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Anti-Inflammatory Activity and Antimicrobial Activity Against Common Oral Pathogens of Cyanthillium Cinereum - An Invitro Study

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ABSTRACT

Background: Cyanthillium cinereum known as Poovamkurunilla in Tamil is one among the traditional medicinal plants which has proven properties.
Aim: Hence, this study is aimed to evaluate the antimicrobial and anti-inflammatory properties of Cyanthillium cinereum in two groups.
Methodology: The oral pathogens such as Streptococcus mutans, Staphylococcus aureus and Enterococcus faecalis and C. albicans were used to assess the antimicrobial efficacy of Cyanthillium cinereum in two groups(Group 1 - Aqueous extract of C.Cinereum leaves; Group 2 – C.Cinereum whole plant using agar well diffusion method at various concentrations that ranges from 25 µL, 50 µL and 100 µL. Anti-inflammatory activity was evaluated using protein denaturation assay. Statistical analysis was performed using SPSS version 23. Independent t test and One-way ANOVA were used for measure between group analysis and Repeated measures ANOVA were used for measure within group analysis.
Results: Increasing the concentration increases the response too against oral microbes. Group 1 shows better antimicrobial properties than group 2. Statistically significant differences were found on all concentrations taken into consideration. Whereas both the groups show equal anti-inflammatory activity when compared with diclofenac. Statistically significant difference was found on all comparisons except Group 1 versus Group 2 in all the concentrations (p=0.358).
Conclusion: The study revealed that C.Cinereum leaves exhibit strong antimicrobial activity against oral microbes except Candida albicans. Both Group 1 and Group 2 exhibit better anti-inflammatory activity than standard values. Further it has to be tested for its cytotoxicity and antioxidant activity for future usage of Cyanthillium cinereum in applications in the pharmaceutical industry.

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INTRODUCTION

Plants which possess enormous medicinal values were extensively utilized in healthcare sectors worldwide. In the past few years, traditional and native plant medicines have gained much importance worldwide. The World Health Organization (WHO) evaluated that almost 80% of the people residing in various countries still depend on traditional medicines for their basic healthcare(1). Plant based medicines always have an advantage in pharmacological industries as it has been used for a very long period by the native people. Natural derivatives from the native plants imbibe antimicrobial properties against pathogens exhibited by humans(2) . Basically medicinal plants have chemical particles such as phytochemicals namely alkaloids, flavonoids etc.

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Cyanthillium cinereum known as Poovamkurunilla in Malayalam and poovamkuruntal in Tamil is one among the traditional medicinal plants which is famously known in Tropical asia and Africa and naturalized in various parts of the world. Cyanthillium cinereum grows up to 120cm tall(almost 4feet). It consists of flat-topped arrays of various flowerheads in pinkish-purple florets but not ray florets. This floral species can be bewildered with Emilia sonchifolia which has longer and vase shaped floral bracts whereas cyanthillium cinereum has short base. Cyanthillium cinereum exhibits analgesic(3), antimicrobial(4) and antifungal properties(5). It also possesses antioxidant properties against oxidative damage to biological molecules such as lipids and DNA.

Traditionally, the whole plant exhibits various medicinal properties in diverse uses in various regions and it also has a huge impact in Ayurveda(6). Basically the whole plant is used to treat fever. It also relieves spasms in the urinary bladder and is used to treat urinary tract infection. Sesquiterpene lactones, which possess antimalarial activity, have been isolated from the plant(7). Seeds of this plant are used as a source of anthelmintic drugs. Cyanthillium cinereum stem is used to treat cuts in skin whereas flowers were used to treat arthritis. Root infusion can also be used for snake venom(8).

Cyanthallium cinereum also has a very notable property which is smoking cessation for chronic smokers in Thailand and also other countries in Asian continent(9). It also decreases cigarette craving in smokers. Among the list of National Essential Medicines released by the Ministry of Public Health, Thailand, C.Cinereum tea is included(10). It has also been used as a replacement for nicotine replacement therapy since its flowers and leaves have 0.1% of nicotine in it. Moreover it also own nitrate salt in it which can reduce the tongue numbness which ultimately results in a decreased level of smoking smell and taste(11). C.Cinereum juice which can also be used as supplementation to reduce oxidative stress and quantity of cigarettes smoked per day by people(12). The miracle plant which imbibe multiple properties as a whole has to be tested for its properties. Our team has extensive knowledge and research experience that has translate into high quality publications (13-22).

To my knowledge this is the first study which compares C.Cinereum leaves Versus C.Cinereum whole plant for its antimicrobial properties against oral pathogens and anti-inflammatory properties. Hence this study is aimed to evaluate the antimicrobial and anti-inflammatory properties of Cyanthillium cinereum in two groups.

MATERIALS AND METHODS

Collection of Plant

Cyanthillium cinereum (whole plant) was collected in the month of September 2021 from Kanchipuram district, TamilNadu, India. Healthy plants were thoroughly screened and washed. Washed plants were dried for 7-14 days and then dried in a Hot air oven for 24 hours before grinding.

Preparation of aqueous extract for both the groups

The dried plants were grinded using a mixer into two groups. Group 1 will be Cyanthillium cinereum leaves and group 2 will be Cyanthillium cinereum whole plant which consists of stem, leaves, flowers and roots. Leaves were made separately and stored in an airtight container. On the other hand, the stem, flower and roots were grinded separately and stored in separate containers each. About 1 g Cyanthallium Cinereum grinded powder was dissolved in 100ml of distilled water and boiled for 5–10 min at 60–70°C. The solution was filtered by using Whatman no. 1 filter paper. The filtered extract was collected and stored in 4°C for further use named as group 1. Now 1g of powdered stem , flowers and roots were dissolved each in 100ml of distilled water respectively. Before boiling, the dissolved stem, root , leaves and flowers were mixed together and boiled for 15-20 minutes at 60–70°C. Then the filtered extract is stored in 4°C for further use and named as Group 2.

Culture and Maintenance of microorganisms

Pure cultures of all experimental bacteria and fungi were obtained from Saveetha Institute of Medical and Technical Sciences, Chennai. The pure bacterial cultures were maintained on nutrient agar medium and fungal culture on potato dextrose agar (PDA) medium. Each bacterial and fungal culture was further maintained by subculturing regularly on the same medium and stored at 4 degree celsius before use in experiments. Antimicrobial activities of different extracts were evaluated by agar well diffusion method.

Agar well diffusion method

Agar well-diffusion method was followed to determine the antimicrobial activity of Cyanthillium cinereum against Streptococcus mutans, Staphylococcus aureus, E.faecalis, Candida albicans. Nutrient agar (NA) and Rose Bengal Agar (PDA) plates were swabbed (sterile cotton swabs) with 8 hour old - broth culture of respective bacteria and fungi. Wells (10mm diameter and about 2 cm apart) were made in each of these plates using sterile cork borers. Stock solutions of both groups were prepared at a concentration of 1 mg/ml in different plant extracts viz. Cyanthillium cinereum leaf extract(Group 1) and C.Cinereum whole plant(Group 2) extract of 25µl, 50µl and 100 µl concentrations were added to the wells and allowed to diffuse at room temperature for 2hrs. The plates were incubated at 37°C for 18-24 h for bacterial pathogens and 28°C for 48 hours for fungal pathogens. The diameter of the inhibition zone (mm) was measured and the activity index was also calculated. Triplicates were maintained and the experiment was repeated thrice, for each replication the readings were taken in three different fixed directions and the average values were recorded. The antimicrobial potential of both the experimental plants was evaluated according to their zone of inhibition against various pathogens and the results (zone of inhibition) were compared with the activity of

the standards, viz Ampicillin (1.0 mg/disc), Fluconazole (1.0 mg/disc).

Anti-Inflammatory Activity (Protein Denaturation Assay)

Bovine serum albumin (BSA) was used as a reagent for the assay. BSA makes up approximately 60% of all proteins in animal serum. It's commonly used in culture, particularly when protein supplementation is necessary and the other components of serum are unwanted. BSA undergoes denaturation on heating and starts expressing antigens associated with Type III hypersensitivity reaction which are related to a disease such as rheumatoid arthritis, glomerulonephritis, serum sickness, and systemic lupus erythematosus. 2 ml of 1% bovine albumin fraction was mixed with 400 µl of plant crude extract in different concentration (500–100 µg/mL), and the pH of reaction mixture was adjusted to 6.8 using 1N HCl. The reaction mixture was incubated at room temperature for 20 min and then heated at 55°C for 20 min in a water bath. The mixture was cooled to room temperature, and the absorbance value was recorded at 660 nm. An equal amount of Aqueous leaf extract of Cyanthillium cinereum(Group 1) replaced with dimethyl sulfoxide for control. Diclofenac sodium in different concentrations was used as standards. The experiment was performed in triplicate.

Test Group

10 µL, 20 µL, 30 µL, 40 µL and 50 µL of the aqueous extract of Cyanthillium cinereum leaves were taken in 5 test tubes respectively. To each test tube 2 ml of 1% Bovine Serum Albumin (BSA) was added. 390 µL, 380 µL, 370 µL, 360 µL and 350 µL of distilled water was added to the test tube containing 10 µL, 20 µL, 30 µL, 40 µL and 50 µL of cyanthillium cinereum leaf extract respectively

Control Group

2 mL of Dimethyl Sulphoxide (DMSO) was added to 2 mL of BSA solution.

Standard Group

10 µL, 20 µL, 30 µL, 40 µL and 50 µL of Diclofenac Sodium was taken in 5 test tubes respectively. To each test tube 2 mL of 1% Bovine Serum Albumin (BSA) was added. The test tubes were incubated at room temperature for 10 minutes. Then they were incubated in a water bath at 55 degree Celsius for around 10 minutes. Absorbance was measured at 660 nm in the UV Spectrophotometer.

The same experiment was repeated for Cyanthillium cinereum whole plant extract too(Group 2)

% Inhibition was calculated using the following formula:

% of inhibition = (Control OD − Sample OD % Control OD) × 100

Statistical analysis

-Data was entered in Microsoft Excel spreadsheet and analyzed using SPSS software (version 23.0). Descriptive statistics were done to interpret the mean and standard deviation of the required variables

-Before proceeding into the inferential analysis , Normality was tested using Shapiro Wilks Analysis since the sample size is less than 50. Since all our normality values ($p>0.05$) are greater than 0.05, our data set is normally distributed.

- Independent t test was done to analyze the mean differences between the unrelated groups

- To analyze mean differences within groups repeated measures ANOVA was used.

RESULTS

Cyanthallium Cinereum leaves aqueous extract and Whole plant extract of Cyanthillium cinereum were taken and tested for antimicrobial activity against Streptococcus mutans, Staphylococcus aureus, Faecalis and C. albicans. Anti-inflammatory activity was also tested for both the group and compared with gold standard diclofenac sodium. From table 1mean streptococcus mutans activity in various concentrations with the standard Amoxicillin was mentioned in which Group 1 has exhibits more activity against Streptococcus mutans in all the concentrations. Though group 1 it does not exhibit more activity even in 100ul (21.1±1.1) than the standard it was almost half of the activity of the standard antibiotic (37.7±0.6). Statistically significant relationship was found ($p<0.05$) on performing between group analysis in Streptococcus mutans activity. In Within group analysis, statistically significant relationship was found on all the concentrations except 25ul($p=1.000$). Increasing the concentration increases the response too against oral microbes.

From table 2, results interpret that Group 1 exhibits more activity (10.2±0.2; 16.4±0.4;21.1±0.1) than Group 2 (9.2±0.2;9.1±0.1;9±0.05) at 25ul,50ul and 100ul concentrations respectively. Statistically significant relationship was found ($p<0.05$) on performing between group analysis in Staphylococcus aureus. In Within group analysis, statistically significant relationship was found on all the concentrations. From table 3, it was found that Group 1 was comparatively better than Group 2. Statistically significant difference on between group analysis for both the groups among Faecalis. Within group analysis, statistically significant relationship was found on all the concentrations except 25ul($p=0.577$). While performing testing Candida albicans using well diffusion method, no activity was found even after 48hours for Cyanthillium cinereum. All the micro-organisms took into consideration exhibits high activity as the concentration increases(zone of inhibition too increases).

Anti-inflammatory activity was represented by mean

percentage inhibition. Group 1 and group 2 almost has the same percentage inhibition and when compared with the standard (diclofenac sodium) both the groups exert better anti-inflammatory activity. On Comparison of mean inhibition of anti-inflammatory activity among groups with respect to different concentrations were represented in table 4. Within group analysis was performed using One-way ANOVA from which statistically significant difference was found on 10ul,20ul,30ul,40ul and 50ul respectively(P=0.000*) (Table 4). Multiple Comparisons of Antioxidant activity among toothpaste groups with standard ascorbic acid using post Hoc Tukey's Test in various concentrations was represented in table 5. Statistically significant difference was found on all comparisons except Group 1 versus Group 2 in all the concentrations. Figure 1 illustrates the comparison of mean inhibition in percentage among Cyanthallium Cinereum toothpaste groups with respect to their concentrations.

Table 1: Comparison of Mean Streptococcus mutans activity in different concentrations

Groups	25ul	50ul	100ul	Ab	P value
Cyanthillium cinereum leaves	9.2±0.2	14.4±0.5	21.1±1.1	37.7±0.6	0.000*
Cyanthillium cinereum Whole plant	9.2±0.2	14.3±0.2	15.2±0.2	35.4±0.5	0.000*
P value (Independent t test)	1.000	0.03*	0.001*	0.008*	

*Statistically significant difference p<0.05

Table 2: Comparison of Mean Staphylococcus aureus activity in different concentrations

Groups	25ul	50ul	100ul	Ab	P value
Cyanthillium cinereum leaves	10.2±0.2	16.4±0.4	21.1±0.1	44.3±0.3	0.000*
Cyanthillium cinereum Whole plant	9.2±0.2	9.1±0.1	9±0.05	45.1±0.1	0.000*
P value (Independent t test)	0.005*	0.000*	0.000*	0.01*	

*Statistically significant difference p<0.05

Table 3: Comparison of Mean E.faecalis activity in different concentrations

Groups	10ul	20ul	30ul	40ul	50ul
Cyanthillium cinereum leaves	76.5±3.6	85.5±3.4	90.2±0.9	91.8±0.5	92.9±0.6
Cyanthillium cinereum Whole plant	73.5±2.0	85.6±1.1	91.3±1.2	93.2±0.2	94.1±0.7
Standard(Ascorbic acid)	47.5±0.5	61.8±1.5	70.5±1.5	77.2±0.8	83.8±0.5
P value (One way ANOVA)	0.000*	0.000*	0.000*	0.000*	0.000*

Table 4: Comparison of mean inhibition of anti-inflammatory activity among groups with respect to different concentrations

Groups	25ul	50ul	100ul	Ab	P value
Cyanthillium cinereum leaves	9.4±0.5	14.3±0.3	18.2±0.2	41±1.1	0.000*
Cyanthillium cinereum Whole plant	9.2±0.2	9.2±0.3	9±0.05	38±0.1	0.000*
P value (Independent t test)	0.577	0.000*	0.007*	0.009*	

*Statistically significant difference p<0.05

Table 5: Multiple Comparisons of Anti-imflammatory activity among toothpaste groups with standard ascorbic acid using post Hoc Tukey's Test in various concentrations

Conc	Pairs	Mean difference (I-J)	Std. Error	Sig (P value)
10ul	Group 1 Vs Group 2 Group 1 Vs Group 3 Group 2 Vs Group 3	3.000 29.000 26.000	2.002 2.002 2.002	0.356 0.000* 0.000*
20ul	Group 1 Vs Group 2 Group 1 Vs Group 3 Group 2 Vs Group 3	-0.100 23.800 -23.800	1.857 1.857 1.857	0.998 0.000* 0.000*
30ul	Group 1 Vs Group 2 Group 1 Vs Group 3 Group 2 Vs Group 3	-1.100 19.700 20.800	1.031 1.031 1.031	0.567 0.000* 0.000*
40ul	Group 1 Vs Group 2 Group 1 Vs Group 3 Group 2 Vs Group 3	-1.366 14.566 15.933	0.491 0.491 0.491	0.07 0.000* 0.000*
50ul	Group 1 Vs Group 2 Group 1 Vs Group 3 Group 2 Vs Group 3	-1.233 9.066 10.300	0.518 0.518 0.518	0.119 0.000* 0.000*

*The mean difference is significant at the 0.05 level

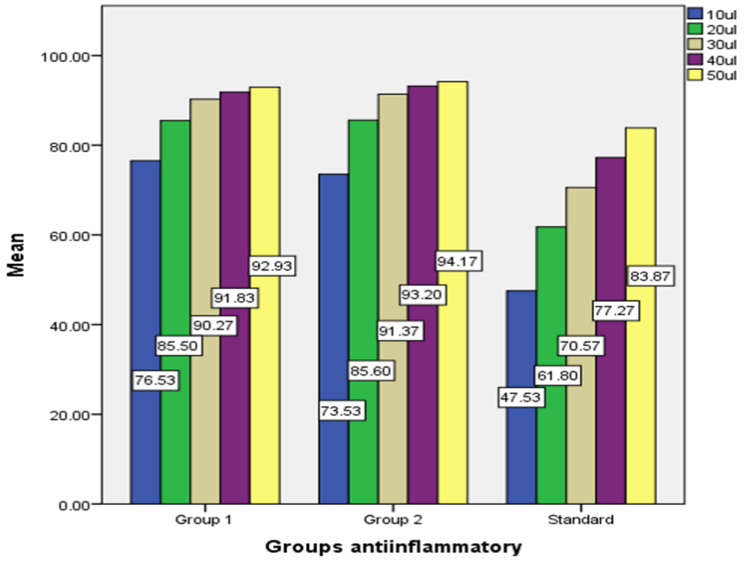

Figure 1 : Comparison of mean inhibition in percentage among Cyanthillium Cinereum toothpaste groups with respect to their concentrations

DISCUSSION

According to the results , the zone of inhibition increases as the concentration of the extract increases too. To my knowledge this is the first study to compare the Cyanthillium cinereum Leaves aversus remaining parts of the plant as another group. In a study conducted by Ourland Alzeous G et al(29) Root extracts of C. cinereum exhibited an inverse dose-response relationship. The anti-staphylococcal activity was the highest at the lowest concentration (25 mg/mL) and it decreased as the concentration increased. This is not in accordance with our study results. Many studies formerly stated the therapeutic potential of C. cinereum against different diseases. One recent study showed antimicrobial activity of C. cinereum ethyl acetate fractions against human bacterial pathogens(6,30). No activity was exhibited against Candida albicans. Alkaloids, phenols, saponins and phlobatannins are the compounds that were screened in aqueous leaf extracts. The zone of inhibition of plant extract against Escherichia coli was found to be 21mm and 19mm against Staphylococcus aureus . The gram negative organism E. coli was found to be more sensitive than the gram positive organism S. aureus due to the compounds such as phenols, saponins and tannins(31).

Although cyanthillium cinereum has the proven antioxidant activity due to their protective effects against oxidative damage to biological macromolecules like lipids and DNA(6), it also has anti-inflammatory activity in it. In this study we compared cyanthillium cinereum leaves with cyanthillium cinereum whole plant, in which we compared with the gold standard agent diclofenac sodium and measured mean percentage inhibition using Protein denaturation assay. Surprisingly, group 1 and 2 both exerts more anti-inflammatory activity than the standard in concentrations like 10ul,20ul,30ul,40ul and 50ul.

The anti-inflammatory activity test is performed by human red blood cell stabilization (HRBC) method. Cyanthillium cinereum have greater activity against inflammation(32) which is in accordance with our study results. In a study conducted by Thitiya Luetragoon et al in 2021, it was found that whole plant of moringa oleifera and cyanthillium cinereum reduces oral inflammation (gingivitis) in healthy smokers.

RECOMMENDATIONS

- Since it is safe for humans to use , especially in smokers it can be used to treat inflammation and it can also be customized like a lozenge or mixed with drinking water for utilization as smoking cessation material as a replacement to nicotine replacement therapy.

- Since it also exhibits good activity against oral microorganisms it can also be safely used as a dentifrice for smokers by which it can help in the de-addiction gradually.

CONCLUSION

The study revealed that C.Cinereum leaves exhibit strong antimicrobial activity against Streptococcus mutans, Staphylococcus aureus and E.faecalis when compared with C.Cinereum whole plant extract. Both Group 1 and Group 2 exhibit better anti-inflammatory activity than standard values. Further it has to be tested for its cytotoxicity and antioxidant activity for future usage of Cyanthillium cinereum in applications in the pharmaceutical industry.

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