Original Article

In Vitro Study of Synergistic Activities of *Phyllanthus emblica* L. Leaves and *Garcinia mangostana* L. Peels Crude Extracts to *Cutibacterium acnes*

Papatsara Asavaphark MD[1], Malai Taweechotipatr PhD[2,3], Nanticha Kamanamool MD[4], Salinee Rojhirunsakool MD[1], Saranya Khunkhet MD[1], Montree Udompataikul MD[1]

[1] Department of Dermatology and Skin Center, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand

[2] Department of Microbiology, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand

[3] Center of Excellence in Probiotics, Strategic Wisdom and Research Institute, Srinakharinwirot University, Bangkok, Thailand

[4] Department of Preventive and Social Medicine, Faculty of Medicine, Srinakharinwirot University, Bangkok, Thailand

Background: Due to the increasing antibiotic resistant *Cutibacterium acnes*, studies have substantiated the effectiveness of botanical extracts to inhibit *C. acnes*. Both *Phyllanthus emblica* L. leaves and *Garcinia mangostana* L. peels have good efficacy in inhibiting *C. acnes* growth. However, the combination of both herbal extracts on antimicrobial synergistic activities has not been studied.

Objective: To perform an *in vitro* study of synergistic activities of *Phyllanthus emblica* L. leaves and *Garcinia mangostana* L. peels crude extracts to *C. acnes*.

Materials and Methods: The present report was an experimental, cross-sectional study. Seventy isolates of *C. acnes* from clinical isolations were tested with each crude extract by agar well diffusion method to evaluate minimum inhibition zone (MIZ) and broth microdilution method to evaluate minimum inhibitory concentration (MIC). Thirty-five isolates of *C. acnes* were tested with the combination of both extracts by antimicrobial synergy study-checkerboard testing to evaluate fractional inhibitory concentration (FIC).

Results: The medians (Q1, Q3) MIZ of *P. emblica* and *G. mangostana* at 5 mg/mL were 15.75 (12.00, 18.50), and 10.00 (10.00, 15.00) mm, respectively, with significant difference (p<0.001). The medians (Q1, Q3) MIC of *P. emblica* and *G. mangostana* were 0.078 (0.039, 0.156), and 0.078 (0.078, 0.078) mg/mL, respectively, without significant difference (p=0.327). The checkerboard testing showed FIC indices of 0.192 to 3.333. The synergy activity was 62.86% of the synergy group, 37.14% of the non-synergy group, and none of antagonism, without significant difference between resistant *C. acnes* and susceptible *C. acnes* (p=0.708).

Conclusion: Both *P. emblica* leaves and *G. mangostana* peels crude extracts could inhibit resistant and susceptible *C. acnes*. The combination of both herbal extracts increases antimicrobial synergistic activity, suggesting a utilization of these herbs in combination therapy against antibiotic-resistant *C. acnes*.

Keywords: *Phyllanthus emblica* L.; *Garcinia mangostana* L.; Antimicrobial synergistic activity; *Cutibacterium acnes*; Crude extract

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Acne vulgaris is a common disorder of the pilosebaceous unit that affects over 80% of teenagers and can persist into adulthood[1]. Acne vulgaris has impact on quality of life, it can lead to significant suffering from impaired self-image, psychological well-being, and may even precipitate suicide[2]. The pathogenesis of acne are multifactorial factors, and one of the key factors is *Cutibacterium acnes*[3]. *C. acnes* is an anaerobic Gram-positive rod bacterium found in the pilosebaceous gland[3]. *C. acnes* induces inflammation and triggers pro-inflammatory cytokines, complement system, innate immune response, and humoral immune response that lead to acne formation[4].

Concerning acne treatment, the monotherapy and increasing use of antibiotics have led to the development of *C. acnes* resistance to antibiotics[5,6]. Antibiotic resistant *C. acnes* has been an emerging

Correspondence to:

Udompataikul M.

Department of Dermatology and Skin Center, Srinakharinwirot University, 114 Sukhumvit 23, Khlong Toei Nuea, Watthana, Bangkok 10110, Thailand.

Phone: +66-81-6148432

Email: umontree@gmail.com

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issue and increasing worldwide[7]. A study in Thailand in 2017 found that the prevalence of antibiotic resistant *C. acnes* was 64% to erythromycin, 62.66% to clindamycin, and 1.33% to tetracycline[8]. There was a tenfold increase in the prevalence rate of antibiotic resistant *C. acnes* to erythromycin and clindamycin compared to the study in 2001[9].

Therefore, several studies have substantiated the effectiveness of botanical extracts to inhibit *C. acnes*[10-12]. *Phyllanthus emblica* L. and *Garcinia mangostana* L. have been traditionally used for various medical purposes[13-15]. The important mechanisms of action of both herbs were antimicrobial, anti-inflammatory, antioxidant, and pro-inflammatory cytokines inhibition[13-15]. Both herbs have good efficacy in inhibiting the growth of bacteria such as *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *C. acnes*[10-15]. The leaves of *P. emblica* consist of bioactive compounds including tannins, flavonoids, and other phenolic compounds[13]. Tannins, the major bioactive compounds in *P. emblica* leaves, have antibacterial activity that inhibit cells envelop to transport proteins, inhibit microbial adhesions, and inhibit extracellular microbial enzymes[15]. The peels of *G. mangostana* consist of bioactive compounds including xanthones, tannins, flavonoids, anthocyanins, and other phenolic compounds[14,16]. Alpha-mangostins, the major xanthones in *G. mangostana* peels, have antibacterial activity that disintegrate the cytoplasmic membrane integrity, inhibit the biofilm formation of microbes, and downregulate the genes involved in cell division, DNA replication, and fatty acid biosynthetic pathway[17]. Antioxidant and anti-inflammatory activities have been reported for xanthones, tannins, flavonoids, anthocyanins, and other phenolic compounds[14,16].

Interestingly, their effects were evaluated using *in vitro* cultures of human epidermal keratinocytes. The 60 mg/mL *P. emblica* fruit crude extract showed no toxicity on cell viability but enhanced the growth of human keratinocytes[18]. The 0 to 2 µg/mL *G. mangostana* fruit crude extract showed no inhibitory effect on cell viability[19].

Studies on the synergistic effects of herbs showed that the combination of different herbal extracts had collaborative antimicrobial actions against bacteria such as *Bacillus cereus*, *S. aureus*, and *Escherichia coli*[20,21]. Moreover, studies have demonstrated the clinical efficacy of both *P. emblica* extract and *G. mangostana* extract as compared to clindamycin gel in mild to moderate acne patients[22,23]. The efficacy of non-inflammatory acne and inflammatory acne reduction was around 50% to 60%, which is a moderate response and comparable to clindamycin gel[22,23]. They were shown that the extracts of *P. emblica* leaves and *G. mangostana* peels have strong antibacterial activity against *C. acnes*[10-12]. Nevertheless, there has been no studies on the combination of both herbs on antimicrobial and collaborative activities against *C. acnes*. Hence, the present research was to investigate the synergistic activities of *P. emblica* leaves and *G. mangostana* peels crude extracts to *C. acnes* isolated from acne patients. This might increase the efficacy of acne vulgaris treatment.

Materials and Methods

Plant crude extracts

The crude extracts of *P. emblica* leaves and *G. mangostana* peels were derived from the Department of Pharmacognosy and Pharmaceutical Botany of the Faculty of Pharmaceutical Sciences, Prince of Songkla University, Thailand. Each dried plant material was grounded into powder and passed through a sieve (No.45). The dried powder was macerated with 95% ethanol for 24 hours with continuous shaking, and then 95% ethanol was evaporated under reduced pressure. Two plant crude extracts were obtained.

Microorganisms and cultured media

Seventy *C. acnes* clinically isolated from 70 Thai acne vulgaris patients[8] were included in this study. The isolated *C. acnes* were stored in brain heart infusion (BHI) broth (Becton Dickinson, USA) with 20% glycerol at –80°C deep freezer in the Microbiology department of the Faculty of Medicine, Srinakharinwirot University, to maintain the viability of bacteria. *C. acnes* that were brought out from the deep freezer were then cultured with BHI agar (Becton Dickinson, USA) and 10% horse serum (GIBCO Invitrogen, England) at 37°C under anaerobic condition and incubated for three to five days until the *C. acnes* grew.

Antibacterial activity tests

Agar well diffusion method: *C. acnes* was prepared in BHI broth and adjusted to yield approximately 1.5×10^8 CFU/mL, according to the 0.5 McFarland standard. Aliquots of molten BHI agar were used as an agar base and poured into each plate then left to solidity. Later, *C. acnes* was inoculated on the agar plates with three-dimensional swab method. Wells of 4 mm in diameter were made in media by using a sterile cork borer. The crude extracts of each plant were diluted with 1% dimethyl sulfoxide

(DMSO) to 5 mg/mL and filled in wells of 40 µL each. One percent of DMSO was used as a negative control. Then, the agar plates were incubated under anaerobic condition at 37°C for three to five days, followed by measurement of the diameter of the inhibition zone expressed in millimeters (mm). The method was performed in two separate experiments and the inhibition zone was described as the minimum inhibition zone (MIZ).

Broth microdilution method: The minimum inhibitory concentration (MIC) was determined by broth microdilution method[24]. A serial two-fold dilution of each plant extract was made in 96-well microtiter plates (Corning, USA) in a beginning concentration 10 mg/mL in 100 µL 1% DMSO. The *C. acnes* was adjusted to 1.5×10^6 CFU/mL and 100 µL was added in each well in equivalent volume of extract. Then microtiter plates were incubated under anaerobic condition at 37°C for three to five days. Finally, 30 µL of 0.02% resazurin solution was added. Resazurin is an oxidation-reduction indicator used for the evaluation of microbial growth. The pink color indicated *C. acnes* growth and the blue color indicated inhibition of *C. acnes* growth. The method was performed in two separate experiments and MIC was defined as the lowest concentration of the tested crude extracts that inhibit *C. acnes* growth. The MIC was reported in milligram per milliliter (mg/mL).

Antimicrobial synergy study - checkerboard testing: The checkerboard testing[25] was performed using 96-well microtiter plates. The microplate assay was arranged as follows: *P. emblica* leaves crude extract was along the rows of the plate, while *G. mangostana* peels crude extract was along the columns of the plate. The concentration started at two times of the MIC value of each crude extract and then diluted by two-fold serial dilution along the rows and columns. The final volume in each well was 100 µL comprising 50 µL of each crude extract dilution. Subsequently, 50 µL of BHI broth containing 1.5×10^6 CFU/mL was added to all wells. The plates were then incubated under anaerobic condition at 37°C for three to five days. Finally, 30 µL of 0.02% resazurin solution was added and interpreted as described above. All experiments were done in duplicate.

The fractional inhibitory concentration (FIC) of each crude extract was calculated as the MIC of the plant in combination, divided by the MIC of the agent alone as shown in the below equation[25].

$$\text{FIC index} = FIC_A + FIC_B = \frac{MIC_{A \text{ in combination with B}}}{MIC_{A \text{ alone}}} + \frac{MIC_{B \text{ in combination with A}}}{MIC_{B \text{ alone}}}$$

where A=*P. emblica* leaves, B=*G. mangostana* peels

The interpretation was made based on the FIC index (FICI), which is the sum of the FICs of both crude extracts. The FICI results were interpreted as FICI of 0.5 or less was synergy, FICI of 0.5 to 1 was additive, FICI of more than 1 to 4 was indifference, and FICI of more than 4 was antagonism[21].

Table 1. Antimicrobial activities of each *C. acnes* group between each plant extract in inhibition zone (mm)

C. acnes	Plant extracts	MIZ; median (Q1, Q3)	p-value*
Overall (n=70)	*P. emblica*	15.75 (12.00, 18.50)	<0.001
	G. mangostana	10.00 (10.00, 15.00)	
Resistant (n=44)	*P. emblica*	12.00 (11.50, 17.00)	<0.001
	G. mangostana	10.00 (9.50, 11.00)	
Susceptible (n=26)	*P. emblica*	18.00 (17.00, 18.50)	<0.001
	G. mangostana	15.00 (10.00, 15.00)	

MIZ=minimum inhibition zone

* Result from Wilcoxon matched signed-rank test

Statistical analysis

Data were performed using the Stata, version 14.0 (StataCorp LP, College Station, TX, USA). Continuous data were presented as medians and interquartile ranges (Q1, Q3). Wilcoxon matched signed-rank test, two-sample Wilcoxon rank-sum test, and Fisher's exact test were used to test the difference of quantitative data. A p-value of less than 0.05 were considered significant.

Ethics consideration

The present research was approved by the Srinakharinwirot University Ethical Committee for considering the use of *C. acnes* from the patients who were included in the previous study by the authors' colleague[8]. The certificate number is SWUEC/X-001/2564.

Results

The crude extracts of *P. emblica* and *G. mangostana* could inhibit the growth of 70 clinically isolated *C. acnes* at the concentration of 5 mg/mL via agar well diffusion method as shown in Table 1. Medians (Q1, Q3) of the MIZ of *P. emblica* crude extract and *G. mangostana* crude extract at concentration of 5 mg/mL were 15.75 (12.00, 18.50) and 10.00 (10.00, 15.00) mm, respectively. Furthermore, medians of the MIZ of *P. emblica* and *G. mangostana* against resistant *C. acnes* at 5 mg/mL were 12.00 (11.50, 17.00) and 10.00 (9.50, 11.00) mm,

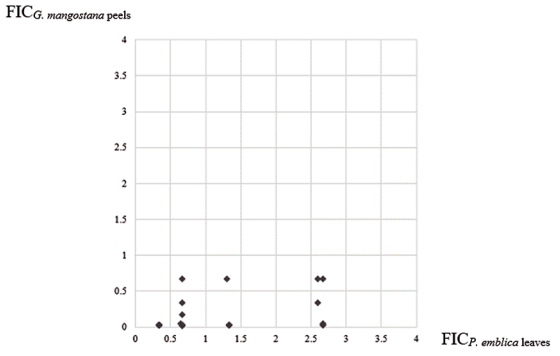

Figure 1. Chart of the FICs of *P. emblica* leaves (axis X) and *G. mangostana* peels crude extract (axis Y) against *C. acnes.*

FICI = $FIC_{P. emblica\ leaves}$ + $FIC_{G. mangostana\ peels}$

respectively. Medians of the MIZ of *P. emblica* and *G. mangostana* to susceptible *C. acnes* at 5 mg/mL were 18.00 (17.00, 18.50) and 15.00 (10.00, 15.00) mm, respectively. The *P. emblica* crude extracts and *G. mangostana* crude extracts were statistically significant in the three groups, overall *C. acnes*, resistant *C. acnes*, and susceptible *C. acnes* (p<0.001, <0.001, and <0.001, respectively). The comparison of MIZ between resistant *C. acnes* and susceptible *C. acnes* was statistically significant of *P. emblica* crude extract and *G. mangostana* crude extract (p<0.001 and <0.001, respectively).

Determination of medians (Q1, Q3) of the MIC values of the crude extracts of *P. emblica* and *G. mangostana* to all clinical isolates, were 0.078 (0.039, 0.156) mg/mL and 0.078 (0.078, 0.078) mg/mL, respectively. Medians of the MIC of *P. emblica* and *G. mangostana* to resistant *C. acnes* were 0.078 (0.039, 0.156) mg/mL and 0.078 (0.078, 0.078) mg/mL, respectively. Medians of the MIC of *P. emblica* and *G. mangostana* to susceptible *C. acnes* were 0.078 (0.039, 0.078) mg/mL and 0.078 (0.039, 0.078) mg/mL, respectively. The crude extracts of *P. emblica* and *G. mangostana* were not statistically significant the three groups, overall *C. acnes*, resistant *C. acnes*, and susceptible *C. acnes* (p=0.327, 0.151, and 0.599, respectively). The comparison of MIC between resistant *C. acnes* and susceptible *C. acnes* was not statistically significant in the two groups, *P. emblica* crude extract and *G. mangostana* crude extract (p=0.280 and 0.546, respectively) as shown in Table 2.

After collecting all the MIC data, the 35 representative MIC from 70 clinically isolated *C. acnes* were selected to test antimicrobial synergy study, checkerboard testing. The FIC indices ranged from 0.192 to 3.333 (Figure 1).

Table 2. Antimicrobial activities of each *C. acnes* group between each plant extract in MIC (mg/mL)

C. acnes	Crude extracts	MIC; median (Q1, Q3)	p-value*
Overall (n=70)	*P. emblica*	0.078 (0.039, 0.156)	0.327
	G. mangostana	0.078 (0.078, 0.078)	
Resistant (n=44)	*P. emblica*	0.078 (0.039, 0.156)	0.151
	G. mangostana	0.078 (0.078, 0.078)	
Susceptible (n=26)	*P. emblica*	0.078 (0.039, 0.078)	0.599
	G. mangostana	0.078 (0.039, 0.078)	

MIC=minimum inhibitory concentration

* Result from Wilcoxon matched signed-rank test

Table 3. Antimicrobial synergy study - checkerboard testing of each *C. acnes* group

C. acnes	Type of interaction; n (%)			
	Synergy	Additive/ partial synergy	Indifference	Antagonism
Overall (n=35)	13 (37.14)	9 (25.72)	13 (37.14)	0 (0.00)
Resistant (n=24)	11 (45.83)	5 (20.84)	8 (33.33)	0 (0.00)
Susceptible (n=11)	2 (18.18)	4 (36.36)	5 (45.46)	0 (0.00)

Table 4. Comparing the synergy and non-synergy groups of each *C. acnes* group

C. acnes	Type of interaction; n (%)		p-value*
	Synergy (synergy + additive/ partial synergy)	Non-synergy (indifference + antagonism)	
Overall (n=35)	22 (62.86)	13 (37.14)	
Resistant (n=24)	16 (66.67)	8 (33.33)	0.708
Susceptible (n=11)	6 (54.54)	5 (45.46)	

* Result from Fisher's exact test

The combination of *P. emblica* and *G. mangostana* crude extracts had 62.86% of the synergy group (37.14% synergy + 25.72% additive or partial synergy) and 37.14% of the non-synergy group (37.14% indifference + 0% antagonism), and none of the antagonism (Table 3). However, there was no statistically significant difference between resistant *C. acnes* and susceptible *C. acnes* (p=0.708) (Table 4).

Discussion

In the present study, the crude extracts of *P. emblica* and *G. mangostana* were investigated for antibacterial activity against clinically isolated *C. acnes*. The results showed that both herbs could effectively inhibit the growth of both antibiotic resistant and susceptible *C. acnes*.

For the qualitative method of antimicrobial

activity of the crude extracts by agar well diffusion method, this method is used to screen the antimicrobial activity of each crude extract. *P. emblica* and *G. mangostana* could inhibit the growth of clinically isolated *C. acnes* at the concentration of 5 mg/mL. *P. emblica* showed larger inhibition zone than *G. mangostana*. It can be explained that both herbs had different diffusion abilities of their main bioactive compounds. The main bioactive compound of *P. emblica* leaves is tannin[13,15], whereas the main bioactive compound of *G. mangostana* peels is xanthone[14,17]. Tannin has better solubility in water than xanthone.

For the quantitative evaluation of antimicrobial activity of the crude extracts by broth microdilution method, *P. emblica* leaves and *G. mangostana* peels could inhibit the growth of clinically isolated *C. acnes*. The MIC results showed no statistically significant difference between *P. emblica* leaves and *G. mangostana* peels in the three groups, overall *C. acnes*, resistant *C. acnes*, and susceptible *C. acnes*. In addition, there was no statistically significant difference between resistant *C. acnes* and susceptible *C. acnes* in both herbal crude extracts. This implied that the efficacy of both herbal crude extracts had no difference against clinically isolated *C. acnes* by broth microdilution method. From the previous studies, the MIC results of *P. emblica* extract against clinically isolated *C. acnes* and *G. mangostana* extract against *C. acnes* ATCC 6919 were 0.559 and 0.039 mg/mL, respectively[11,12]. The results were inconsistent with the present study because the amount of the main bioactive compounds in each extraction and the isolates of *C. acnes* used were different from the previous studies. Moreover, there was no evidence of *G. mangostana* crude extract in inhibiting the growth of *C. acnes* from clinical isolation in the previous studies.

For the FIC evaluation of *P. emblica* and *G. mangostana* crude extracts by antimicrobial synergy study, checkerboard testing, this suggests the combination has synergistic activities. There were 62.86% of the synergy group and 37.14% of the non-synergy group in overall *C. acnes*. The MIC of each herb in combination was lower than the MIC of individual herb. To the best of the authors' knowledge, this is the first study to demonstrate the antimicrobial synergistic activity of *P. emblica* and *G. mangostana* crude extracts against clinically isolated *C. acnes*, which are antibiotic resistant isolates. Further investigation of *in vitro* synergistic combination of both herbal extracts should be performed on human keratinocyte cells. Then, a clinical trial should be investigated.

Conclusion

The crude extracts of *P. emblica* and *G. mangostana* could inhibit the growth of clinically isolated *C. acnes* with no difference in antibacterial effect. The combination of *P. emblica* and *G. mangostana* crude extracts has synergistic activities against antibiotic resistant and susceptible *C. acnes*.

What is already known on this topic?

P. emblica leaves and *G. mangostana* peels are known to contain phytochemicals, which have antibacterial activity. *P. emblica* leaves crude extract could inhibit the growth of standard *C. acnes* and clinically isolated *C. acnes* from Thai acne vulgaris patients. *G. mangostana* peels crude extract could inhibit the growth of standard *C. acnes*.

What this study adds?

G. mangostana peels crude extract could inhibit the growth of *C. acnes* isolated from Thai acne vulgaris patients. The combination of *P. emblica* leaves and *G. mangostana* peels crude extract has synergistic antimicrobial activities against clinically isolated *C. acnes*.

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Conflicts of interest

The authors declare no conflict of interest.

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