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Formulation Development and Evaluation of Herbal Cream for Candidiasis

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ABSTRACT: The present work describes the formulation and evaluation of topical herbal cream prepared from the leaf extract of *Camellia sinensis* effective against the yeast *Candida albicans*. The physicochemical and phytochemical screening was performed for the extract along with antifungal activity and minimum inhibitory concentration. The herbal cream was optimized using different concentrations of white petrolatum and lanolin as independent variables; Spreadability, viscosity, zone of inhibition, and % drug release as dependent variables using 3^2 factorial designs. The optimized formula was evaluated by different parameters like anticandidal activity, pH, Spread ability, viscosity, homogeneity, consistency, acid value, saponification value, thixotropy study, *in vitro* drug release study, comparison with marketed formulation, skin irritation study, and stability study. FTIR study showed compatibility of excipients with the extract. The optimized formulation was found brown, having a characteristic odor, pH 6.7, zone of inhibition was 14.96 ± 0.11 mm, Spreadability 15.13 gm.cm/sec, viscosity 1556 cps, homogenous, consistency 5.5 mm, acid value 0.66 and saponification value 185. The drug release was found to be 84.41 % over 180 minutes. Further, an animal study showed no skin irritation, and the prepared formulation was found to be stable. *Camellia sinensis* extract showed good antifungal activity against the yeast *Candida albicans*.

Keywords: *Camellia sinensis*, *Candida albicans*, Candidiasis, herbal cream, herbal formulation.

INTRODUCTION

Fungal infections of the skin, hair, or nails affect 25 % of the world's population (~1.5 billion) (Havlickova *et al*., 2008). Candidiasis is a fungal infection caused by yeast that belongs to the genus Candida. There are over 20 species of Candida yeast that can cause infection in humans, the most common of which is *Candidaalbicans* (Fallis *et al.*, 2013). Candida yeast normally lives on the skin and mucous membranes without causing infection, however, overgrowth of these organisms can cause symptoms to develop. It affects 5 - 7 % of newborns, 9 – 13 % of AIDS patients, and 20 % of cancer patients (Havlickova *et al.*, 2008). The common cause of Candidiasis may be the frequent use of antibiotics that destroy harmful and disease-causing microorganisms in the body, but may also destroy the beneficial microorganisms which help keep the growth of fungi (yeast) in check. It is also recorded that untreated candidiasis infections resulted in systemic infection with the involvement of other internal organs. Furthermore, this infection is common to occur in immunocompromised individuals like in patients with leukemia, or lymphoma as they consumed corticosteroids or cytotoxic drugs which compromised their immunity. Antibiotic usage, diabetes, pregnancy, use of oral contraceptives, HIV, TB, and hypoparathyroidism are other conditions where candidiasis is found infect commonly. Patients with Xerostomia in which they are in absence of antifungal proteins like histatin and calprotectin are liable to get candidiasis more commonly than other individuals. The most common antifungal agents recommended for candidiasis are derivatives of azoles, Echinocandins, polyenes, nucleoside analogs like flucytosine and allylamines, and thiocarbamates are also known to have antifungal activities (Vanani *et al.*, 2019). The destruction of these microorganisms may lead to uncontrolled multiplication resulting in yeast infection. Other causes may be metabolic disturbances like diabetes, weakened or undeveloped immune systems, people working in wet conditions, etc (Armayanti *et al*., 2021; Lawton, 2018). The clinical manifestations include rashes (area of reddening, usually itchy), red or purple patches (area with an altered surface), white substance over the affected area, scaling (shedding of the skin with flakes), cracking (cracks in the skin), soreness, erythema (area of redness), maceration (appearance of soft white skin) and creamy satellite pustules at margins of affected areas (pimples filled with pus) (Armayanti *et al*., 2021; Lawton, 2018).

Herbal drugs are defined as a branch of science where plant-based formulations are used to treat diseases. It is also known as phytomedicine or botanical medicine. In the earlier times, when analgesics and antibiotics were not yet discovered herbal medicines were used as the primary healthcare system. Recently a shift has been observed in the universal trend from synthetic back to herbal medicine, which can be said "Return to Nature". The search for eternal health, longevity, and remedies to relieve pain and discomfort made man explore his surrounding and found the use of many plants, minerals, and animal products, etc. for the development of various therapeutic agents (Diorio *et al.*, 2020; Sharma *et al.,* 2008). *Camellia sinensis* L. (Green tea) is an important commercial plant that is produced in over 30 countries and has been consumed worldwide primarily as a beverage made from processed lead (Rha *et al.,* 2019). It contains a broad spectrum of active ingredients like polyphenols, methylxanthines, flavanols, amino acids, glycosides, etc. The amount of catechins is higher in green tea as compared to other varieties which area rich dietary source. These compounds in green tea are well known for their broad spectrum of biological activities such as antidiabetic, anti-carcinogenic, antioxidant, anti-inflammatory, anti-hypertensive, and antitumor functions. Recent research has shown *Camellia sinensis* to have a wide range of antimicrobial activity (LIczbiński and Bukowska 2022; Mabe *et al*., 1999; Sakanaka *et al.*, 2000).

MATERIALS AND METHODS

Materials: Candida albicans (MTCC, Chandigarh), *Camellia sinensis* (Hindustan Biosynth Ltd.), White petrolatum, Liquid paraffin (AaturInstru Chem), Lanolin, Triethanolamine (Chemdyes), Stearic acid (Suvidhinath laboratory), Propylene glycol (Qualikems), Tween 60 (Krishna-Chem), Methylparaben (Oxford laboratory), Propylparaben (Chiti-Chem Corporation), Potato Dextrose Agar medium, Sabouraud Dextrose Agar medium (HIMEDIA).

Physicochemical characteristics (Natekar *et al.,* 2022; Xue-Feng *et al.,* 2011)

The percentage of moisture content, ash value, acid insoluble ash, water soluble ash, alcohol extractive value, and water extractive value of *Camellia sinensis* extract was determined according to WHO guidelines on quality control methods for medicinal plant materials (Table 3).

Phytochemical screening (Natekar *et al.,* 2022; Xue-Feng *et al.,* 2011)

The extract was tested for phytochemicals present in the extract as per the textbook of Practical Pharmacognosy for the detection of alkaloids, carbohydrates, glycosides, tannins and phenolic compounds, steroids, flavonoids, and saponins (Table 4).

FTIR Study. The FTIR study of *Camellia sinensis* was carried out using a pressed pellet technique in which KBr was dried in a hot air oven and this dried KBr was used for the preparation of pellets of extract. The prepared pellet was placed in a sample holder and the scanning range used was 4000 to 400 cm^{-1} to obtain the spectra (Table 5 and Fig. 1).

Determination of antifungal activity (**Satpathy *et al.*, 2011)**

Standard: -Amphotericin B
(500 µg/ml, 1000 µg/ml, 1500 µg/ml)

Test solution: -*Camellia sinensis* leaf extract
(500 µg/ml, 1000 µg/ml, 1500 µg/ml)

Sabouraud dextrose agar acquired from HIMEDIA was used as a medium. It was filled in tubes and sterilized by autoclave. These tubes were stabilized at 45°C and seeded with 0.1 ml of a broth culture of *Candida albicans*. After complete mixing, these tubes were poured into sterile petri-plates and allowed to be set at room temperature. Wells were bored using a sterile borer size 5 and an internal diameter of 10 mm. Each well was filled with different concentrations of *Camellia sinensis* leaf extract aqueous solution. These plates were incubated overnight at 25°C and observed for the zone of inhibition after 24 hrs, 48 hrs, and 72 hrs (Table 6 and Fig. 2).

The same procedure was carried out for the standard solution of Amphotericin B prepared in methanol.

Determination of MIC (P. Sharma *et al.*, 2021). Different concentrations of *Camellia sinensis* extract were prepared. Potato Dextrose Agar (PDA) medium was taken in test tubes and 200, 400, 600, and 800 µg/ml concentrations of *Camellia sinensis* extract were added to it. The control test tube was used having only PDA (without extract). In each of these test tubes, 10^3 cells of *Candida albicans* in 0.02 ml volume were added. These test tubes were poured into sterile petri-plates and incubated at 28°C for 72 hrs. The number of colonies was then counted and the concentration that showed zero colonies was considered MIC.

Standard calibration curve. 100 mg *Camellia sinensis* extract was diluted upto 100 ml with phosphate buffer pH 7.4 (1000 µg/ml). Different aliquots of 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 ml were transferred to a volumetric flask and diluted upto 10 ml with phosphate buffer pH 7.4 (50 - 300 µg/ml respectively). The absorbance was measured at 274 nm using phosphate buffer pH 7.4 as a blank solution using a UV spectrophotometer (Table 7 and Fig. 3).

Preparation of cream formulation: The oil phase was prepared by dissolving oil-soluble components (White petrolatum, liquid paraffin, lanolin, stearic acid) at 75°C. The aqueous phase containing extract was also prepared by dissolving water-soluble components (Propylene glycol, triethanolamine, tween 60, methyl paraben, propyl paraben) and heated at 75°C. After the oil phase and aqueous phase reached the same

temperature, the oil phase was added to the aqueous phase with continuous stirring until the mixture cooled. 3^2 factorial design was used and the parameters Spreadability, viscosity, zone of inhibition, and % drug release were evaluated for optimization of the batch using Design Expert software 10.0.0.

Table 1: Composition of cream formulations based on factorial design.

	White Petrolatum	Liquid Paraffin	Lanolin	Stearic acid	Propylene glycol	Triethanolamine	Tween 60	Methyl Paraben	Propyl Paraben	Water (upto 100ml)
F1	0.6	8.3	0.6	16.7	3.5	1.0	5.0	0.18	0.02	q.s
F2	0.6	8.3	0.8	16.7	3.5	1.0	5.0	0.18	0.02	q.s
F3	0.6	8.3	1.0	16.7	3.5	1.0	5.0	0.18	0.02	q.s
F4	0.8	8.3	0.6	16.7	3.5	1.0	5.0	0.18	0.02	q.s
F5	0.8	8.3	0.8	16.7	3.5	1.0	5.0	0.18	0.02	q.s
F6	0.8	8.3	1.0	16.7	3.5	1.0	5.0	0.18	0.02	q.s
F7	1.0	8.3	0.6	16.7	3.5	1.0	5.0	0.18	0.02	q.s
F8	1.0	8.3	0.8	16.7	3.5	1.0	5.0	0.18	0.02	q.s
F9	1.0	8.3	1.0	16.7	3.5	1.0	5.0	0.18	0.02	q.s

Evaluation test:

Anticandidal activity

Same as described above.

pH (Giradkar and Rode 2021). One gram cream formulation containing *Camellia sinensis* extract was weighed and added to 50 ml water and shaken well. This solution was filtered and used for pH determination using a pH meter that had been previously calibrated.

Spreadability (Abd El Aziz *et al.*, 2019). The spreadability of formulations was determined by an apparatus, which consisted of a wooden block, with a fixed glass slide and a movable glass slide with one end tied to the weight pan rolled on the pulley, which was at a horizontal level with a fixed slide.

Spreadability (S) = M × L / T

Where,

M = weight tied to upper slide

L = length of glass slide

T = time taken to separate the slide from each other

Viscosity (Kolesnikov *et al*., 2020; Richtering, 2019). The viscosity of the formulated creams was determined using a Brookfield viscometer using spindle no. S64 at 100 rpm. About 100 gms of cream was taken for measurement and the temperature was maintained at around 20°C.

Homogeneity (Abd El Aziz *et al.*, 2019). The formulation was tested by pressing a small quantity of cream between the thumb and index finger. The consistency of the formulation and the appearance of coarse particles on the fingers were used to evaluate the homogeneity of the formulations.

Consistency (Abd El Aziz *et al.*, 2019). The measurement of the consistency of prepared cream formulations was done by dropping a cone attached to a holding rod from a fixed distance of 10 cm in such a way that it falls on the center of the glass cup filled with the cream. The penetration by the cone was measured from the surface of the cream to the tip of the cone inside the cream. The distance traveled by the cone was noted down after 10 seconds.

Acid value. 10 grams cream formulation was dissolved in a 50 ml mixture of an equal volume of alcohol and solvent ether, the flask was collected to a reflux condenser and heated slowly until the sample was completely dissolved. To this solution, 1 ml of phenolphthalein was added and titrated with 0.1 N KOH until the appearance of faint pink color.

Acid value = n × 5.61 / w

Where,

n = the number of ml of KOH required

w = the weight of the substance

Saponification value. 2 grams of the cream formulation was refluxed with 25 ml of 0.5 N alcoholic KOH for 30 minutes. To this, 1 ml of phenolphthalein was added and immediately titrated with 0.5 N HCl.

Saponification value = (b – a) × 28.05 / w

Where,

a = volume of titrant in ml

b = volume of titrate in ml

w = weight of the substance in gm

Thixotropy study (Vinod *et al.*, 2011). A fixed quantity of 10 gms cream was taken in a 10 ml beaker and kept intact for 1 hour. The beaker was inclined to one side and observed whether the cream was liquefied or not. After that, the beaker was shaken to and fro for continuous 5 minutes and again the beaker was tilted and checked for consistency and pourability.

In-vitro drug release study (Ansari, 2021; Baudonnet *et al.*, 2004). A glass cylinder with both ends open, 7 cm height, 2.1 cm outer diameter, and 1.7 cm inner diameter was used as a permeation cell. A cellophane membrane prehydrated with distilled water (24 hrs before use) was fixed to one end of the cylinder with the help of thread to form a permeation cell.

One gram of cream formulation was taken in the cell (donor compartment) and the cell was immersed in a beaker containing 80 ml of phosphate buffer pH7.4 as receptor compartment. The cell was immersed to a depth of 1 cm below the surface of receptor fluid. The medium in the receptor compartment was agitated using

a magnetic stirrer and 37°C ± 17°C temperature was maintained.

The required amount of sample (5 ml) was withdrawn at a predetermined time interval and the sample volume was replaced by a fresh solution in the receptor compartment. The withdrawn sample was analyzed by UV spectrophotometer at 274 nm along with required dilutions.

Skin irritation study (**More *et al.*, 2013; Premkumar *et al.*, 2015).** A skin irritation study was performed (proposal number-OGECT/PPDC/IAEC/2016/12/4) on an Albino rabbit weighing 1.5 – 2.5 kg. A single rabbit was used for the study.

The hair from the back of the rabbit was shaved off and the region was divided into three different areas, first as control, second for *Camellia sinensis* extract containing cream, and third area for the blank cream base (without extract).

The observations for erythema and edema were made after 0, 24, 48, and 72 hours and recorded according to the scoring. (Fig. 4 and 5)

Table 2: Classification system for skin reaction.

Reaction	Score
Erythema	
No erythema	0
Very slight erythema	1
Well defined erythema	2
Moderate to severe erythema	3
Severe erythema (beet redness) to scar formation	4
Edema	
No edema	0
Very slight edema	1
Well defined edema	2
Moderate edema	3
Severe edema	4
The total possible score for primary irritation	**8**

Stability study. The formulation of cream was monitored for up to 1 month for short-term stability conditions of temperature and relative humidity (40 ± 2°C /75% ± 5%RH). The cream formulation was packed in an aluminum tube and kept in a humidity chamber. Samples were withdrawn at intervals of 15 days and the parameters observed were phase separation, pH, Consistency, Viscosity, and % Drug release (Table 10).

RESULTS AND DISCUSSION

Physicochemical Characteristics. The color of the *Camellia sinensis* leaf extract was found to be brown, and the odor was characteristic. The pH was found to be 6.7.

Table 3: Results of physicochemical parameters.

Parameters	Observed values (% w/w)
Moisture content (%w/w)	5.50
Ash value (%w/w)	5.16
Acid Insoluble ash (%w/w)	0.53
Water soluble ash (%w/w)	3.04
Alcohol extractive value (%w/w)	43
Water extractive value (%w/w)	21

Phytochemical Screening. The tests for the identification of constituents present in the *Camellia sinensis* leaf extract were performed and the results obtained are listed in the Table.

Table 4: Results of phytochemical screening.

Sr. No.	Chemical test	Observed value
1.	**Alkaloids** Dragendorff's test Mayer's test Hager's test Wagner's test	 -ve -ve -ve -ve
2.	**Carbohydrates** Molisch's test Benedict's test	 -ve -ve
3.	**Glycosides** Legal's test Keller killiani test	 -ve -ve
4.	**Tannins and phenolic compounds** Lead acetate solution 5% $FeCl_3$ solution	 +ve +ve
5.	**Steroids** Salkowski reaction Liebermann-Burchard reaction	 -ve -ve
6.	**Flavonoids** Shinoda test	 +ve
7.	**Saponins** Foam test	 -ve

FTIR Study. Identification of green tea extract was studied by scanning the sample in the wave number range 400-4000 cm^{-1} using FTIR spectroscopy by the KBr pellet method.

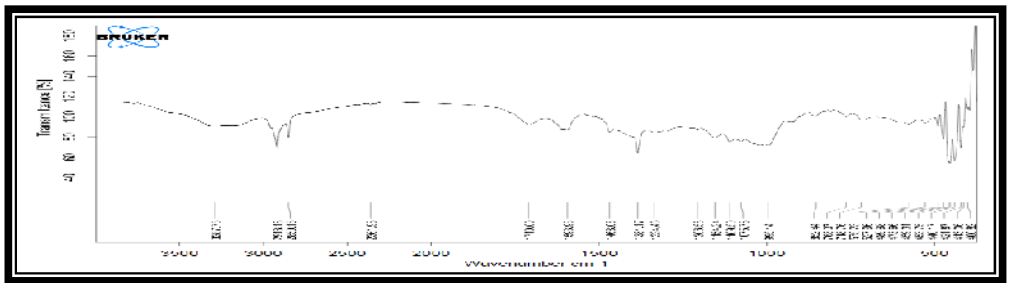


Fig. 1. FTIR spectra of *Camellia sinensis* extract.

Table 5: Interpretation of FTIR spectra of *Camellia sinensis* leaf extract.

Sr. No.	Functional Group	Wave No. (cm^{-1}) *Camellia sinensis* extract
1.	OH	3287.76
2.	CH Aromatic	2918.18
3.	C=O	1710
4.	C-O-C	1384.17

Determination of Antifungal activity. The antifungal assay was performed using the agar well diffusion method for *Camellia sinensis* leaf extract and standard Amphotericin B solutions. The effect of *Camellia sinensis* extract against *Candida albicans* was observed at 1000 µg/ml and increased at 1500 µg/ml. The test and standard solutions showed nearby same results on the concentration of 1000 µg/ml.

Table 6: Results of antifungal assay of *Camellia sinensis* leaf extract and standard Amphotericin B solution.

	Concentration (µg/ml)	Zone of inhibition (mean ± Standard Deviation)		
		After 24 hr	After 48 hr	After 72 hr
Camellia sinensis extract	500	-	-	-
	1000	-	8.13 ± 0.30	14.26 ± 0.12
	1500	-	9.26 ± 0.11	16.46 ± 0.31
Amphotericin B	500	-	4.13 ± 0.11	8.26 ± 0.05
	1000	-	7.90 ± 0.20	15.30 ± 0.10
	1500	-	12.16 ± 0.11	23.93 ± 0.23

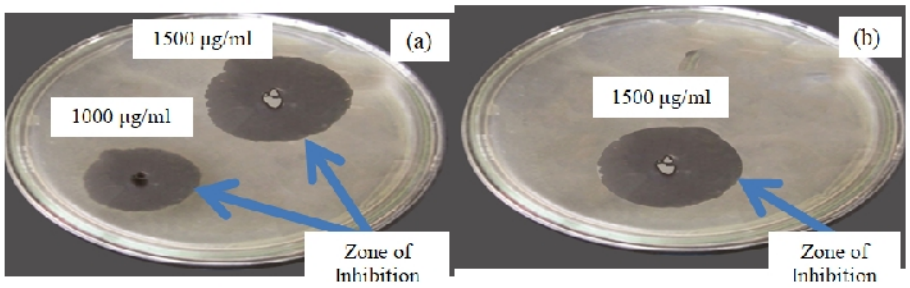


Fig. 2. Images of the zone of inhibition of (a) *Camellia sinensis* leaf extract (b) Amphotericin B.

Determination of Minimum Inhibitory Concentration. The different concentrations of *Camellia sinensis* extract 200, 400, 600, and 800 µg/ml were tested by tube dilution method for MIC. The results showed less number of colonies in 600 µg/ml solution whereas no growth was observed in 800 µg/ml concentration.

Standard Calibration curve. The standard calibration curve was found to be linear with an R^2 value of 0.997.

Table 7: Standard Calibration curve of *Camellia sinensis* leaf extract.

Concentration (µg/ml)	Absorbance (mean ± S.D*)
50	0.159 ± 0.0015
100	0.321 ± 0.0005
150	0.444 ± 0.0011
200	0.646 ± 0.0020
250	0.808 ± 0.0017
300	0.949 ± 0.0005
N* = 3	

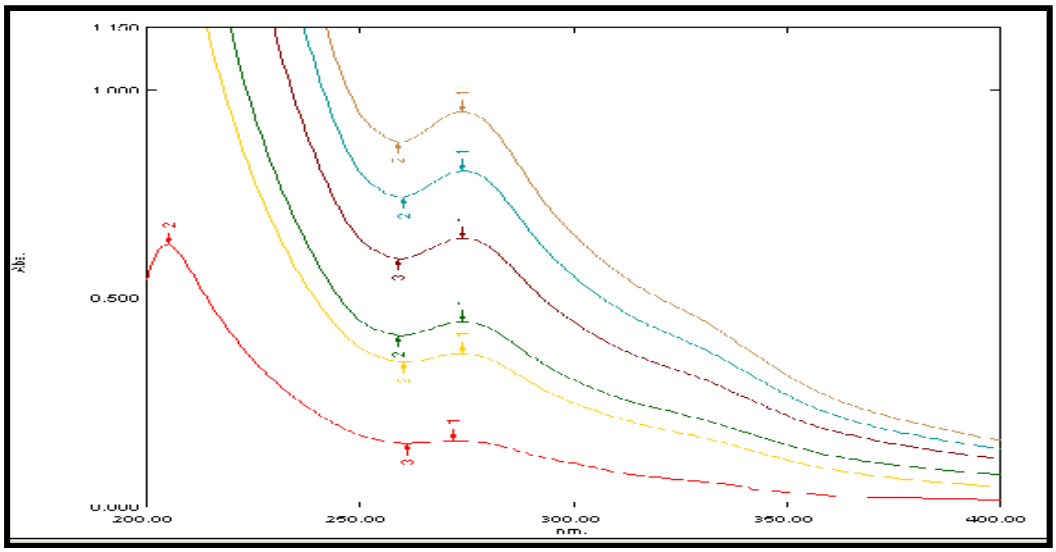


Fig. 3. Spectra of calibration curve of *Camellia sinensis* in phosphate buffer pH 7.4.

Composition and evaluation of the final optimized batch. The final optimized batch was selected based on Design Expert software (10.0.0). Further evaluation tests were performed on the final batch (Table 8).

Table 8: Composition of Final optimized formulation.

***Camellia sinensis* extract**	**5 % w/w**
White petrolatum	0.823 % w/w
Lanolin	0.835 % w/w
Liquid paraffin	8.3 % v/v
Stearic acid	16.7 % w/w
Propylene glycol	3.5 % v/v
Triethanolamine	1.0 % v/v
Tween 60	5.0 % v/v
Methyl paraben	0.18 % w/w
Propyl paraben	0.02 % w/w
Purified water (upto)	100 %

Table 9: Evaluation of cream formulation.

Evaluation parameters	**Observed values**
Zone of Inhibition	9.23 ± 0.05 (After 48 hr)
	14.96 ± 0.11 (After 72 hr)
pH	6.7
Spreadability	15.13
Viscosity	1556
Homogeneity	Homogenous
Consistency	5.5 mm
Acid value	0.66
Saponification value	185
Thixotropy	No
In vitro drug release	84.41 %
Skin irritation	No

Skin irritation study. The observations of the skin irritation study are shown in Fig. 5.

The result of skin irritation studies indicated that the formulation was non-irritant to the skin. No signs of erythema or edema were observed.

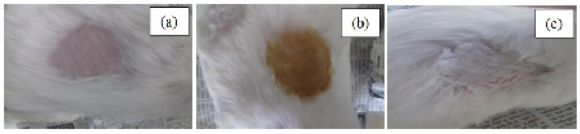
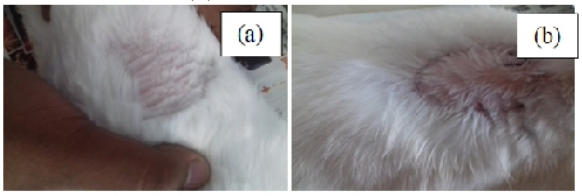
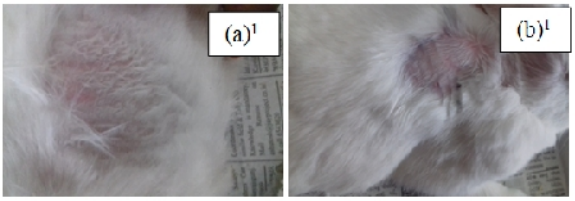


Fig. 4. Skin irritation study of optimized batch: (a) Normal controlled area, (b)Applied *Camellia sinensis* extract cream formulation, (c) Applied cream base (without extract)

(1) After 24 hours



(2) After 48 hours



(3) After 72 hours

Fig. 5. Observations for skin irritation study: (a), (a^1) and (a^{11}) show the images of *Camellia sinensis* extract formulation applied area: (b), (b^1) and (b^{11}) show the images of the cream base (without extract) applied area.

Stability study. From the results, it has been observed that no phase separation was observed for the formulation. It showed no significant change in pH, Consistency, Viscosity, and % drug release. So the prepared formulation was found to be stable at accelerated conditions.

Table 10: Stability data for optimized formulation.

Days	Stability study at the accelerated condition 40 ± 2°C /75% ± 5%RH				
	Phase separation	pH	Consistency (mm)	Viscosity (cps)	% Drug release
Initial	No	6.7	5.5	1556	84.41
15	No	6.7	5.5	1554	84.30
30	No	6.7	5.4	1554	84.06

Camellia sinensis L. being an important commercial plant is consumed worldwide as a beverage made from the processed leaf. The secondary metabolites catechin, caffeine, theanine, and saponin have a broad spectrum of biological activities like antibacterial, antifungal, antitumor, and antioxidant. This work aimed to formulate and evaluate topical herbal cream for improving therapeutic efficiency to treat Candidiasis. The optimization of polymers and preparation of formulation was carried out using design expert software. The optimized formulation was then evaluated for various parameters like homogeneity, % drug release, release kinetics, and consistency. Skin irritation study on rabbits showed no irritancy explaining that the formulation shows no sensitivity to skin tissues. A short-term accelerated study for 1 month showed no changes at 4°C ± 1°C RH for physicochemical properties.

CONCLUSION

A herbal formulation was prepared using *Camellia sinensis* L. for the treatment of Candidiasis. A reformulation study of physicochemical and phytochemical screening was carried out and the results obtained were satisfactory. The standard calibration curve was taken in water and phosphate buffer pH 7.4 at λ_{max} 274 nm. The optimized formulation has pH 6.7, a Spreadability of 15.13 gm.cm/sec, a viscosity of 1556 cps, 14.96 ± 0.11 mm zone of inhibition, and 84.41 % drug release. Skin irritation study on rabbits showed no irritancy explaining that the formulation shows no sensitivity to skin tissues. The short-term stability study showed no changes in the physicochemical properties of formulation during 1 month.

FUTURE SCOPE

The prepared and evaluated cream can become a good alternative for patients having drug resistance towards commercial and conventional creams. The authors recommend this formulation for further detailed animal and clinical trial studies.

Conflict of Interest. None.

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