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Evaluation Of Growth Inhibitory Activity of Phytoconstituents of Ethanolic Green and Red Leaf Extracts of Lagerstroemia Speciosa Against Uropathogenic Escherichia Coli Transurethral Inoculation in Female Albino Rat

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ABSTRACT

Urinary Tract Infections (UTI) are common infections affecting the urinary tract with Escherichia coli being the most common. About 80 to 90 percent of UTIs are caused by a single type of bacteria. Plant medicines, including medicinal herbs are used to prevent and treat UTIs. Lagerstroemia speciosa is commonly called poomaruthu in Tamil. The leaves of L. speciosa are dark green in colour and turn attractively red before falling in the winter season. This study aimed to evaluate the growth inhibitory activity and phytochemicals of ethanolic green and red leaf extracts of L. speciosa for urinary tract infections. The qualitative phytochemical investigation of L. speciosa leaf extracts shows Carbohydrates, Tannins, Saponins, Flavonoids, Alkaloids, Quinones, Glycosides, Triterpenoids, Coumarins, and Steroids. The mouse UTI model is extremely flexible allowing the study of different bacterial strains and species of uropathogens in a broad range of mice. This experiment consists of inoculum preparation on the day of infection, transurethral inoculation, tissue harvest and post-harvest processing of experimental animals. The experimental plant extracts were given orally in all experimental groups except the control group for 21 days. Group II is treated as a standard group. The result indicates that the high dose of ethanolic red leaf extract is more effective than the green. The low dose of the ethanolic green leaf shows the same effect as the standard group, treated with commercially available antibiotics.

Keywords: Escherichia coli, Lagerstroemia speciosa, Urinary Tract Infections, TLC.

INTRODUCTION

Medicinal plants provide essential healthcare and nutrition to developing countries, aiding in urinary tract infections and providing essential resources. *Lagerstroemia speciosa* is a tropical and subtropical Asian plant is a potential candidate. The Western Ghats are one of the richest biodiversity regions of India, especially Coimbatore, Tamil Nadu. The experimental plant *L. speciosa* is commonly called Pride of India and Poomaruthu in Tamil [1]. A wide variety of phytochemical compounds such as secondary metabolites are synthesised by plants. The secondary metabolites of medicinal plants have very strong antioxidant properties and act as an efficient source of natural antioxidants [2]. The chemical constituents, pharmacological effects and therapeutic effects of the selected parts of *L. speciosa* are discussed in this study. The sample plant we used has two different leaf types: a green leaf and a red leaf. The leaf pigments exhibit the colour variation [3]. Urinary tract infections (UTIs) are common in humans, with *Escherichia coli* being the most common causative agent. Around 80-90% of UTIs are caused by *E. coli,* which lives in the intestines but can also enter the urinary tract [4]. Antibiotics are

Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

typically the first treatment, with levofloxacin being a widely studied third-generation fluoroquinolone [5,6]. The anti-uropathogenic and bactericidal activity of many plant extracts has been reported by many researchers; cranberry is the best-studied home remedy for UTI [7]. Cranberry also contains other biologically active constituents such as anthocyanidin, catechin, flavanols, myricetin, quercetin, and phenolics, which are supposed to be responsible for its activities [8]. Many reports are available on the antiviral, antibacterial, antifungal, anthelmintic, anti-molluscal, and antimicrobial activities of medicinal inflammatory properties of plants [9]. *L. speciosa* has antimicrobial properties. Antibacterial activity of ethanol and water extracts of leaves of *L. speciosa* was tested by the plate agar diffusion method against Gram positive and Gram-negative bacteria [10]. Leaf decoction or infusion was used for bladder and kidney inflammation, dysuria and other urinary dysfunctions, cholesterol deduction, hypertension, and diabetes [11]. Flavonoids provide pigments for plants, with anthocyanins and proanthocyanins being condensed tannins. polyphenols, such as ellagitannins, are found in fruits, nuts, and seeds [12]. The objective of the study is to evaluate the growth inhibitory activity of phytoconstituents in ethanolic green and red leaf extracts of *L. speciosa* against uropathogenic *E. coli* transurethral inoculation in albino rats.

MATERIALS AND METHODS:

Collection and authentication of Experimental plant:

The leaves of *L. speciosa* were collected from the PG Girls Hostel, Government Arts College (Autonomous), Coimbatore District, Tamil Nadu, India. The identification and authentication of *L. speciosa* are done by the Botanical Survey of India, Coimbatore, and the voucher specimens numbered BSI/ SRC/ 5/ 23/ 2020/ Tech/ 50 were placed in the Department of Zoology, Government Arts College (Autonomous), Coimbatore.

Plant extracts preparation:

L. speciosa leaves were collected, washed, and dried for 2 weeks. The leaves were ground to powder (100g) and soaked in ethanol (1000 ml). The powder was solubilized and mixed well with intermittent stirring for 4 days. After that, the extract was filtered using Whatman No. 1 filter paper and kept in a plastic tray to dry at room temperature [13].

Quality Control Analysis

Qualitative phytochemical analysis of the green and red leaves of *L. speciosa* ethanolic extracts were carried out according to the methodology of Horbone [14] and Trease and Evans [15]. The GC-MS analysis at The South Indian Textile Research Association in Coimbatore identified important compounds in *L. speciosa* ethanolic extracts of green and red leaves. The analysis used a Thermo GC-Trace Ultra ver. 5.0, Thermo MS DSQ 11 chromatography [16].

Bacterial Strain

The culture plates from Microbiology Lab in Coimbatore. *E. coli* DSM682 is the bacterial strain that was purchased. This well-known bacterial culture is administered by transurethral inoculation into the urethra of the experimental animal [17].

Specimen Culture and Bacterial Identification

Urine samples were collected and cultured in the biomedical laboratory of MHC on MAC or CLED agar media. Urine cultures with a count of ≥ 105CFU/ml were considered indicative of UTI and analysed for bacterial pathogen identification [18].

Drugs

The animals were divided into six groups. Group I, the control group, is treated with a normal diet. Standard Group II is treated with commercial antibiotics at the minimum concentration. The Standard drug is dissolved in 1% saline and 250mg/kg of Levofloxacin [19].

Acute Oral Toxicity Studies

The crude ethanol extract is non-toxic in rats, it was well tolerated at a concentration of 500, 1000, 2000, and 3000 mg/kg, no biochemical and histological changes were recorded [20]. There were no side effects in human, with the using of the recommended dosages (8-48 mg/day). However, higher doses associated with lowered blood glucose levels,

headache, dizziness, and fatigue [21]. The experimental groups received an ethanolic leaf extract orally for three days, was monitored for behaviour changes, and a toxicological examination was conducted to determine mortality. The experiment continued until proven safe [22].

Experimental Animal

The Institutional Animal Ethics Committee of KMCH College of Pharmacy in Coimbatore authorized all the experimental techniques employed in these experiments (Approval No: KMCRET/ReRc/PhD/24/2021). The animals were housed in polypropylene cages with stainless steel top grills, area to hold pellet food and feeder bottle with sipper tubes for water. Six animals were housed in each cage. Every single one of the test animals had unlimited access to potable water and a regular pelleted laboratory animal food. The bedding was made from paddy husk.

Experimental Design

This experiment consists of inoculum preparation on the day of infection, transurethral inoculation, tissue harvest and post-harvest processing of experimental animals. The animals were divided into six groups. Group I the Control group is treated with a normal diet. Standard Group II is treated with commercial antibiotics at the minimum concentration. Groups III and IV are treated with antidrug A, and Groups V and VI are treated with antidrug B. The antidrug of ethanol plant extract low (250 mg/kg) and high (500 mg/kg) was uniformly suspended in 1% carboxymethyl cellulose (CMC) and fed orally for 21 days. The Standard drug is dissolved in 1% saline and 1 ml of levofloxacin (250 mg/kg).

Inoculation of Bacterial Strain

Most of the superficial cells had exfoliated in response to the infection after the transurethral method of microbe inoculation [23]. *E. coli* was slowly injected into the urethra with a 1 mL sterile syringe to establish a rat model of UTI. The control group was injected with an equal volume of sterile normal saline solution. After the establishment the experiment was orally treated with plant extracts with low and high dose for 21 days. The group II is the standard model, treated orally with levofloxacin [24]. After treatment, the rats were sacrificed by cervical dislocation, urine was collected for bacterial colony culture, and serum was collected for subsequent microbial experiments [25]. Additionally, blood biochemical indexes were measured, and a histopathological examination of the kidney, urinary tract and urinary bladder was performed [26].

Urine Collection

Rat bladder urine was collected using aseptic techniques, with positive controls positive for *E. coli* and no microorganisms isolated in negative controls. It includes the diagnostic Combur-10 test strips, focusing on pH, specific gravity, blood, protein, ketones, and nitrites. 50 µL of urine was put onto the plate medium, and it was cultured for 24 hours at 37 °C. Bacterial growth was noticed (a positive result was recorded for a bacterial count > 105 CFU/mL) [25]

Biochemical Analysis

The study measured Analyses of creatinine, Blood Urea Nitrogen (BUN), triglycerides, and total cholesterol were performed [28].

Histopathological Analysis

Histopathological examinations of urinary tract, urinary bladder and kidney specimens were performed by the method described by Lillie and Fulman. The tissue samples were embedded in paraffin wax after being fixed in 10% formalin. The paraffin-embedded tissues were sliced into sequential sections that were 5 micrometres thick. Using an Olympus BX51 light microscope, the tissues were stained with hematoxylin and eosin. Evaluations were made of the epithelization, necrosis, and ulcerations [29].

Statistical Analysis

Each group (n=6), each value represents Mean ± SEM. One way ANOVA, followed by Dunnett comparison was performed. (***P<0.001) control group was compared with std group-II. (***P<0.001, **P<0.01, *P<0.05) treated groups III, IV, V, VI and VII was compared With Group I. GraphPad Prism

8.02 (California, USA) was the statistical software used for the analysis of biodata obtained.

RESULTS

Result I: Phytochemical Analysis

The qualitative phytochemical analysis revealed the following components (Table 1). *L. speciosa* leaf extracts show carbohydrates, tannins, saponins, flavonoids, alkaloids, quinones, glycosides, Terpenoids, triterpenoids, coumarins, and steroids.

Table 1. Phytochemical analysis of Ethanolic green Leaf and red leaf extracts of *L. speciosa*

Phytoconstituents	LEGLE	LERLE
Carbohydrates	+	+
Tannins	+++	++
Saponins	+++	++
Flavonoids	++	+++
Alkaloids	++	+++
Quinones	+	-
Glycosides	+	+
Terpenoids	++	++
Triterpenoids	++	++
Phenols	+++	+++
Coumarins	++	++
Protein and Amino acids	+++	+
Reducing Sugars	+	+
Phytosterols	++	++
Steroids	++	++

"+" indicates the presence of phytoconstituents
"++" indicates the phytoconstituents present in moderate level
"+++" indicates the phytoconstituents present abundantly
"-" indicates the absence of phytoconstituents

Result II: Acute Toxicity Studies

Administration of *L. speciosa* at a dosage of 2000 mg/kg to rats throughout an acute toxicity test indicated no toxicity, mortality, or morbidity, and there were also no significant changes in behaviour or gait.

Result III: Bio-chemical Analysis

The control group shows 33.23 mg of urea and 0.92 mg of creatinine, and the standard group total amount of urea is 25 mg and the creatine level is 0.85mg. Groups VI and V are treated with a high dose, and the low dose of ethanolic red leaf extract shows the TC and TG are 223±32.6 and 212±24.6 and 473±10.7 and 386±15.8. The total difference between the low and high doses of LERLE reveals that the percentage is lower than the control group. The urea level was higher in the experimental group VI and lower in group III. The low dose of ethanolic extract of green leaf shows 412±10.5 of TC and 438±76.3 of TG. Group IV shows a moderate amount of urea and creatinine. The amount of TC and TG is 279±20.7 and 216±23.9 in Group IV.

Table 2. Biochemical Analysis

Groups	Urea (mg/dl)	Creatinine (mg/dl)	TC (mg/dl)	TG (mg/dl)
Group I	33.7±0.88	0.62±0.502	250±73.4	260±40.4
Group II	36.3±1.2 ^{ns}	0.66±0.061^{ns}	357±75.4^{ns}	288±57.3^{ns}
Group III	33.3±2.67 ^{ns}	0.52±0.088^{ns}	412±10.5^{ns}	438±76.3^{ns}
Group IV	32±1.15 ^{ns}	0.5±0.087^{ns}	279±20.7^{ns}	216±23.9^{ns}
Group V	30±1.73 ^{ns}	0.44±0.05*	473±10.7^{ns}	386±15.8^{ns}
Group VI	29.7±0.88 ^{ns}	0.4±0.012**	223±32.6^{ns}	212±24.6^{ns}

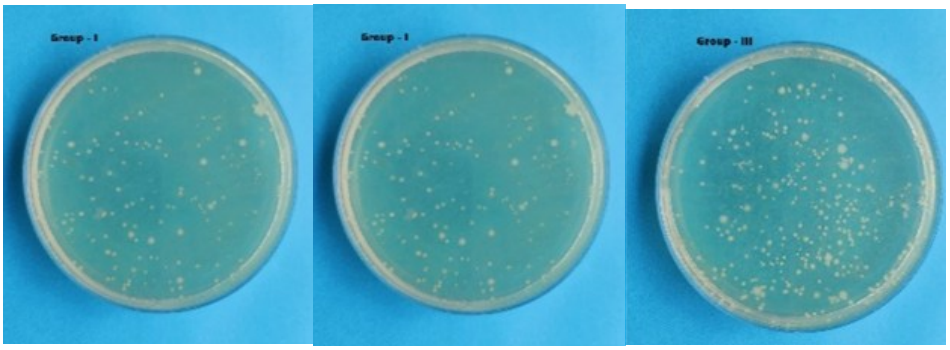
Result IV: Urine Analysis - Spread Plate Method

From the spread plate method produced by the extracts, it was observed that High doses of experimental leaf extract showed prominent antimicrobial activity against all microorganisms. Thus, the ethanol red leaf extract was more potent compared to ethanol green leaf extract. The standard group shows negative 13% of colony formation compare to control group. The experimental group III, IV, V, and VI shows 27%, 20%, 16%, and 9% compare to standard group.

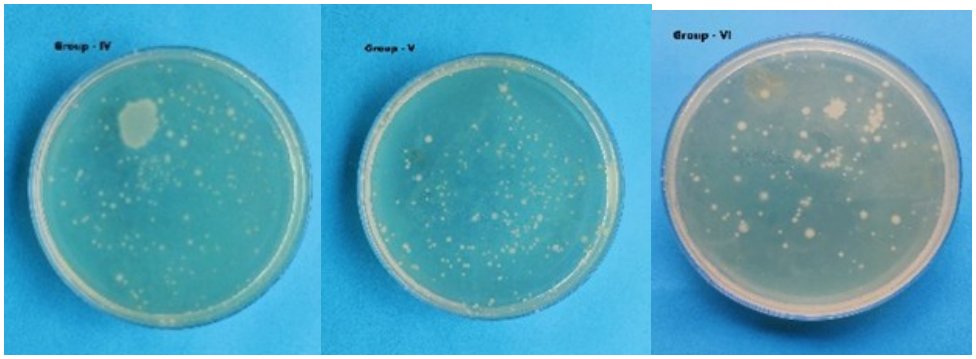
E. coli was found to be the most predominant uropathogen isolated from the patients with UTI and the development of multi drug resistance among uropathogens that causes a complicated UTI. The urine specimens showed greater variation in colour, odour, appearance and pH when they were subjected into physical examination. The urine specimens were subjected to different selective and differential media. The uropathogens were identified based on colour morphology. Biochemical tests were carried out to confirm the presence of the species of uropathogens from the selected groups. The results show that *E. coli* were predominant isolates isolated from the urine specimen followed by *P. aeruginosa*, *K. pneumoniae, S. aureus, P. mirabilis* and *E. faecalis* (Table 3).

Table 3. Bacterial Colonies Counting in Spread Plate method

SL No	Test Parameter	UOM	Result
1	Group I	CFU/mL	146
2	Group II	CFU/mL	127
3	Group III	CFU/mL	161
4	Group IV	CFU/mL	152
5	Group V	CFU/mL	147
6	Group VI	CFU/mL	138



Group I **Group II** **Group III**



Group IV **Group V** **Group VI**

Fig. 1: Bacterial colonies counting in Spread Plate method

Result VI: Histopathological Analysis

The urinary tract epithelial cells consist white blood cells along with multi bacterial cells with formation of pod-like bulges on the bladder surface that is indicative of apoptotic cells. In urinary bladder samples from albino rat that had only a fake infection, no bacteria were found. The superficial cells that were still present seemed smaller, had lost their characteristic pentagonal and hexagonal shapes, and commonly showed membrane blebbing. The kidney samples from the experimental animal with minimal infection and slight changes in the epithelial and endothelial cells. Control groups show normal urinary tract, Standard groups show normal urinary tract, green leaves low and High Dose shows muscular layer with epithelium and red leaves low and high groups shows urinary tract. There is no evidence of malignancy/ calculi.

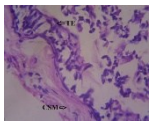
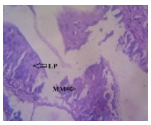
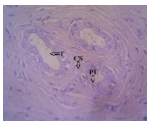
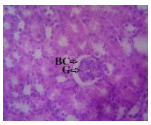
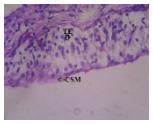
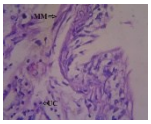
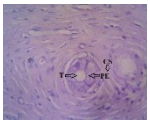
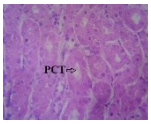
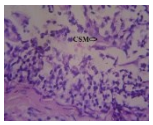
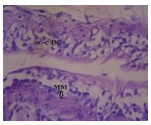
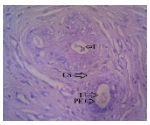
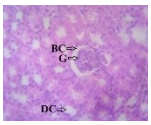
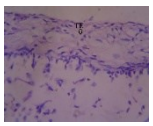
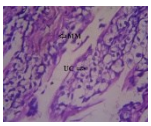
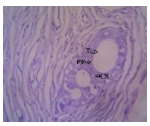
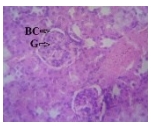
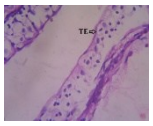
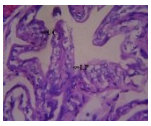
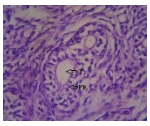
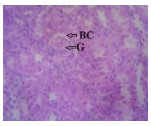
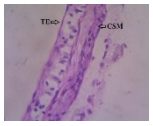
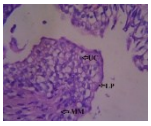
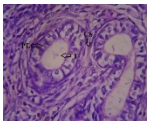
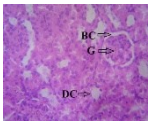
Groups/ Organs	Urinary Tract	Urinary Bladder	Uterus	Kidney
Group I - Control				
Group II - Standard				
Group III - LEGLE L. D				
Group IV - LEGLE H. D				
Group V- LERLE L. D				
Group VI - LERLE H. D				

Fig. 2: Histological Slides (40X) of Urinary Tract, Urinary Bladder, Uterus, and Kidney

URINARY TRACT: The abbreviations used in the study are: **CSM –** Circular Smooth Muscle, **TE** – Transitional Epithelium, **LEGLE**- *L. speciosa* Ethanolic Green Leaf Extract, **LERLE**- *L. speciosa* Ethanolic Red Leaf Extract.

URINARY BLADDER: The abbreviations used in the study are: **Std** - Standard, **UC** - Umbrella Cells, **LP** - Lamina Propria, **MM** - Muscularis Mucosae, **LEGLE** - *L. speciosa* Ethanolic Green Leaf Extract, and **LERLE** - *L. speciosa* Ethanolic Red Leaf Extract.

UTERUS: The abbreviations used in the study are: **Std-** Standard, **CS**- Cortical Stroma, **T-** Tubules, **PE**- Pseudostratified Epithelium, **LEGLE**- *L. speciosa* Ethanolic Green Leaf Extract, **LERLE**- *L.speciosa* Ethanolic Red Leaf Extract.

KIDNEY: Std- Standard, **A**- Adipocytes, **BC**- Bowmans Capsule, **G**- Glomerulus, **DC-** Distal Convoluted Tubule (Simple Cuboidal), **PCT**- Proximal Convoluted Tubule (Simple Cuboidal with microvilli), **LEGLE**- *L. speciosa* Ethanolic Green Leaf Extract, **LERLE**- *L. speciosa* Ethanolic Red Leaf Extract.

DISCUSSION:

Gupta [30] found that urinary tract infections are more common in females due to shorter urethras. *E. coli* can cause serious infections in the urinary tract, and mouse urine is more concentrated than larger animal urine [31]. IgA from urethral mucosal epithelial cells prevents infections, neutralizes pathogens, and provides local immune defence. Infected cells may harbour a bacterial biofilm, identifying them through membrane blebbing and pod-like bulges on bladder surface [32]. Low molecular weight immune-modulatory chemicals, dominated by terpenoids, phenolic compounds, and alkaloids, are being researched for their immune-stimulating potential, while glycosides, such as saponins and anthocyanin derivatives, play a significant role in medicine. Low molecular weight immune-modulatory chemicals are dominated by terpenoids, phenolic compounds, and alkaloids, whereas high molecular weight compounds are dominated by polysaccharides [33].

The immune-stimulating potential of many alkaloids is being researched. Saponins and anthocyanin derivatives are examples of glycosides that are significant in medicine. Glycosides mainly participate in the stimulation of the cardiac system, central nervous system, and immune systems; they also possess antimicrobial activity. Tannic acid and hydrolysable tannins have been found to prevent adaptive mutations in *S. aureus* resistant to methicillin. Combining these compounds with sweet chestnut and anthocyanosides from cranberry could provide a wider spectrum of antimicrobial action and potential synergistic effects. Herbal treatments for urinary tract infections have been used for centuries to strengthen and tone the body [34].

In this study, *L. speciosa* ethanolic green and red leaf extracts were evaluated for antibacterial activity against *E. coli in* experimental animals, revealing tannins, triterpenoids, proteins, and amino acids. The experimental group VI exhibits the most significant inhibitory action at 50 µl, primarily due to the presence of anthocyanins, or condensed tannins, in red leaf. Plant-derived alkaloids are frequently found to possess antimicrobial properties, as noted by [35]. Herbal treatments for urinary tract infections strengthen and tone the body, combat pathogens, reduce discomfort, and heal tissues. Control group showed bacteria in urine, with-treated animals showing normal hepatic and renal parenchyma, and some nephrotic abnormalities. The experimental group showing normal epithelium and sub epithelium red leaves groups show normal epithelium and sub epithelium.

CONCLUSION

L. speciosa demonstrated activity against the most prevalent Gram-negative bacteria in urinary infections, namely *E. coli*, the use of the plant as a urinary anti-infective is validated, scientifically supported by the results obtained in this work. Urinary tract infections are chronic, with one clearing just before another, making it easier for bacteria to enter. Combining herbal therapy can help manage recurrent UTIs. Herbal medicines offer safe, economical, and easy-to-use alternatives to conventional medicine, as they do not develop resistance to bacteria. Active immune system protects urinary tract from bacteria, eliminating them with double-speed action and consistent herb consumption for antibacterial properties. Traditional medicines are used by 60% of the world population for primary health care, including for infectious diseases, and almost half of current antibiotics are derived from plants or fungi. Medicinal plants are therefore a precious heritage for humanity and especially for the majority of poor communities in developing countries who depend on them for primary health care and livelihoods. Herbal therapy is widely used for treating urinary tract infections, as phytocompounds increase urine production, fight bacteria, and alleviate discomfort.

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