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SARS-CoV-2 Clearance from *Andrographis paniculata*, *Boesenbergia rotunda*, and Favipiravir among Mild COVID-19 Cases in Klong Prem Central Prison during Mid-2021: a Retrospective Study

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Abstract

This study aims to assess the effectiveness of two herbal medicines, *Andrographis paniculata* (Burm.f.) Nees capsule (AP) and *Boesenbergia rotunda* (Linn.) Mansf. extract capsule (BR), on the rate of SARS-CoV-2 virus clearance among inmates of Klong Prem Central Prison, Bangkok. Cases with mild COVID-19 were allocated into four groups: four capsules of AP thrice daily (n=30), one capsule of BR once daily (n=30), a combination of AP and BR (AP-BR) (n=30), or favipiravir (n=30) for five days. The primary outcome was time until undetected SARS-CoV-2 infection after starting treatment. The median period of SARS-CoV-2 clearance was shorter in the AP and AP-BR groups (9 days) compared to the BR (11 days) and favipiravir (13 days) groups. No one developed pneumonia; however, one participant in the AP group developed hyperkalemia. Our results suggest that *A. paniculata* with or without *B. rotunda* may be used as an alternative treatment for mild COVID-19 when access to favipiravir is limited. Further clinical trials are needed to determine their efficacy and safety.

Keywords: *Andrographis paniculata*, *Boesenbergia rotunda*, favipiravir, mild COVID-19

Background

In June 2021, more than 15,000 prisoners in Bangkok and surrounding provinces were infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19). An alpha variant was identified from the specimens of prisoners. At that time, there was no vaccine for prevention of COVID-19, and available treatment was limited. Only favipiravir, imported from Japan and China, was recommended for COVID-19 cases with pneumonia.[1]

Nearly 5,000 inmates in the Klong Prem Central Prison had mild COVID-19 infections. Due to their mild illness, they did not qualify to receive favipiravir as treatment. Consequently, the Department of Corrections, Ministry of Justice, in collaboration with the Ministry of Public Health, initiated a project to curb COVID-19 outbreaks in prisons by treating the cases with herbal medicines. Two herbs were identified as having potential effects against SARS-Cov-2; *Andrographis paniculata* (Burm. f.) Nees capsule (AP) and *Boesenbergia rotunda* (Linn.) Mansf. extract capsule (BR).

Andrographolide is the major active component in *A. paniculata*. In an *in vitro* study, *A. paniculata* extract and andrographolide significantly inhibited the production of infectious virions of SARS-CoV-2.[2] The result from a randomized controlled trial showed promising efficacy and safety of *A. paniculata* in cases with mild COVID-19 due to its anti-inflammatory effect.[3] In contrast, real-world data revealed that treatment with *A. paniculata* might increase the risk of pneumonia, but confounding factors that may affect clinical outcomes were not excluded due to the study's observational design.[4] Currently, the Department of Medical Services (DMS), Ministry of Public Health recommends using *A. paniculata* for cases with symptomatic COVID-19 without pneumonia.[5]

B. rotunda has been used in Thai cuisine as a cooking spice. An *in vitro* study showed that *B. rotunda* extract and panduratin A, a major active compound in *B. rotunda*, potentially inhibited protease enzyme of SARS-CoV-2.[6] However, the effect of *B. rotunda* extract as treatment for COVID-19 has yet to be studied in humans.

The primary objective of this study was to compare the period between treatment initiation and undetected SARS-CoV-2 in cases with mild COVID-19. A secondary objective was to assess the safety of these regimens, in particular, development of adverse events and pneumonia.

Methods

Study Design

In May 2021, a project to explore alternative treatments for controlling the spread of SAR-CoV-2 was initiated. All inmates of Klong Prem Central Prison with mild COVID-19 were informed about the project and invited to participate in the study, of which 120 agreed.[7] Those who refused to participate received *A. paniculata* four capsules three times a day for five days. Participants were randomly assigned into one of four treatment groups: *A. paniculata* (AP), *B. rotunda* (BR), a combination of AP and BR (AP-BR), or favipiravir. The strength and dosage of each treatment regimen is shown in Table 1. The medical records of participants were retrieved after approval from the Director General of the Department of Corrections. The study flowchart is displayed in Figure 1.

Table 1. Dosage regimens of each treatment group (of standardized AP capsules, BR extract capsules, a combination of AP capsules and BR extract capsules, and favipiravir)

Treatment	Strength	Dosage regimen
AP capsules	400 mg (andrographolide 12 mg)	4 capsules thrice daily for 5 days
BR extract capsules	500 mg	1 capsule once daily for 5 days
AP capsules and BR extract capsules	AP 400 mg, BR 500 mg	4 AP capsules thrice daily for 5 days, 1 BR capsule daily for 5 days
Favipiravir tablets	200 mg	9 tablets twice on day 1, followed by 4 tablets twice a day for 5 days

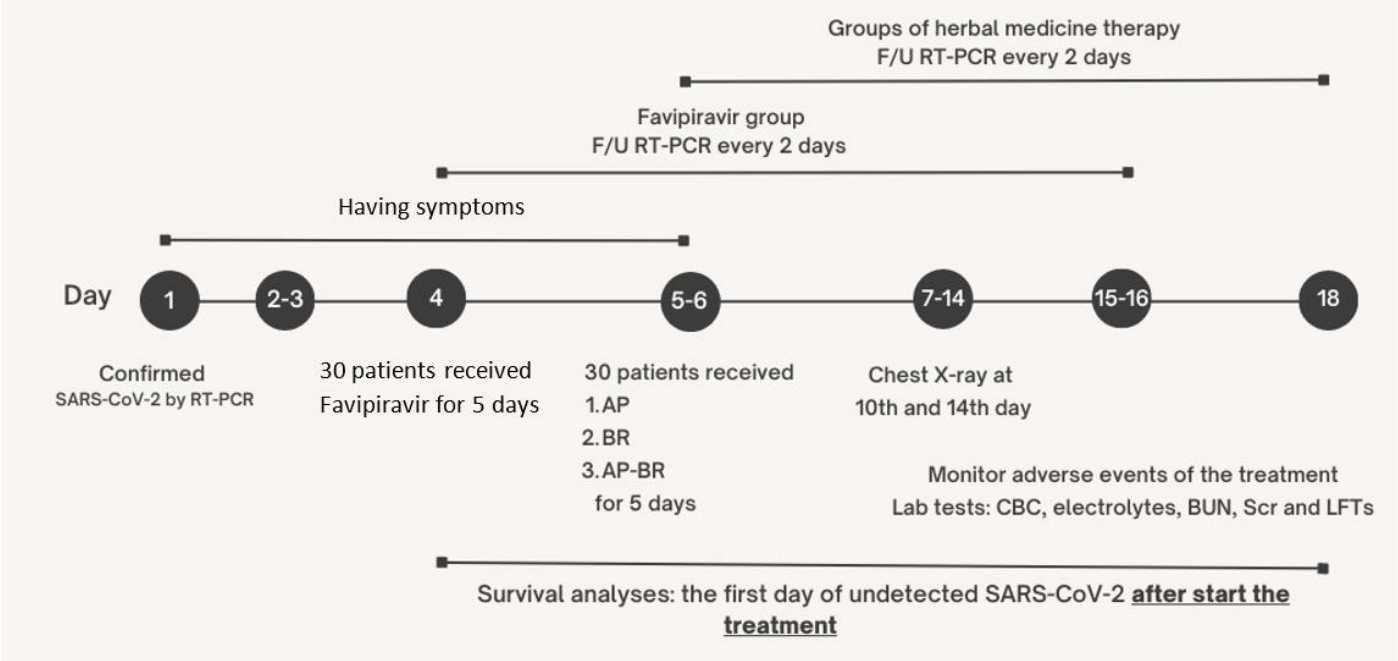
Note: AP: Andrographis paniculate, BR: Boesenbergia rotunda

Outcome Assessment

SARS-CoV-2 viral loads in all cases were measured using cycle threshold (Ct) values of ORF1a/b gene and N gene at baseline. Reverse transcription polymerase chain reaction (RT-PCR) assays of nasopharyngeal swab specimens were conducted every two days after treatment initiation. The primary outcome was the interval between the day of starting treatment (day 1) and the day when the participant returned a negative SAR-CoV-2 test. The secondary outcomes were the development of pneumonia and adverse events on day 14. Data collected from medical records included age, body mass index (BMI), underlying diseases, Ct values of ORF1a/b gene and N gene, date and results of RT-PCR tests, and results of chest X-rays on days 10 and 14. Complete blood counts (CBC), electrolytes, blood urea nitrogen (BUN), serum creatinine, and liver function tests were performed on day 14 to monitor the safety of the interventions.

Study Products

A. paniculata (Burm. f.) Nees capsule (AP) is manufactured by the Chaophya Abhaibhubejhr Hospital Foundation, Thailand. Each capsule contains 3% andrographolide in 400 milligrams (mg) of dried AP powder (andrographolide 12 mg per capsule). *B rotunda* (Linn.) Mansf. extract capsule (BR) is manufactured by the Pharma Herbal Company, Thailand. Each capsule contains 8% panduratin A and 18% pinostrobin in 500 mg powder (28 mg of panduratin A and 63 mg of pinostrobin).



Note: AP: Andrographis paniculate, BR: Boesenbergia rotunda, AP-BR: a combination of AP and BR, CBC: complete blood counts, BUN: blood urea nitrogen, Scr: serum creatinine, LFTs: liver function tests, F/U: follow-up

Figure 1. Study diagram of collected and analyzed health information on COVID-19 therapy

Data Analysis

Baseline characteristics of participants such as age, Ct values and duration of COVID-19 illness before receiving treatment were summarized using mean and standard deviation (SD) whereas BMI and underlying diseases were summarized using frequencies and percentages. Comparison of baseline characteristics among the four groups were tested using analysis of variance for continuous variables and Pearson's chi-square test for categorical variables. The median interval from treatment initiation to the first day of undetected SARS-CoV-2 with 95% confidence interval in each group was calculated. Analysis of time-to-event outcome was performed using survival analysis. Kaplan-Meier survival curves were created to compare the distribution of the outcome between groups. Multiple comparisons will be conducted if the log-rank test shows statistical significance to find out which groups were different. Cox-regression analysis was performed to determine associated risk factors for undetected SARS-CoV-2 within 14 days. The level of statistical significance was set at 0.05.

Ethical Approval

Ethical approval to conduct the study was not required due to the public health emergency. In addition, both products used in the study were approved by the Thai Food and Drug Administration as herbal medicine (for *A. Paniculata*) and dietary supplement (for *B. rotunda*). However, verbal informed consent was requested and obtained from participants before interview and sample collection.

Results

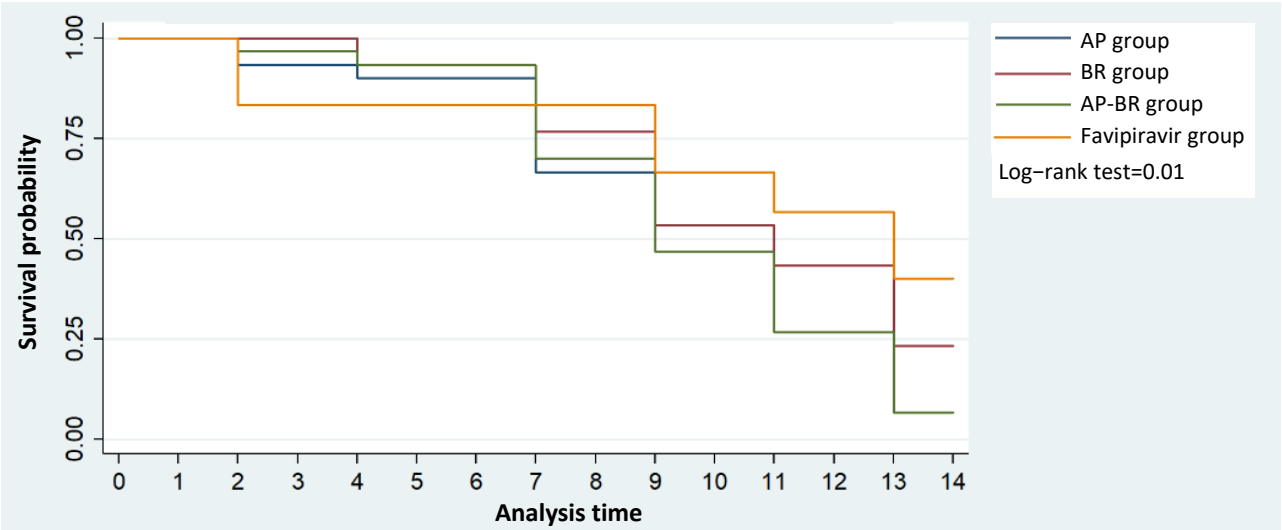
All participants in this study reported muscle pain. The mean (SD) age of participants was 37.4 (8.7) years and all were male. Table 2 shows a comparison of the baseline characteristics between the four groups. The mean age and mean BMI of the four groups were not significantly different. Most (85.8%) did not have any underlying chronic diseases; however, the AP group had a higher percentage of participants with underlying diseases (three hypertension and four asthma) than the other groups (p-value 0.005). Regarding mean Ct values of ORF1a/b gene and N gene, the AP-BR group had the highest amount of viral load compared to other groups, followed by the AP, BR, and favipiravir groups (p-value <0.05). There was a significant difference in the mean duration of illness prior to initiation of treatment among the four groups (p-value <0.001). The mean duration of illness prior to treatment among participants who received favipiravir (3.9 days) was shorter than that for the other groups (AP 6.0 days, BR 5.5 days, and AP-BR 6.0 days).

Table 2. Comparison of baseline characteristics between the four groups

Characteristic	N (%)					*P*-value
	Total (N=120)	AP (n=30)	BR (n=30)	AP and BR (n=30)	Favipiravir (n=30)	
Age (years) (Mean±SD)	37.4±8.7	39.9±9.5	37.3±8.4	34.7±7.8	37.6±8.6	0.140[a]
BMI (kg/m^2)						0.757[b]
<18.5	4 (3.3)	0 (0.0)	2 (6.7)	0 (0.0)	2 (6.7)	
18.5–22.9	67 (56.7)	18 (60.0)	18 (60.0)	16 (53.3)	16 (53.3)	
23.0–24.9	25 (20.8)	6 (20.0)	4 (13.3)	8 (26.7)	7 (23.3)	
25.0–29.9	17 (14.2)	6 (20.0)	4 (13.3)	4 (13.3)	3 (10.0)	
≥30	6 (5.0)	0 (0.0)	2 (6.7)	2 (6.7)	2 (6.7)	
Underlying chronic diseases						0.005[b]
No	103 (85.8)	21 (70.0)	30 (100.0)	27 (90.0)	25 (83.3)	
Yes	17 (14.2)	9 (30.0)	0 (0.0)	3 (10.0)	5 (16.7)	
Ct value (mean ± SD)						
ORF1a/b gene	24.9±6.7	24.5±5.7	26.0±7.7	21.8±4.5	27.3±7.2	0.008[a]
N gene	26.2±6.5	25.4±5.6	27.1±7.5	23.7±5.0	28.4±7.0	0.028[a]
Period of illness[c] (days) (Mean±SD)	5.4±1.1	6.0±0.0	5.5±1.1	6.0±0.0	3.9±1.0	<0.001[a]

Note: [a]Analysis of variance, [b]Fisher's exact test, [c]Prior to treatment initiation

Participants in the AP and AP-BR groups had a median period of 9 days from treatment initiation to the first day of undetected SARS-CoV-2, this was shorter than that among participants in the favipiravir (13 days) and BR (11 days) groups (Table 3). Although the favipiravir group had lower amounts of detected SARS-CoV-2 on treatment initiation, AP, BR, and AP-BR groups had shorter duration of detected SARS-CoV-2 compared to the favipiravir group (log-rank test 0.01) (Figure 2). Multiple comparisons revealed that participants in the AP and AP-BR groups had a significantly higher rate of SARS-CoV-2 virus clearance than the favipiravir group, with log-rank tests of 0.005 and 0.006, respectively. The percentage of participants with undetected SARS-CoV-2 within 14 days since diagnosis of COVID-19 was higher in the AP (57%), AP-BR (54%) and BR (50%) groups compared to the favipiravir group (45%, *p*-value >0.05).



Number at risk	Day														
	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14
AP	30	30	28	28	27	27	27	20	20	14	14	8	8	6	2
BR	30	30	30	30	28	28	28	23	23	16	16	13	13	7	7
AP-BR	30	30	29	29	28	28	28	21	21	14	14	8	8	2	2
Favipiravir	30	30	25	25	25	25	25	25	25	20	20	17	17	12	12

Figure 2. The Kaplan–Meier survival curve for comparing the first day of undetected SARS-CoV-2 PCR test after treatment by AP (Blue), BR (Purple), AP and BR (Green) and Favipiravir (Orange)

Table 3. A median period from treatment start to the first day of undetected SARS-CoV-2

Treatment (n)	Median period (days)	95% CI
AP (30)	9	7.25–11.00
BR (30)	11	9.00–13.00
AP-BR (30)	9	9.00–11.00
Favipiravir (30)	13	9.26–14.00

Cox-regression analysis showed that neither age, BMI, nor underlying diseases were associated with undetected SARS-CoV-2 within 14 days after receiving treatment (Table 4). During treatment, none of the participants developed pneumonia. Regarding adverse events of treatment, there was no difference in alanine aminotransferase (ALT) levels among the four groups and all participants had ALT ≥2 times of upper limit of normal (*p*-value 0.65, Table 5). One participant in the AP group developed hyperkalemia (serum potassium 7.0 milliEquivalents per liter). Hematologic and kidney adverse events were not seen

Table 4. Hazard ratio and 95% confidence intervals from cox-regression analysis between risk factors and event of undetected SARS-CoV-2 within 14 days (n=120)

Variables	Hazard ratio	95% CI
Age	0.99	0.96–1.01
BMI	1.00	0.95–1.06
Underlying diseases	1.27	0.70–2.32

Table 5. Monitoring of hepatotoxicity from the treatment

Treatment group	Number of participants who had ALT ≥2 x ULN (%)
AP	5 (16.7)
BR	3 (10.0)
AP-BR	2 (6.7)
Favipiravir	4 (13.3)

Note: ALT: alanine aminotransferase, ULN: upper limit of normal, Chi-square test: p-value=0.65

Discussion

This is the first study to assess the effectiveness of *A. paniculata* and *B. rotunda* on increasing the rate of viral clearance of SARS-CoV-2. Other studies assessing the effectiveness of AP treatment primarily aimed to investigate clinical recovery.[3,5] We found that mild COVID-19 cases treated with *A. paniculata* (with or without *B. rotunda*) had a shorter period of viral clearance compared to favipiravir, which corroborates with a clinical trial by Zhang et al who administered the sulfonate form of *A. paniculata* to their participants with mild to moderate COVID-19 infection.[8]

The latest DMS guidelines for COVID-19 management recommends starting treatment with *A. paniculata* and favipiravir within 5 days of symptoms onset.[6] In this study, participants in the favipiravir group received their treatment before the other groups because the conventional medicine arrived before the herbal medicines. Since the treatment groups were initiated on different days, findings of survival analyses, therefore, should be interpreted with caution. In this study, participants treated with herbal medicine showed a faster viral clearance period compared to those given favipiravir. The AP and AP-BR groups showed a shorter median period (9 days) between the start of the treatment and the first day of undetected SARS-COV-2 compared to the BR (11 days) and favipiravir (13 days) groups. This result contrasts with previous studies that reported early treatment with favipiravir (approximately 4 days after symptom onset) enhanced viral clearance to 6–10 days.[9,10] SARS-CoV-2 viral clearance varied among our participants, and our small sample size did not allow a more precise estimate of this outcome.

The percentage of participants with undetected SARS-CoV-2 within 14 days post-infection was higher in the AP group than the BR group, which may be attributed to the dosage of *B. rotunda* extract. The effective dosage of *B. rotunda* extract for the treatment of COVID-19 is not yet known; therefore, further clinical trials to determine the optimum dosage and regimen are needed.

Categorized at 14 days, more than half of the participants in this study that were treated with herbal medicine had a shorter period of viral clearance compared to the natural viral clearance duration of 16 days reported among mild COVID-19 cases infected with the alpha variant.[11] Given the severity of COVID-19 as a life-threatening disease, the findings from this study are, potentially, of clinical significance.

In summary, both *A. paniculata* and *B. rotunda* were primarily demonstrated to be safe for the treatment of mild COVID-19. None of the participants in this study developed pneumonia. Furthermore, our results showed no difference in hepatic adverse events among all groups. One participant who received *A. paniculata* developed hyperkalemia. Therefore, potential adverse events should be further investigated in larger studies. Currently, there is an ongoing clinical trial assessing the efficacy and safety of *A. paniculata* and *B. rotunda* compared to standard supportive treatment among asymptomatic COVID-19 cases in Thailand.[12]

The findings of this study should be interpreted with caution due to certain limitations. Firstly, generalization of the results is limited due to the small sample sizes in each group. Secondly, only young male participants were included in this study. Thirdly,

several factors may influence the Ct values of ORF1 a/b gene and N gene, such as specimen type, the timing of sample collection, collection technique, transportation method, and storage conditions, none of which were collected in this study.

Recommendations

The DMS guidelines recommend that physicians consider *A. paniculata* and favipiravir for symptomatic COVID-19 cases without pneumonia. Although *A. paniculata* is more accessible than favipiravir, the quality of the product should be emphasized to the public. Only standardized products with andrographolide should be used. The dosage of andrographolide given to our study participants was 144 mg per day while DMS recommends 180 mg. We used 144 mg for two reasons. Firstly, the majority of Thai residents have already received the COVID-19 vaccine, which can help mitigate disease *severity* when infected. Additionally, in our study, we found that mild COVID-19 cases responded well to *A. paniculata*, even though they did not get vaccinated. Secondly, *A. paniculata* has been shown to have dose-dependent side-effects such that lower dose utilization would minimize side effects.[13]

Although *B. rotunda* was shown to have a slower viral load clearance than *A. paniculata*, possibly due to its unknown effective dose, patients may use it for health promotion, not treatment for COVID-19, as this product is already available in the market as a dietary supplement.

Conclusion

A. paniculata and *B. rotunda* use is associated with a quicker viral clearance in mild COVID-19 infections compared to favipiravir and may be used as an alternative when access to favipiravir is limited. Further clinical trials are needed to assess the efficacy and safety of these two herbal medicines for the treatment of mild COVID-19. Healthcare providers should be aware of possible adverse effects such as hyperkalemia.

Declarations

Consent for Publication

Not applicable

Availability of Data and Materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

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Authors' Contributions

PP guided and revised the manuscript. AM and PK revised the manuscript. MT analyzed study data and wrote the first draft of the manuscript. TP analyzed study data. KC, CC, DM, and TK carried out the research. All authors approved the final manuscript.

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