Research Article

Effect of Katuk Leaves Ethanol Extract Gel as an Antibacterial and Antifungal in Orthodontic Treatment

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Abstract.
Fixed orthodontic treatment is one option for treating malocclusion. The intricate design makes it difficult for patients to clean their teeth and can cause the emergence of microorganisms in the oral cavity. Katuk plant (*Sauropus androgynus* (L.) Merr.) is commonly used as herbal medicine. Flavonoids in katuk leaves have antimicrobial properties. The purpose of this study was to determine the effect of katuk leaf ethanol extract gel as an antimicrobial by inhibiting the growth of bacteria and fungi involved in orthodontic treatment. The study was an experimental study with a post-test-only control group using katuk leaves ethanol extract gel formulation as treatment, aquadest gel as a negative control, ketoconazole as a positive control against *Candida albicans*, and amoxicillin against *Streptococcus mutans*. Data were analyzed using the Kruskall–Wallis and Mann–Whitney tests ($P < 0.05$). The results show that katuk leaves have inhibition on *Streptococcus mutans* ($P = 0.000$) growth but have no inhibition on *Candida albicans* ($P = 1.00$) growth. The conclusion of this study is that the gel of katuk leaves ethanol extract (*S. androgynus (L.) merr.*) has antibacterial activity against *S. mutans* in the oral cavity but no antifungal effect on *C. albicans*.

Keywords: *Candida albicans*, fixed orthodontics, katuk leaves, *Streptococcus mutans*

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1. Introduction

Malocclusion is a condition in which the relationship of a tooth to another tooth deviates from the normal relationship [1]. The goal of orthodontic treatment is to improve oral function, but, orthodontic treatment still has a negative impact [2]. The oral cavity is in direct contact with fixed orthodontic appliances such as power chains or elastomer chains, brackets, bands, and wires, which are connected together, and the complex design can cause the emergence of microorganisms in the oral cavity because the patients is difficult to clean their teeth [3].

In the oral cavity, bacteria classified as normal flora were found, including Streptococcus mutans and Candida albicans. Normal flora, under certain circumstances, can be a problem [4]. This can occur when the amount of normal flora exceeds the normal amount or when the individual's immune system is unable to prevent normal flora from growing excessively. The most common problem caused by microorganisms in the oral cavity is canker sores, dental caries, and candida fungal infections [5,6].

Saliva contains protein, which will cause a selective protein absorption process that will then produce a pellicle layer. Streptococcus mutans is a bacterium that has a major role in causing dental caries by live in colonies encountered within the first 4 hours of the biofilm and can increase in the presence of carbohydrates. Acid causes tooth demineralization, and carbohydrates are substrates that are fermented by bacteria so that they get energy. If carbohydrates are consumed in excess accompanied by poor oral hygiene, it can have the potential for caries, especially in fixed orthodontic users. So, it is recommended that patients who are undergoing orthodontic treatment maintain healthy teeth to reduce bacteria in the oral cavity [7].

Candida albicans is a normal flora of the human oral cavity. If fixed orthodontic users don't pay attention to oral hygiene, it can cause candidiasis. In a study conducted by Grzegocka et al., 10 out of 17 (59%) patients who used fixed orthodontic treatment experienced an increase in the growth of Candida albicans fungus after orthodontic use [8].

Since ancient times, Indonesian people have used plants as ingredients for traditional medicine. Katuk leaves (Sauropus androgynus (L.) Merr) are potential alternative plants in traditional medicine because they have active compounds that include carbohydrates, triterpenoids, proteins, glycosides, saponins, tannins, flavonoids, steroids, and alkaloids. Flavonoids are often researched and believed to have antimicrobial activity [9]. One of the modern products is a gel preparation made from medicinal plant ingredients. Gels are preparations with a semi-solid consistency consisting of small and large molecules made into a kind of jelly with a gelling agent. The advantages of gel preparations are that they are non-sticky, have little forming material, and have no change in viscosity at storage temperature. Selection in gel dosage form has good potential as a topical medicinal ingredient compared to ointments due to the non-adhesive nature of the gel, a stable formulation, and better aesthetics [10].

Based on the description above, this study aims to determine the effect of katuk leaf ethanol extract gel (Sauropus androgynus (L.) Merr.) as an antimicrobal by inhibiting the

growth of Candida albicans and Streptococcus mutans bacteria involved in orthodontic treatment.

2. Experimental Details

2.1. Materials and procedures

There were two research subjects used in this study: Candida albicans, cultured in Saboraud Dextrose Agar (SDA) media, and Streptococcus mutans, cultured in Mueller Hinton Agar (MHA) media. The number of SDAs used was 8 each for 32 samples using the Federer formula. Each petri dish is filled with four samples.The object of this study was katuk leaves obtained from the Cisarua Lembang garden and made into a gel. The place to do the research is the Biochemistry Laboratory and Microbiology Laboratory, Faculty of Medicine, Jenderal Achmad Yani University, Cimahi. The materials used in this study include materials for making katuk leaf extract, including 70% ethanol and katuk leaves. The ingredients for making katuk leaf ethanol extract gel include carbopol, TEA, and distilled water. Ingredients for rejuvenation and treatment of fungi and bacteria are Candida albicans, Streptococcus mutans bacteria, Saboraud Dextrose Agar (SDA), Mueller Hinton Agar (MHA), ketoconazole, distilled water, aquades gel base, KOH, and katuk leaf ethanol extract gel. The katuk leaves used are green katuk leaves taken from the Manoko Experimental Garden, Lembang, West Java. Katuk leaf extract with ethanol solvent obtained by the maceration method.

2.2. The preparation for making katuk leaf ethanol extract gel

As much as 100 grammes of katuk leaf simplicia powder are put in a glass container, soaked in 1 litre of 70% ethanol solution, covered with aluminium foil, and left for 5 days with occasional stirring. After 5 days, the soaked samples were filtered through filter paper. Then the solvent evaporation was carried out with a rotary evaporator to obtain a thick extract. The preparation of gel preparations with a carbopol base is carried out by heating water to a temperature of 70–80 °C. The hot water used is stirred with the carbopol until it expands and a gel is formed for approximately 30 minutes, then TEA is added to the gel base and can be stirred until the gel base thickens and is homogeneous. Then the extract can be added with propylene glycol and methyl

paraben so that it dissolves. The dissolved extract can be transferred to the base and stirred until it is homogeneous.

2.3. Inhibition test of katuk leaf ethanol extract gel

First, the tools and materials were sterilised in an autoclave. Prepare 4 petri dishes given MHA added with 2 µL of Streptococcus mutans suspension and 4 more pieces poured with 2 ml of SDA each and added with 2 µL of Candida albicans suspension. The method used in this research is the well method, which involves making 4 well holes in each agar medium. After the holes were formed, the gel preparations of ethanol extract of katuk leaves, gel base, and amoxicillin were put in the wells and then observed for 4 days. After that, the clear zone was measured using a vernier calliper around the well. In the measurement, the outer zone is used from around the well to the outer boundary of the clear zone to determine its size.

2.4. Data analysis

Analysis of the test results was carried out by SPSS calculations using the normality test with the Shapiro-Wilk test. The Kruskall-Wallis test if the data is not normally distributed ($p<0.05$) and the Mann Whitney test if the data is not normally distributed ($p<0.05$) aim to find out whether there is effectiveness of katuk leaf ethanol extract gel from within in inhibiting bacterial growth in orthodontic treatment.

2.5. Research ethics

This research has risks for researchers, but these risks can be overcome by the use of Personal Protective Equipment (PPE). The PPE used in this study included a laboratory coat, gloves, and closed shoes, and masks to protect researchers from fungus contamination. The research was carried out after obtaining approval from the Research Ethics Commission (REC) of Jenderal Achmad Yani University (Number 029/UH3.12/2022 and 009/UH3.01/2023). Approval was obtained after the researchers sent the files and thesis proposals to the Ethics Commission.

3. Results and Discussion

3.1. Results

3.1.1. Streptococcus mutans

This study was conducted to determine the effect of ethanol extract gel of katuk leaves (Sauropus androgynus (L.) Merr.) as an antibacterial for Streptococcus mutans in orthodontic treatment.

TABLE 1: Test the diameter of the clear zone for each group Streptococcus mutans bacteria.

Group	Means	p.s	Interpretation
Day 1			
Group 1 (-)	0.00	0.000	There is a difference
Group 2 (test)	8.94		
Group 3 (+)	30.49		
Day 2			
Group 1 (-)	0.00	0.000	There is a difference
Group 2 (test)	8.89		
Group 3 (+)	31.70		
Day 3			
Group 1 (-)	0.00	0.000	There is a difference
Group 2 (test)	8.54		
Group 3 (+)	30.27		
Day 4			
Group 1 (-)	0.00	0.000	There is a difference
Group 2 (test)	8.25		
Group 3 (+)	30.96		

**) Kruskall Wallis, $p \leq 0.05$ (There is a significant difference).

The results of the research show that the calculation of the 1st, 2nd, 3rd, and 4th days shows a significant difference between each treatment group.

To find out more about the comparison between groups, further tests were carried out, namely pairwise comparisons, and the results can be seen in Table 2.

In the comparison test between groups on day 1, the results showed that there were significant differences between Group 1 (-), group 2 (test), and group 3 (+). But, there was no significant difference between group 2 (test) and group 3 (+).

Table 2: Comparison test of clear zone diameter on day 1 Streptococcus mutans bacteria.

Comparison between groups	P-Value	Interpretation
Group 1 (-) with group 2 (test)	0.000	There is a difference
Group 1 (-) with group 3 (+)	0.000	There is a difference
Group 2 (test) to group 3 (+)	0.102	No difference

Mann-Whitney test, $p<0.05$ (there is a significant difference).

Table 3: Comparison test of the diameter of the clear zone on the second day Streptococcus mutans bacteria.

Comparison between groups	P-Value	Interpretation
Group 1 (-) with group 2 (test)	0.000	There is a difference
Group 1 (-) with group 3 (+)	0.000	There is a difference
Group 2 (test) to group 3+	0.102	No difference

* Mann Whitney test , $p<0.05$ (there is a significant difference)

In the comparison test between groups on day 2, the results showed that there were significant differences between groups. Group 1 (-), group 2 (test), and group 3 (+) There was no significant difference between group 2 (test) and group 3 (+).

Table 4: Comparison test of clear zone diameter on day 3 Streptococcus mutans bacteria.

Comparison between groups	P-Value	Interpretation
Group 1 (-) with group 2 (test)	0.000	There is a difference
Group 1 (-) with group 3 (+)	0.000	There is a difference
Group 2 (test) to group 3 (+)	0.102	No difference

Mann Whitney test, $p<0.05$ (there is a significant difference)

In the comparison test between groups on day 3, the results showed that there were significant differences between groups. Group 1 (-), group 2 (test), and group 3 (+) There was no significant difference between group 2 (test) and group 3 (+).

Table 5: Comparison test of the diameter of the clear zone on the 4th day Streptococcus mutans bacteria.

Comparison between groups	P-Value	Interpretation
Group 1 (-) with group 2 (test)	0.000	There is a difference
Group 1 (-) with group 3 (+)	0.000	There is a difference
Group 2 (test) to group 3 (+)	0.102	No difference

*Mann Whitney test , $p<0.05$ (there is a significant difference)

Prior to statistical analysis, a normality test was performed using the Shapiro-Wilk test and a data homogeneity test with the Levene test. The results of the normality test

Figure 1: V +Source: Personal documentation. (a) Katuk leaf ethanol extract gel; (b) Base gel; (c) Amoxicillin.

showed that the p-value could not be obtained because the results of the study on all samples in the treatment and negative control groups showed the number 0.

In this study, it was continued with the Kruskall-Wallis test to determine the differences between the three groups.

Hypothesis:

Ho: a = 0 (antibacterial inhibition between the two groups showed no difference on days 1, 2, 3, and 4).

Ha: a 0 (the antifungal inhibition between the two groups was different on days 1, 2, 3, and 4).

3.1.2. Candida albicans

In the comparison test between groups on day 4, the results showed that there were significant differences between groups. Group 1 (-), group 2 (test), and group 3 (+) There was no significant difference between group 2 (test) and group 3 (+).

This research was conducted to determine the effect of katuk leaf ethanol extract gel (Sauropus androgynus (L.) Merr.) as an antifungal against Candida albicans fungus in orthodontic treatment. For the negative control treatment group (group 1) and the katuk leaf ethanol extract gel test group (group 2), there were 16 samples each. For the positive

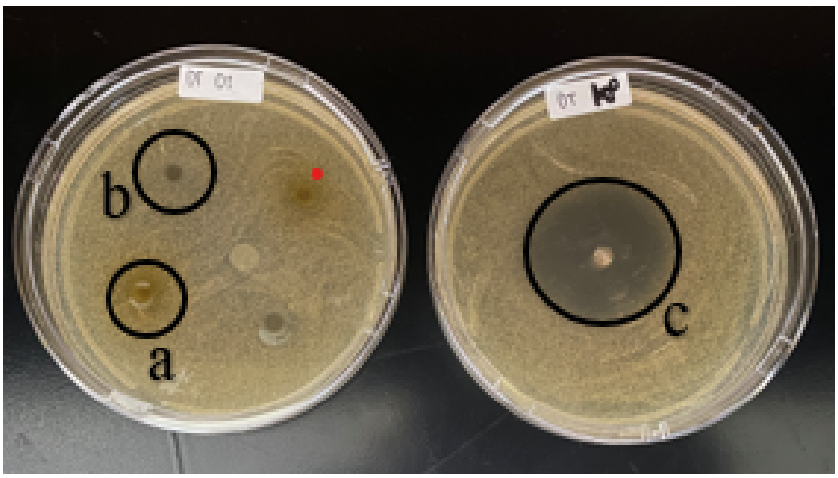

Figure 2: Source: Personal Documentacion. (a) Katuk leaf ethanol extract gel (b) base gel (c) Ketoconazole.

TABLE 6: Test the effectiveness of katuk leaf ethanol extract gel on Candida albicans fungi.

	Means	p.s	Interpretation
Day 1			
Group 1 (-)	0.0	0.000	There is a difference
Group 2 (test)	0.0		
Group 3 (+)	34.81		
Day 2			
Group 1 (-)	0.0	0.000	There is a difference
Group 2 (test)	0.0		
Group 3 (+)	34.55		
Day 3			
Group 1 (-)	0.0	0.000	There is a difference
Group 2 (test)	0.0		
Group 3 (+)	33.02		
Day 4			
Group 1 (-)	0.0	0.000	There is a difference
Group 2 (test)	0.0		
Group 3 (+)	33.02		

**) Kruskall Wallis, p≤0.05 (There is a significant difference)

group (group 3), there is only one sample. Group 1 (negative control): Candida Albicans mushroom culture in SDA media given an aquadest gel base. Group 2 (test): Candida Albicans mushroom culture in SDA media given the ethanol extract gel of katuk leaves (Sauropus androgynus (L.) Merr.). Group 3 (positive control): Candida Albicans cultured in SDA media given ketoconazole

Based on the results of measurements of the Minimum Inhibitory Concentration (MIC) on days 1 to 4, the diameter of the clear zone on the growth of Candida albicans using the well method, the ethanol extract gel of katuk leaves (Sauropus androgynus (L.) Merr.) did not show inhibition of the growth of the fungus Candida albicans. Table 1 shows that in the treatment group given katuk leaf ethanol extract gel on days 1, 2, day 3, and day 4, there was no change, while the positive control had effectiveness in inhibiting the growth of the Candida albicans fungus. The size of the diameter of the clear zone in the positive control was greatest on day 1, day 2, and so on, decreasing until 4^{th} day.

3.2. Discussion

This study used katuk leaves to determine the effectiveness of katuk leaf ethanol extract gel against the growth of Streptococcus mutans and Candida albicans in orthodontic treatment. Orthodontic treatment is a treatment performed to correct the abnormal position of teeth and jaws which divided into two categories: fixed orthodontic treatment and removable orthodontics [11]. A combination of brackets, wire, and orthodontic rubber is needed as a series of interconnected devices make a complex structure in the human oral cavity, and it will come into contact with saliva. Saliva contains protein, which will cause a selective protein absorption process that will then produce a pellicle layer. The pellicle is a thin layer of salivary, colorless glycoproteins that can come into direct contact with the surface of teeth and components in the oral cavity, including orthodontic devices. Within 2 hours of contact, the composition and activity in the oral cavity against the complex components of fixed orthodontic devices will form pellicles, which become the initial medium for the attachment of oral microorganisms such as bacteria and fungi, including Streptococcus mutans and Candida albicans [12,13].

Katuk (Sauropus androgynus (L.) Merr) beslongs to the Euphorbiaceae family. The dark green leaves are usually used as a potential treatment alternative, as they have many vitamins and nutrients. Active compounds that can be found in katuk leaves are saponins, tannins, flavonoids, steroids, and alkaloids, which have properties as antidiabetic, antiobesity, antioxidants, and antimicrobial [14].

In the oral cavity, humans have a wide variety of commensal bacterial species [15]. One of them is the bacterium Streptococcus mutans that play a very important role in the occurrence of dental caries. Streptococcus mutans is a facultative anaerobic, gram-positive bacterium belonging to the Streptococcus viridans group [16,17]. Streptococcus mutans plays a major role in the occurrence of caries because it can produce acid from

carbohydrate fermentation metabolism, which makes the oral cavity area acidic and increases the risk of caries. This acid causes demineralization, and carbohydrates are a substrate from which fermented bacteria get energy. If carbohydrates are consumed in excess, they can increase the incidence of caries, especially in patients using fixed orthodontics [7].

The study was conducted to test the antibacterial The results of the antibacterial effectiveness test in this study showed that the ethanol extract gel of katuk leaves could inhibit the growth of Streptococcus mutans bacteria. The result shows, each replicate didn't show too great a difference, so clear zone measurements were carried out with a calliper in order to find out the average diameter of the clear zone and the difference between treatments. The inhibition zone occurs because katuk leaves have flavonoid compounds that work to inhibit the function of cell membranes by forming complex compounds with extracellular and dissolved proteins that can damage the bacterial cell membrane and followed by the release of intracellular compounds [18,19]. It is proven that the antibacterial content of katuk leaves can inhibit growth of Streptococcus mutans bacteria used as a supportive therapy that can prevent of caries in orthodontic treatment. In the oral cavity, in addition to Streptococcus mutans bacteria, there are also other microbes in the form of fungi called Candida albicans fungi, which can be pathogenic as well.

Candida albicans is one of the microorganisms common in the human mouth, but it can become pathogenic if the amount is excessive [20]. Prevalence of Candida albicans as part of the normal flora of the gastrointestinal tract, upper respiratory tract, and genital mucosa in mammals Research conducted says that, on average, 35% are obtained in the oral cavity [20-22]. The pathogenesis of Candida albicans can be triggered by the use orthodontics applicance. The main factor causing the fungus Candida albicans is the physiological status of the host itself, which favors the virulence factor of the fungus [23].

Katuk leaves have flavonoid-active compounds [24]. Flavonoids inhibit fungal growth by various fungistatic mechanisms, such as disrupting plasma membrane formation, inducing mitochondrial dysfunction, inhibiting cell wall formation, inhibiting cell division, and inhibiting RNA and protein synthesis [25]. Fungistatic is the workings of antifungal compounds that can inhibit fungal growth but not kill it, characterized by turbid inhibitory zones in agar media [19]. Flavonoid fungstatic activity, among themdisrupts plasma membrane induction, inhibiting cell wall formation, induces mitochondrial dysfunction, inhibition of cell division, inhibition of the efflux pump, RNA/DNA inhibition and protein

synthesis [18]. Katuk leaves have a direct antibacterial role by disrupting the function of microorganisms such as bacteria or viruses and can be used to increase the body's immunity. Katuk (Sauropus androgynus (L.) Merr.) is a plant that contains chemical compounds, namely flavonoids, proteins, papaverine alkaloids, saponins, tannins, and fats [25].

Flavonoids can be obtained from a plant through the extraction process. Maceration is one of the most common extraction methods. In research conducted by Kusumawardhani et al. in 2020, it was stated that the content of flavonoid secondary metabolites in the best katuk leaves is best obtained by means of maceration using 70% ethanol extract with an average of 0.425mgQE/gr; therefore, researchers used 70% ethanol as a solvent in extraction in order to obtain antifungal power [26].

Based on the result of our research, there is no antifungals for Candida albicans. It was found that there was no inhibition zone around the katuk leaf ethanol extract gel treatment group and also the gel base, but a large inhibition zone was found around the wells given a positive control, namely ketoconazole. This difference can be due to several factors. According to research on plant extracts by Gunawan et al 2016 and Makhfirah et al 2020, metabolite compounds such as flavonoids, tannins, saponins, alkaloids, polyphenols, triterpenoids can be effective as antioxidants, anti-inflammatory, anticancer, antimicrobials such as antibacterial and antifungal, but the study did not mention the minimum amount of a secondary metabolite compound to inhibit Candida albicans [25,27]. A similar study on katuk leaf extract (Sauropus Andogynus (L.) Merr) was also conducted by Japar et al, 2021 which stated that there was no effectiveness of 96% katuk leaf ethanol extract against the growth of Candida albicans using a concentration of 5 extracts, namely 20%, 40%, 60%, 80%, and 100% [28]. This can state that ethanol solvents with a concentration of 96% or a concentration of 70% are not able to inhibit the growth of Candida albicans fungi. When compared to testing on other microorganisms, testing the activity of an extract as an antifungal, especially Candida albicans, requires more specific secondary metabolite compounds. Research conducted by Saleh et al. states that the content of specific flavonoids such as isoflavones, daidzein, genistein, favonol, flavones, flavans, and others plays a role in the death process of Candida albicans fungi [25,29]. Another study conducted by Adamu et al, 2021 about Pegangan leaves mentions the specific value of flavonoids to inhibit parasitic Aspergillus bacterial microorganisms, which is as much as 140 mg/g GAE [30]. This indicates the need for specific levels of flavonoids in plants to determine antifungal activity.

Another possible cause is that the ethanol extract of katuk leaves (Sauropus androgunys (L.) Merr) had no effect on fungi used in studies such as Candida albicans. Research by Kusumanegara in 2020 compared rose petal extract and katuk leaf extract, with the results showing that both inhibit the growth of Candida albicans fungus by the infusion method [9]. This study tested the antifungal activity of katuk leaf ethanol extract gel against the growth of Candida albicans fungus as an initial research project or is still a preliminary test, using different extraction methods that allowed this study to not succeed in obtaining good results. positive in having an inhibitory zone against the growth of the fungus Candida albicans [31].

4. Conclusion

Based on the results of the study, it can be concluded that administration of ethanol extract gel of katuk leaves (S. androgynus (L.) Merr) using the well method has an effect as an antibacterial on Streptoccus mutans bacteria but has no effect as an antifungal on the Candida albicans fungus present in the oral cavity of orthodontic users.

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