Tamala & S. acmella	26	24	26
Std. drug (Tetracycline)	33	33	33

Fig: 2. Zone of Inhibition of C. Tamala, S. acmella, Combination of both & Std. drug (Tetracycline) against (a) E.Coli, (b) *S.Aureus*, (c) *S.Mutans*

(a)



(b)

(c)

The antimicrobial activity of different extracts of *Cinnamomum Tamala* , *Spilanthes Acmella*, Combination of both & Std. drug (tetracycline) were tested for different strains of bacteria & zone of inhibition was recorded. In table no.5. shown antimicrobial activity of different extract against tested microorganisam & Fig.2. shown the zone of inhibition of various extract.

The antimicrobial activity of C. Tamala extract was studied comparatively onE.coli, *S.aureus*, *S.mutan*. The C. Tamala extract was showed greater antimicrobial activity on tested microorganism, S. aureus than E.coli & *S.mutans*. The antimicrobial activity of S. Acmella extract was studied comparatively on E. coli, *S.aureus*, *S.mutan*. The S. Acmella extract was showed equal antimicrobial activity on tested microorganism, E.coli, *S.mutans* & more against *S.aureus*.

The antimicrobial activity of std. drug was studied comparatively on E. coli, *S.aureus*, *S.mutan*. The zone of inhibition of std. drug

(Tetracycline) shown equal activity of test microorganisms & greater activity than extract. The antimicrobial activity of Combination of both exract (*C. Tamala* & *S. Acmella* extract) was studied comparatively on *E. coli*, *S.aureus*, *S.mutan*. The combination of both extract was showed greater antimicrobial activity on tested microorganism, E.coli, *S.mutans* & *S.aureus* than single one, & that was shown the greater zone of inhibition.

It indicates the combination of both extract was effective against the E. coli, *S.aureus*, *S.mutans*.

Evaluation of pre-compression studies

Table 6. Flow & density parameter of the powdered mix:

Batch	Angleof repose (^{0})	Bulk density g/cm^3	Tap density g/cm^3	Hausner's ratio	Carr,s index %
F1	37.95	0.62	0.83	1.33	25.30
F2	36.86	0.66	0.83	1.25	20.41
F3	35.37	0.68	0.83	1.22	18.07
F4	36.86	0.68	0.86	1.26	20.93
F5	35.37	0.66	0.83	1.25	20.41

The results obtained for the evaluation of flowability and density of the powdered mix is presented in Table 6. As a general guide Angle of repose 30-40 has a passable flow property. The powered mix showed passable flow property of the Carr's index & Hausner,s ratio. These formulations indicated passable flow property for all the batches. The value of pre-compressional parameter evaluated was found to be within prescribed limit, indicate the suitability for compression process.

Evaluation of post-compression studies

Tablets were for evaluated hardness, friability, thickness, diameter, weight variation & disintegration time. Results of all parameter are mentioned along with a standard deviation in table 7.

Table7. post-compression studies of tablet

Batch	Weight variation (mg)	Thickness (mm)	Diameter	Hardness (kg/cm^2)	Disintegration time (min)	Friability (%)
F1	492±1.42	4.93±0.15	11.2±0.02	4.31±0.04	1.42±0.02	0.8
F2	481±0.62	4.94±0.02	11.17±0.01	5.40±0.05	32.45±0.02	0.6
F3	494±0.20	4.9±0.05	11.14±0.01	5.67±0.02	24.33±0.03	0.5
F4	494±0.20	4.95±0.4	11.16±0.02	6.34±0.02	29.21±0.04	0.4
F5	496±0.80	4.94±0.02	11.16±0.02	5.82±0.02	26.33±0.03	0.4

Mean ±S.D. *n=3

As per pharmacopoeia limit, the percent deviation of ± 5% is allowed to approximately 500mg average weight. No more than two of the individual weight deviates from the average weight by more than 5% deviation. The weight variation of all batches was found to be in the range of 481±0.62 to 496±0.80 which was found to pass the specific limit. Thickness was found to be in the range 4.9±0.05 to 4.95±0.4mm& diameter was found to be in the range 11.2±0.02 to 11.17±0.01mm.

The standard acceptable range for the tablet hardness is 5-10kg/cm^2. Hardness of tablet was found to be in the range of 4.31±0.04 to 6.34±0.02 kg/cm^2. All the prepared batches except F1. Passed the hardness test. The standard acceptable range for disintegration time is 30 min. The prepared batches have disintegration time was found to be 24.33±0.03 to 29.21±0.04 which was found to pass the specific limit, expect batch F1& F2. The friability of all batches was found to be in range

of 0.4 to 0.8 which was found to pass the specific limit.

Conclusion: The present study was carried out in order to develop lozenges of *Cinnamomum Tamala* & *Spilanthes Acmella* extract for the treatment of sore throat & toothache. The combination of *C. Tamala* & S. acmella extract exhibit antimicrobial property against the selected test microorganisam (E. coli, S. Aureus S. Mutans).

From the result obtained it can be concluded that the Optimized formula F3 was selected for the formulation of ethanolic extract of tablet lozenges. The optimized formula was prepared by direct compression & exhibited optimum friability, weight uniformity, hardness & disintegration time with less amount of binder use.

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