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Antibacterial effects of *Andrographis paniculata* extract, *Curcuma domestica* extract, chloramphenicol and their combinations on the growth of *Salmonella typhi* bacteria

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ABSTRACT : Typhoid fever caused by *Salmonella typhi* remains a serious health threat. Although standard treatment with antibiotics such as chloramphenicol has helped reduce mortality rates, bacterial resistance to this antibiotic is increasing. New treatment approaches are urgently needed, including combining antibiotics with natural compounds from medicinal plants, such as *Andrographis paniculata* and *Curcuma domestica*. This study aimed to compare the antibacterial effects of *A. paniculata* extract, *C. domestica* extract, chloramphenicol, and their combinations on the growth of *S. typhi*. This in vitro experimental study used the disc diffusion method to evaluate antibacterial activity. Antibacterial activity tests were performed against *S. typhi* using discs soaked in 70% ethanol extract solutions of *A. paniculata* and *C. domestica*, chloramphenicol, and their combinations. Inhibition zones were measured after incubation for 24 hours at 37 °C. Chloramphenicol showed the strongest antibacterial activity with a mean inhibition zone of 28.33±0.58 mm. Single extracts of *A. paniculata* and *C. domestica* had relatively weak antibacterial activity (inhibition zones of 9.67±1.15 mm and 9.83±0.29 mm) and there was no significant difference between them ($p>0.05$). Combinations of extracts with chloramphenicol showed increased antibacterial activity compared to single extracts (inhibition zones of 23.17 ± 1.26 mm for A. paniculata + chloramphenicol and 21.00±2.65 mm for C. domestica + chloramphenicol) and there were significant differences between combinations and single extracts ($p<0.05$), but still lower than single chloramphenicol and statistically significant ($p<0.05$). Although combining medicinal plant extracts with chloramphenicol increased antibacterial activity compared to single extracts, it did not exceed single chloramphenicol.

KEYWORDS: *Andrographis paniculata*, *Curcuma domestica*, chloramphenicol, *Salmonella typhi*.

INTRODUCTION

Typhoid fever caused by *S. typhi* bacteria remains a serious health threat, especially in developing countries with poor sanitation. In Indonesia, the average incidence rate is 500 cases per 100,000 population, with a mortality rate of 0.6-5% [1]. Standard treatment using antibiotics such as chloramphenicol has helped reduce mortality rates due to this infection. However, bacterial resistance to chloramphenicol is increasing, necessitating new treatment approaches that are more effective and capable of overcoming this resistance. One interesting approach is the use of combinations of antibiotics with natural compounds from medicinal plants, such as extracts of *A. paniculata* (green chiretta) and *C. domestica* (turmeric) [2].

C. domestica, with its main active compound curcumin, has various biological activities, including antibacterial, anti-inflammatory, and antioxidant properties. Curcumin has been proven to inhibit the growth of various bacterial pathogens, including *S. typhi*. Its mechanism of action includes disruption of bacterial cell wall structure, inhibition of biofilm formation, and modulation of host immune response [3-5].

A. paniculata, which contains andrographolide as its main bioactive component, has also been proven to have strong antibacterial activity. Andrographolide is known to inhibit the growth of various bacteria, both gram-positive and gram-negative, including *S. typhi*. Andrographolide works by inhibiting important

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enzymes in bacterial cell wall synthesis and modulating the host immune response, enhancing the body's ability to fight bacterial infections [6-8].

Antimicrobial resistance in *S. typhi* isolates is a significant problem in Asian and African countries. Among all *S. typhi* isolates, 25.9% were resistant to Chloramphenicol, 38.8% to Ampicillin, 61.2% to Amoxicillin, 37.9% to Trimethoprim-sulfamethoxazole, 64.7% to Nalidixic acid, 15.0% to Ciprofloxacin, 45.0% to Ceftriaxone, 45% to Azithromycin and 35.5% are multidrug-resistant [2]. Combining chloramphenicol with medicinal plants is an innovation in treating typhoid fever. However, the mechanism and effects still need to be discovered with certainty, whether there is a synergistic effect or the opposite. Therefore, research is needed to compare the antibacterial effects of *A. paniculata* extract, *C. domestica* extract, and chloramphenicol and their combinations on the growth of *S. typhi*.

MATERIALS AND METHODS

This research is a pure experimental in vitro study with a post-test-only control group design [9]. This study measured the inhibition zones formed by 70% ethanol extract of *A. paniculata*, 70% ethanol extract of *C. domestica*, chloramphenicol, and their combinations against *S. typhi* bacteria. Extract preparation was carried out at the Faculty of Pharmacy, University of Indonesia, and bacterial culture and testing was carried out at the Faculty of Medicine, Prof. Dr. Hamka University, in August 2024.

Plant preparation

The plants used in this study were *A. paniculata* and *C. domestica*. For *A. paniculata*, all components including leaves, flowers, and stems were used, for *C. domestica*, while the rhizome was used. *A. paniculata* (aged 3-4 months after planting, harvested during flowering stage) and *C. domestica* rhizomes (aged 8-10 months after planting, harvested when the leaves had turned yellow and dried) were collected from the Tawang Mangu area in Central Java in July 2024. Both plants were washed with running water to remove dirt until clean, chopped and cut into small, thin pieces, and dried using an oven at 40 °C until completely dry. After drying, both medicinal plants were placed and stored in airtight containers at room temperature until used in the extraction process [6],[10].

Extraction process

The dried plants were then ground using a blender and sieved with a 60-mesh sieve to obtain a fine powder. The extraction process used the maceration method with 70% ethanol as the solvent. One kg of powder from each plant was macerated with 5 L of 70% ethanol in dark containers for 72 hours at room temperature. The mixture was shaken every 24 hours during the maceration process to increase the interaction between the solvent and plant material. After 72 hours, the mixture was filtered using a cloth filter and Whatman No.1 filter paper. The obtained filtrate was evaporated using a rotary evaporator at 40°C until a thick extract was obtained. The extract was then stored in glass bottles at 4 °C until further used for antibacterial activity tests [11].

Bacterial culture rejuvenation and inoculum preparation

The bacterium used in this study was *S. typhi*, a gram-negative bacterium that causes typhoid fever. The bacterial strain was obtained from the Microbiology Laboratory of the Faculty of Medicine, Prof. Dr. Hamka University, and stored in Glycerol solution. *S. typhi* bacteria from glycerol were cultured on Nutrient Agar (NA) media and incubated for 24 hours. After the bacteria were grown on NA media, some colonies were taken with a pre-heated loop and then suspended by dissolving the colonies in 0.9% NaCl until homogeneous using a vortex machine. After the suspension was homogenized, the turbidity of the bacterial suspension was compared with a 0.5 McFarland standard solution. After homogenization, 0.15 ml of the suspension containing *S. typhi* colonies was taken and transferred to Mueller Hinton (MH) media using a pipette and spread evenly with a single-use sterile L-shaped spreader, then incubated at 37°C for 24 hours after the test discs were placed on the media [12].

Antibacterial activity test

The antibacterial activity test was carried out using the disc diffusion method. Sterile paper discs and chloramphenicol discs with a diameter of 6 mm were dripped and soaked with 40 µl of 70% ethanol extract solution from *A. paniculata* and *C. domestica* for 20 to 30 minutes. Then, the sterile paper discs soaked in the test solution were placed on the surface of MH media inoculated with *S. typhi* bacteria. Chloramphenicol antibiotic discs were used as a positive control, and discs soaked in DMSO solvent were used as a negative control. Each treatment was performed in three replicates. After disc placement, the petri dishes were incubated at 37°C for 24 hours. The inhibition zones formed were measured using callipers, expressed in millimetres (mm), and presented as mean ± standard deviation [13].

Data analysis

The inhibition zone data were analyzed using SPSS software version 25. A normality test was first performed to ensure normal data distribution. If the distribution was normal, then a One-way ANOVA and post hoc tests were conducted to see differences between treatment groups. If the distribution was not normal, data normalization was attempted. A Kruskal Wallis test was performed if it was still not normal. Results were considered significant if the p-value <0.05, followed by post hoc analysis with the Mann-Whitney test. The analysis results are presented in table form for ease of interpretation [9].

RESULTS

The extract obtained was then weighed, and the yield of each extract was calculated. The extract and yield can be seen in Figure 1 and Table 1.

Andographis paniculata *Curcuma domestica*

Figure 1. extract of *Andographis paniculata* and *Curcuma domestica*

Tabel 1. The weight and yield results of the medicinal plant extract.

Medicinal Plant	Weight of Simplicia (g)	Weight of Extract (g)	Yield (%)
Andographis paniculata	1000.69	130.46	13.04
Curcuma domestica	1000.05	172.07	17.21

Based on the data obtained, *A. paniculata* produced an extract weight of 130.46 g from 1000.69 g of simplicia, with a yield of 13.04%. Meanwhile, *C. domestica* produced an extract weight of 172.07 g from 1000.05 g of simplicia, with a higher yield of 17.21%. The extract yield was calculated using the following formula:

$$\text{Yield (\%)} = \frac{\text{Weight of Extract (g)}}{\text{Weight of Simplicia (g)}} \times 100$$

From these results, it can be seen that *C. domestica* provides a higher yield compared to *A. paniculata*. The extract yield of *C. domestica*, which reaches 17.21%, indicates that this plant produces more extract per unit of simplicia weight compared to *A. paniculata*, which only yields 13.04%. This suggests that *Curcuma domestica* may contain active components that are easier to extract or have higher concentrations of phytochemical compounds in 70% ethanol solvent.

This study aimed to evaluate the antibacterial effects of 70% ethanol extract from *A. paniculata*, 70% ethanol extract from *C. domestica*, chloramphenicol, and their combinations on the growth of *S. typhi* using the agar diffusion method. The data obtained from measuring the inhibition zones describe the effectiveness of each treatment in inhibiting bacterial growth.

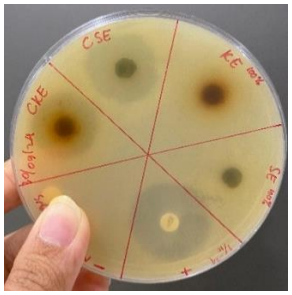

Figure 2. Antibacterial activity of etanol extract 70% *Andographis paniculata*, etanol extract 70% *Curcuma domestica,* chloramphenicol and their combination by disc diffusion method

Table 2. Antibacterial activity of etanol extract 70% *Andographis paniculata*, etanol extract 70% *Curcuma domestica,* chloramphenicol and their combination by disc diffusion method

Preparations	Inhibition Zone (mm)			
	I	II	III	Mean ± SD
Andographis paniculata (A)	9	11	9	9.67±1.15
Curcuma domestica (B)	9.5	10	10	9.83±0.29
Chloramphenicol (C)	29	28	28	28.33±0.58
Combination of Andographis paniculata and Chloramphenicol (A+C)	24.5	23	22	23.17±1.26
Combination of Curcuma domestica and Chloramphenicol (B+C)	24	20	19	21.00±2.65
DMSO (D)	0	0	0	0

Kruskal Wallis Test, p = 0.007 (p<0.05), n = 3

Post Hoc, Mann Whitney Test : (A vs B; p = 0.500), (A vs C; p = 0.043), (A vs A+C; p = 0.046), (A vs B+C; p = 0.046), (A vs D; p = 0.034), (B vs C; p = 0.043), (B vs A+C; p = 0.046), (B vs B+C; p = 0.046), (B vs D; p = 0.034), (C vs A+C; p = 0.046), (C vs B+C; p = 0.046), (C vs D; p = 0.034), (A+C vs B+C; p = 0.275), (A+C vs D; p = 0.037), (B+C vs D; p = 0.037)

Based on the data presented in Figure 2 and Table 2, the antibacterial activity test was carried out using the disc diffusion method on several samples, namely 70% ethanol extract of *A. paniculata*, 70% ethanol extract of *C. domestica*, chloramphenicol, and their combinations. The test results showed significant differences in inhibition zones between treatment groups ($p<0.05$).

Chloramphenicol showed the strongest antibacterial activity with an average inhibition zone of 28.33 ± 0.58 mm. Single extracts of *A. paniculata* and *C. domestica* had relatively weak antibacterial activity, with inhibition zones of 9.67±1.15 mm and 9.83±0.29 mm, respectively. No significant difference existed between these two single extracts ($p=0.500$).

Combining extracts with chloramphenicol showed increased antibacterial activity compared to single extracts and was statistically significant ($p<0.05$). The combination of *A. paniculata* and chloramphenicol resulted in an inhibition zone of 23.17±1.26 mm, while the combination of *C. domestica* and chloramphenicol resulted in an inhibition zone of 21.00±2.65 mm. However, these two combinations did not differ significantly ($p=0.275$).

Interestingly, although combining extracts with chloramphenicol increased antibacterial activity compared to single extracts, its effect was still lower than single chloramphenicol and was statistically significant (P<0.05). All treatments showed significant differences from the negative control DMSO (p<0.05), confirming that the solvent did not cause the observed antibacterial activity.

Overall, these results indicate that chloramphenicol has the strongest antibacterial activity, followed by combining extracts with chloramphenicol and the single extracts. Although combining extracts with chloramphenicol increased antibacterial activity compared to single extracts, its effect did not exceed that of single chloramphenicol.

DISCUSSION

Extract characteristics and yields

The extraction process yielded 13,4% and 17,21% for *A. paniculata* and *C. domestica* respectively. The difference in yield between these two plants may be attributed to several factors, including differences in the chemical composition of the simplicia, the polarity of the active compounds, and the solubility of bioactive components in the solvent used [11]. Active compounds in *Curcuma domestica*, such as curcuminoids, are known to have properties that make them more soluble in polar solvents like ethanol, thereby increasing the extract yield [10]. Conversely, *Andrographis paniculata* may contain active compounds with lower solubility in ethanol, or its active compounds may be more tightly bound to the plant matrix, affecting extraction efficiency. Technical factors in the extraction process, such as time and temperature, may also influence the results obtained [14].

The yield percentage of *A. paniculata* was higher than previously reported by Sukardiman et al. (2018) who obtained 10,29% yield using similar extraction conditions [15]. For C. domestica, our yield was comparable to findings by Wati et al. (2022), who reported yields 17,93% using ethanol extraction [16]. This difference might be attributed to several factors including plant age, harvesting time, and geographical location which have been shown to significantly influence the bioactive compound content in A. paniculata. Hayati et al. (2021) demonstrated that A. paniculata harvested during flowering stage, as used in our study, typically contains higher concentrations of andrographolide, which contributes to its therapeutic properties [17].

Antibacterial activity of single medicinal plant extracts and chloramphenicol

The results showed that 70% ethanol extracts of *A. paniculata* and *C. domestica* had relatively weak antibacterial activity compared to chloramphenicol. The antibacterial activity may be due to bioactive compounds in these extracts. *A. paniculata* contains diterpenoid lactone compounds, especially andrographolide, which have been reported to have antibacterial activity [14]. This is consistent with research conducted by Nasution (2019), where ethanol extract of *A. paniculata* had an inhibition zone against *S. typhi* bacteria [18] and research conducted by Abraham (2019), where methanol and hexane fractions of *A. paniculata* had inhibition zones against *S. typhi* bacteria [19].

Meanwhile, *C. domestica* contains curcumin, also known to have antibacterial properties [4]. This is also consistent with research conducted by Setiyawati (2022), where ethanol extract of *C. domestica* had an inhibition zone against *S. typhi* bacteria [20]. Nevertheless, the antibacterial activity was relatively weak, possibly due to the different mechanisms of action of medicinal plants compared to the antibiotic chloramphenicol.

The exact mechanisms of antibacterial action of medicinal plants have yet to be fully understood. However, they are believed to involve several targets, including inhibition of bacterial cell wall synthesis, enzymes, and protein formation. In addition, medicinal plants can bind metals needed by bacteria for growth, affect quorum sensing systems, have anti-inflammatory properties, and stimulate the host's immune response [5],[7],[21]. On the other hand, chloramphenicol has a specific target of inhibiting bacterial protein synthesis by binding to the 50S ribosomal subunit [22].

Furthermore, the weak antibacterial activity of medicinal plants compared to chloramphenicol could also be due to the low concentration of active compounds in the extract or limitations in the diffusion of active compounds in the agar medium [23].

Antibacterial activity of combinations of medicinal plant extracts and chloramphenicol

The results showed increased antibacterial activity when medicinal plant extracts were combined with chloramphenicol, compared to single extracts. However, the antibacterial activity of this combination was still lower than that of single chloramphenicol. This phenomenon can be explained through several mechanisms that may occur at the molecular level.

Several recent studies have demonstrated successful synergistic interactions between plant extracts and antibiotic. Zahli et al. (2023) reported significant synergistic action of *Thymus capitatus* or *Syzygium aromaticum* essential oils and antibiotics combinations against multi-resistant Salmonella strains [24]. Similarly, Atta et al. (2023) documented synergistic interaction between natural polyphenolic extracts and synthetic antibiotic [25]. In contrast to these findings, our results showed that while the combinations of A. paniculata or C. domestica with chloramphenicol did show increased activity compared to single extracts (23.17 ± 1.26 mm and 21.00 ± 2.65 mm respectively), they were less effective than chloramphenicol alone (28.33 ± 0.58 mm).

One possibility is the occurrence of molecular interactions between compounds in the extract and chloramphenicol that can affect the physicochemical properties of the antibiotic, which in turn can affect its diffusion in the agar medium and alter its activity profile. In addition, compounds in plant extracts may compete for targets, where some compounds in the extract may compete with chloramphenicol for the same cellular targets, resulting in a partial antagonistic effect that reduces the potential for increased antibacterial activity [26].

Statistical analysis showed no significant difference between the combination of *A. paniculata* with chloramphenicol and *C. domestica* with chloramphenicol ($p=0.275$). This finding indicates that both plant extracts have similar effects when combined with chloramphenicol, although the underlying molecular mechanisms may differ. This opens up opportunities for further research to identify specific compounds in both extracts and to understand the interaction mechanisms at the molecular level more deeply.

The results of this study provide a new perspective on the interaction between medicinal plant extracts and conventional antibiotics, particularly chloramphenicol, where in this study, it was found that the combination of medicinal plant extracts with chloramphenicol does not always result in the expected increase in antibacterial effectiveness. On the contrary, in this study, such combinations can even reduce therapeutic potential compared to single chloramphenicol. This phenomenon highlights the importance of a deeper understanding of the molecular mechanisms underlying the interaction between active compounds in plant extracts and antibiotics [27].

These findings have important implications in the context of developing antibacterial treatment strategies. Although the use of combinations of antimicrobial agents is often considered a promising approach to overcoming antibiotic resistance, the results of this study show that this approach requires more careful evaluation. Complex interactions between natural compounds and synthetic antibiotics can produce unexpected beneficial and detrimental effects.

▪ CONCLUSION

The combination of the extracts with chloramphenicol showed an antagonistic interaction. The combinations were more effective increased antibacterial activity than single extracts, but they significantly reduced chloramphenicol's effectiveness, as evidenced by smaller inhibition zones compared to chloramphenicol alone.

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