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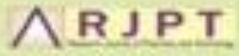

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Author(s): *Roma Chandra*

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Stability Indicating HPTLC Method for Simultaneous Determination of Amlodipine Besylate and Lisinopril in Combined Dose Tablet Formulation (AbstractView.aspx?PID=2021-14-12-11)

Author(s): *Sagar B. Wankhede, Deepak S. Khobragade, Sukeshini B. Lote, S. Patil*

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RESEARCH ARTICLE

The Role of Andrographolide in *Andrographis paniculata* as a Potential Analgesic for Herbal Medicine based Drug Development

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ABSTRACT:

Background: *Andrographis paniculata* is a herbaceous plant in the Acanthaceae family, that is widely used as a traditional medicine in Asian countries and known to exhibit a wide range of pharmacological effects. Recent studies have provided an overview of the great potential of *A. paniculata* as an analgesic. The ethanol extract and ethyl acetate (EA) fraction of *A.paniculata* were shown to contain diterpene lactone compounds, which may be useful as a potential active ingredient in analgesic drugs. The development of a herbal medicine based drug requires an effective and high quality active ingredient. Therefore, this research was aimed to compare the analgesic activity of ethanol extract and EA fraction based on their andrographolide content and further to determine the more viable active substance for analgesic herbal medicine based drug development. **Method:** The andrographolide content in the ethanol extract and EA fraction was determined by High Pressure Liquid Chromatography (HPLC). Measurement of analgesic activity was performed by writhing test. The experimental animals were randomly divided into eight groups consisting of 5 mice in each. Group 1 (negative control) received 1% Tween-80 in normal saline. Group 2 (positive control) received a standard analgesic drug (diclofenac sodium) at a dose of 40 mg/kg body weight. Group 3, 4, and 5 received ethanol extract while Group 6, 7, and 8 received EA fraction, each at a dose of 12.5, 25, and 50 mg andrographolide/kg body weight, respectively. Each mouse was injected intraperitoneally with 1% acetic acid at a dose of 10 ml/kg body weight 30 minutes after oral administration of the treatments. The number of writhes were counted 5 min after acetic acid injection over a period of 45 min. **Results:** Andrographolide content in ethanol extract and EA fraction was 15.66±0.28 and 21.25±1.08 % w/w, respectively. Ethanol extract and EA fraction displayed analgesic activity of 67.68% and 70.91% respectively, at a dose of 50 mg andrographolide/kg body weight. The positive control at a dose of 40 mg/kg body weight showed an analgesic activity of 74.33%. Statistical analysis showed no significant differences between EA fraction at a dose of 50 mg andrographolide/kg body weight and ethanol extract at the same dose as well as the positive control ($P > 0.05$). The effective dose 50% (ED_{50}) of the ethanol extract and EA fraction was determined to be 29.49 and 25.55 mg/kg body weight, respectively. **Conclusion:** It was possible to use andrographolide content as an indicator for the analgesic activity of *A.paniculata*. Ethanol extract and EA fraction of *A. paniculata* at the same dose of andrographolide showed similar analgesic activity. The amount of ethanol extract which needed to reach similar analgesic activity was higher than EA fraction. Therefore, EA fraction likely has greater potential as an analgesic active substance due to its higher content of andrographolide; however further study is needed to develop it as a dosage form.

KEYWORDS: *Andrographis paniculata*, extract, ethyl acetate fraction, analgesic activity.

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INTRODUCTION:

Pain and inflammation are a defense mechanism of body to initiate the tissue healing process. It is a common nonspecific manifestation of many diseases[1]. Drugs

presently used for the management of pain and inflammatory conditions are narcotics (e.g., opioids), non-narcotics (e.g., salicylates) or corticosteroids (e.g., hydrocortisone). All of these drugs cause well known side effect, such as a low potency, and toxic effects, such as renal failure, allergic reactions, and occasionally hearing loss while also potentially increasing the risk of haemorrhage by affecting platelet function[2,3]. The use of nonsteroidal substances such as aspirin is also increasing due to its utility in reducing the incidence of a number of common disorders including stroke, myocardial infarction and cancer[4]. Therefore, the discovery of alternative substances to treat pain is crucial.

Plants are important sources of new drugs. Many plants were reported to have a potential analgesic activity including *Solanum surattense*, *Plumbago indica*, *Clerodendrum inerme*, *Lagenaria siceraria*, *Cuscuta reflexa*, *Alpinia conchigera*, *Sida Spp* and *Andrographis paniculata*. These plants extracts were showed inhibition on acetic acid induced writhing on mice compared to aspirin or diclofenac sodium as a positive control[5-12].

Andrographis paniculata is a herbaceous plant in the Acanthaceae family that is widely used as a traditional medicine in Asian countries[13]. This plant is known to have pharmacological effects, such as anti-inflammatory, antibacterial, antioxidant, anticancer, antidiabetic, antimalarial, hepatoprotective, immunostimulant, allergic, analgesic, and antipyretic activity[14-17]. Several studies have been conducted to determine the analgesic activity of *A. paniculata*. Previous investigations reported that the aqueous extract of *A. paniculata* at a dose of 100 mg/kg and 500 mg/kg per orally, significantly reduced (P<0.01) acetic acid induced writhing in both acute and chronic examinations. The test drug at a dose of 100 mg/kg and 500 mg/kg fared better than the standard drug (aspirin) at 150 mg/kg in acute cases[12]. The ethanol extract of *A. paniculata* is known to display an analgesic activity of 34%[18]. Andrographolide has also been shown to exhibit analgesic activity at a dose of 4 mg/kg, when given intraperitoneally[19]. These studies provide an overview of the significant potential of *A. paniculata* as an alternative analgesic drug.

In consideration of these results, *A.paniculata* has been identified as a prospective plant than could be used to address the current need for alternative analgesic drugs. Although many reports on the analgesic activity of *A. paniculata* have been published, little attention has been directed towards the development of analgesic herbal medicines based on effective and high quality active ingredients. The ethanol extract and ethyl acetate (EA) fraction of *A.paniculata* have been shown to contain diterpene lactone compounds and importantly andrographolide as a potential active substance. Therefore, this research was aimed to compare the analgesic activity of ethanol extract and EA fraction based on their andrographolide content and to further determine the more viable active substance for analgesic drug development.

MATERIALS AND METHODS:

Plant Material:

The plant material used in this research was *A. paniculata* dried powder containing 1.82% andrographolide (PT. Kimia Farma Tbk). Andrographolide standard was purchased from Sigma-Aldrich (Cat No.365645-100MG).

Preparation of the ethanol extract and ethyl acetate (EA) fraction:

A.paniculata dried powder was extracted by maceration method using ethanol 96% as a solvent. The liquid ethanol extract was then evaporated using a rotary evaporator. The concentrated extract was then further separated *via* liquid-liquid fractionation using ethyl acetate and water (1:1 v/v) to obtain the ethyl acetate (EA) fraction.

Determination of andrographolide content:

Analysis of andrographolide content in the extract and EA fraction was conducted by High Pressure Liquid Chromatography (HPLC) method. The analysis used an Agilent HPLC system, Poroshell RP-18 column (4.6x250 mm, 5µm), mobile phase methanol:water pH 3.05 (50%: 50% v/v) and a flow rate of 1 ml/min. The extract and EA fraction were weighed out (10 mg) and dissolved in 10 ml of methanol. Standard working solutions was made at concentrations of 100, 200, 400, 800, and 900 ppm in methanol, taking into account the 98% standard potential. The sample and standard solutions were filtered using a filter membrane with a pore size of 0.22 µm. The solutions were subsequently inserted into an auto sampler and injected into the HPLC system. Andrographolide content in the extract and EA fraction was then determined based on the chromatogram peak areas.

Animals:

This study used male mice BALB/C strain (25–30 g), were maintained on standard animal pellets and water *ad libitum* at the Animal Laboratory of the Institute of Tropical Disease, Universitas Airlangga, Surabaya. Animals were kept at constant temperature (25 ± 1°C) and underwent a regular 12/12 h light/dark cycle, while having free access to standard laboratory feed and water. Permission and approval for animal studies were obtained from the Faculty of Veterinary Medicine, Universitas Airlangga with the approval code 753-KE.

Evaluation of analgesic activity by acetic acid induced writhing test:

The mice were divided into eight groups (n = 5). Group 1 (Negative control) received 1% Tween-80 in normal saline. Group 2 (Positive control) received a standard drug (diclofenac sodium) at a dose of 40 mg/kg body weight. Group 3 to Group 8 were treatment groups. Group 3 to Group 5 received ethanol extract at a dose of 12.5, 25, and 50 mg andrographolide/kg body weight respectively. Group 6 to Group 8 received EA fraction at doses of 12.5, 25, and 50 mg andrographolide/kg body weight respectively. All treatments were administered orally. Each mouse was injected with 1% acetic acid intraperitoneally at a dose of 10 ml/kg body weight, 30 minutes after administration of the standard drug and test samples. The number of writhes (constriction of abdominal muscles along with the stretching of hind limbs) were counted 5 min after acetic acid injection over a period of 45 min. The percentage of analgesic activity was calculated as follows[20].

$$\% \text{ Analgesic activity} = \frac{\text{N negative control - N test}}{\text{N negative control}} \times 100$$

Where N is the mean number of writhes for the each group.

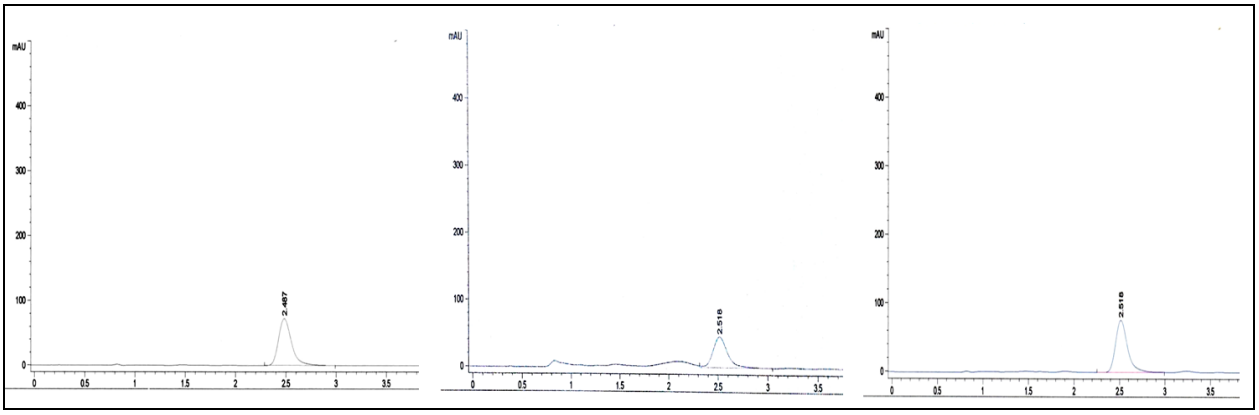
Statistical analysis:

Mean and standard error of mean (SEM) was calculated for the observed values in each experimental group (n=5). Statistical analysis was performed by one way analysis of variance (ANOVA) followed by Least Significant Difference (LSD). An effect was considered to be significant at the $P<0.05$ level. Effective Dose 50% (ED_{50}) was analyzed by probit analysis. SPSS 17.0 was used for the statistical analysis.

RESULTS:

Determination of andrographolide content:

The andrographolide content in extract and EA fraction was determined by HPLC method using andrographolide as an external standard. The analysis was done used a Poroshell RP-18 column (4.6x250 mm, 5µm), mobile phase methanol:water pH 3.05 (50%: 50% v/v) and a flow rate of 1 ml/min. Under these conditions, the andrographolide standard was observed at Rt 2.46 min. Meanwhile, andrographolide in extract and EA fraction was detected at Rt 2.51 min (Figure 1). The peak area of the andrographolide standard at concentrations of 100, 200, 400, 800 and 900 ppm was determined. The peak areas of the known standard concentration were used for linier regression analysis as shown in Table 1. Andrographolide content in extract and EA fraction was 15.66±0.28% and 21.25± 1.08% w/w as shown in Table 2.



(a) (b) (c)

Figure 1. HPLC Chromatogram of Andrographolide standard at a concentration of 200 ppm (a), ethanol extract of *Andrographis paniculata* (b), EA fraction of *Andrographis paniculata* (c).

Table 1. HPLC results of andrographolide standard (concentration vs area)

Concentration (ppm)	Area
100	209.84308
200	654.00830
400	1522.93140
800	3129.94482
900	3545.97778

$Y=4.1461x-177.57$, $R^2=0.9997$

Table 2. HPLC result of andrographolide content in extract and EA fraction

Sample	Area	Sample Concentration (ppm)	Andrographolide content (% w/w)	Andrographolide content (% w/w) Average±SD
Extract	486.47580	160.14	16.01	15.66±0.28
	461.17447	154.04	15.40	
	476.88068	157.83	15.78	
	463.30511	154.55	15.45	
EA Fraction	707.80560	213.53	21.35	21.25±1.08
	655.43182	200.90	20.09	
	668.67413	208.91	20.89	
	762.83105	226.80	22.68	

Table 3. Analgesic activity of extract and EA fraction of *A. paniculata* by acetic acid induced writhing in mice

Groups	Dose (mg/kg bw)	Number of writhes in 45 min (Mean±SEM)	Inhibition (%)
Negative control	-	105.2 ± 1.80^{abcd}	
Diclofenac sodium	40	27.0 ± 1.92^{abc}	74.33±1.83
Ethanol extract	12.5	85.8 ± 1.16^{acd}	18.44±1.10
	25	54.6 ± 1.94^{abcd}	48.10±1.84
	50	34.0 ± 1.14^{abd}	67.68±1.08
EA fraction	12.5	83.0 ± 1.61^{acd}	21.10±1.53
	25	47.4 ± 1.62^{abcd}	54.94±2.49
	50	30.6 ± 1.12^{ab}	70.91±1.07

Value are reported as Mean±SEM for all groups. The data was analyzed by ANOVA followed by LSD test. Letters (abcd) indicate statistically significant difference, $P<0.05$

Evaluation of analgesic activity by acetic acid induced writhing test:

The effects of the ethanol extract and EA fraction of *A. paniculata* on the acetic acid-induced abdominal constrictions in mice are presented in Table 3 and Figure 2. The results indicated that ethanol extract, EA fraction of *A. paniculata* (at a dose of andrographolide 12.5, 25, and 50 mg/kg body weight) and diclofenac sodium (40 mg/kg body weight) significantly ($P<0.05$) reduced abdominal writhing in mice when compared to the negative control group. Interestingly, the reduction occurred in a dose dependent manner. Maximum inhibition from treatment with ethanol extract (67.68%) and EA fraction (70.91%) was observed at a andrographolide dose of 50 mg/kg body weight. The effective dose 50% (ED_{50}) was analyzed by probit log analysis using SPSS. The results showed that the ED_{50} values of extract and EA fraction were 29.49 mg/kg body weight and 25.55 mg/kg body weight, respectively. Hence, the EA fraction displayed higher activity compare to the extract based on their ED_{50} value.

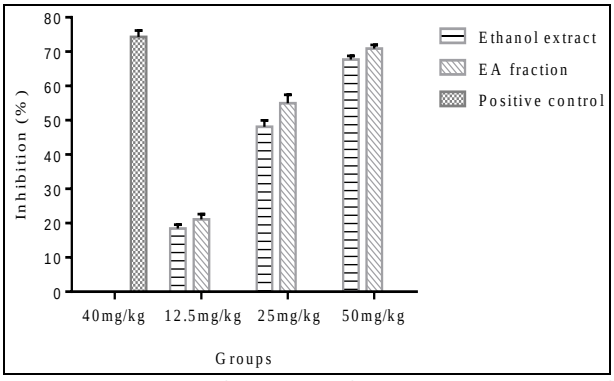


Figure 2. Percentage of inhibition of abdominal contractions of acetic acid induced writhing in mice.

DISCUSSION:

In order to facilitate the use of *A.paniculata* for its analgesic activity, this study aimed to determine the active substance involved and its potential for development into an analgesic herbal medicine based drug. This was undertaken by comparing the analgesic activity of the ethanol extract and EA fraction based on their andrographolide content.

The determination of andrographolide content in ethanol extract and EA fraction was conducted by HPLC method. Several methods to quantify the andrographolide content in extract and pharmaceutical dosage form were reported including High Performance Thin Layer Chromatography (HPTLC) and spectrophotometric method[21-23]. HPLC methods was adopted in this study because of its simple, precise and accuracy. The determination result reveal that andrographolide content in extract was 15.66±0.28% w/w. Meanwhile, EA fraction was contain andrographolide 21.25± 1.08% w/w, which was higher compared to the extract.

In this study, experimental animals in the form of mice (*Mus musculus*) were divided into eight groups consisting of a positive control group, negative control group, and six treatment groups. The number of animals used for each test group was determined based on the Federer formula[24]. The ideal number of animals per group according to the Federer formula was a minimum of four animals. The experimental animals were randomly divided into eight groups where each group consisted of five mice. Thus the total for all control and treatment groups amounted to forty male mice. The negative group was given CMC-Na 0.5%. The positive

control group was given the analgesic drug sodium diclofenac at a dose of 40 mg/kg body weight of mice. Group 3 to 5 were treated with 96% *A. paniculata* ethanol extract and Groups 6 to 8 were treated with *A. paniculata* EA fraction at an andrographolide dose of 12.5, 25, and 50 mg/kg body weight of mice.

The acetic acid-induced abdominal constriction method is widely used for the screening new analgesic drugs, because it is very simple and sensitive[25]. The working principle of this method is to observe the stretching response that occurs due to pain stimulation by an irritant. The irritants are administered by injecting acetic acid as an intraperitonial pain inducer in mice[26]. Administering acetic acid can cause a local inflammatory response because of the release of arachidonic acid from phospholipid tissue via Cox, prostaglandin production (PGE2 and PGE2α) and increased production of lipoxygenase which can increase intraperitoneal fluid. The production of prostaglandin and lipoxygenase causes swelling and release of endogenous substances that stimulate nerve endings in the visceral area, especially in the chest and abdominal cavity so that pain arises. This pain is characterized by the appearance of stretching which is classified as the foot being pulled back (stretched) and the abdomen touching the base of the form plate[27-29].

Based on ANOVA analysis, it was shown that significant differences occurred between the treatment groups (P<0.05). Hence, the administration of different test materials produced different amount of stretching. Regarding the results of the ethanol extract and EA fraction in the acetic acid-induced abdominal constriction assay, a prominent inhibition of the writhing reflex was observed. The ethanol extract and EA fraction of *A. paniculata* display analgesic activity as determined by significantly (P<0.05) reduced abdominal writhing in mice when compared to the negative control group.

Post hoc-tests were performed using the Least Significant Difference (LSD) analysis to reveal any differences between treatment groups. LSD test results showed that EA fraction at a dose of andrographolide of 12.5 mg/kg was not significantly different to the ethanol extract treatment at the same dose. Furthermore, the EA fraction at an andrographolide dose of 50 mg/kg did not differ significantly from the ethanol extract treatment at the same dose as well as from the positive control. From this it can be concluded that the administration of sodium diclofenac at a dose of 40 mg/kg and the EA fraction at a andrographolide dose of 50 mg/kg have reduce writhing in mice to a similar degree.

Diclofenac sodium, like other non-steroidal anti-inflammatory drugs, inhibits the biogenesis of prostaglandins, thus inhibiting the writhing in experimental animals like mice. The presence of phytochemicals in *A.paniculata*, such as diterpenes, lactones, and flavonoids has been reported in previous work[30]. Flavonoids were reported to have a role in analgesic activity primarily by targeting prostaglandins[31,32]. Moreover, andrographolide was detected in diterpene lactone compounds which are known to have analgesic effects[19]. Madav et al. (1995) reported that 300 mg/kg of andrographolide, administered orally, had significant analgesic activity on acetic-induced writhing in mice[33]. The results of our study showed that both ethanol extract and EA fraction at the same andrographolide dose of 50 mg/kg showed similar analgesic activity. Andrographolide, which was a major compound contained in the ethanol extract and EA fraction can be considered as a marker for analgesic activity. In agreement with previous work, *A.paniculata* analgesic activity was entirely explained by the presence of a high content of andrographolide[34]. The presence of other secondary metabolites did not influence the analgesic activity as shown by their similar activity. The EA fraction might be chosen as potential active substance in analgesic drug development based on its higher andrographolide content. The amount of EA fraction equal to 50 mg andrographolide (235.30 mg) needed to reach the similar analgetic activity was lower than ethanol extract (319.28 mg). Nevertheless, further study is needed to increase the analgesic activity of the EA fraction to enable practical applications. Specifically, formulating a study of the EA fraction wherein the solubility of active substance is increased will be of great interest study as well as working towards an understanding of the mechanism of action.

CONCLUSION:

Ethanol extract and EA fraction of *A. paniculata* at the same dose of andrographolide showed similar analgesic activity. Andrographolide could take a role as a marker for the analgesic activity of *A.paniculata*. The EA fraction contained a higher andrographolide content compared to the ethanol extract. The amount of ethanol extract which needed to reach similar analgesic activity was higher than EA fraction. Therefore, the EA fraction has great potential as an analgesic active substance, but further study is needed to elucidate the appropriate dosage form.

CONFLICT OF INTEREST:

The authors declare there is no conflict of interest.

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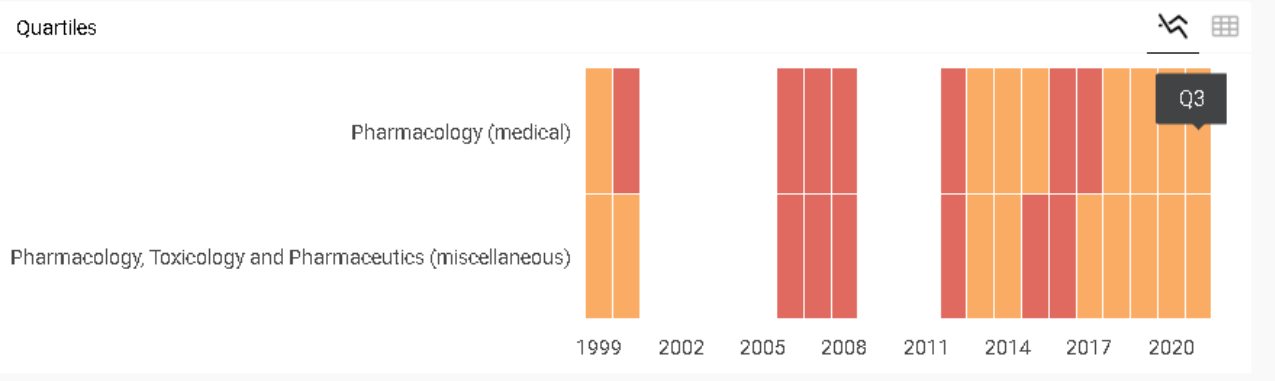

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