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THE DEVELOPMENT OF TABLET FORMULATION OF *ARTOCARPUS CHAMPEDEN* STEMBARK EXTRACT AS ANTIMALARIAL DRUG

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Abstract: Parasite resistance to antimalarial drug, chloroquine and sulfadoxin-pirimetamin, still become a major problem in malaria control worldwide, therefore, the effort in developing a new and different target of antimalarial drug become a high priority. Our preliminary test revealed that extract from *A. champeden* exhibited potent antimalarial activities against *P. falciparum* in vitro and *P. berghei* in vivo. Several isolated compounds from this plant exhibited antimalarial activity. One of the isolated compound identified as heteroflavon C, a prenylated flavone, have a higher antimalarial activity than chloroquine. Therefore, it is potential to be developed as antimalarial drug. The research was conducted to develop tablet formulation of ethanol extract of *A. champeden* stembark (EEAC). The formula that composed : EEAC 150 mg, lactose 140 mg, cabosil 5%, amilum 46 mg, avicel PH 101 7%, primogel 5%, and Mg stearat 1% was the selected formula. The tablet hardness of the formula has span between 9.0-12.27 kP and the average is 10.78 kP, the disintegration time of formula 12 minutes 47 seconds. A standard 4 days test on *P. berghei* Infected mice was used to evaluated in vivo antimalarial activity of the tablet. This research revealed that EEAC tablet has antimalarial activity against parasite *P. berghei* in vivo. Oral administration of EEAC tablet at a dose of 10 mg/kg body weight multiple dose (twice 1 day) inhibited the parasite growth better than 100 mg/kg body weight single dose (once a day). Antimalarial activity of tablet in multiple dose per oral showed inhibition of parasite growth of 73.88 %, while at single dose per oral showed inhibition of parasite growth of 83.32%.

Keywords: *A.champeden*, tablet formulation, *P. berghei*, in vivo antimalarial activity.

INTRODUCTION

Parasite resistance to antimalarial drug, chloroquine and sulfadoxin-pirimetamin, still become a major problem in malaria control worldwide, therefore, the effort in developing a new and different target of antimalarial drug become a high priority. *Artocarpus champeden* (family Moraceae) known as 'cempedak", is widely distributed in Indonesia and has been traditionally used in malarial remedies (Heyne, 1987). Previous study reported that prenylated stilbene from *Artocarpus integer* (syn *A. champeden*) exhibited antimalarial activities against *P. falciparum* (Boonlaksiri et al., 2000). Our preliminary test revealed that extract from *A. champeden* exhibited potent antimalarial activities against *P. falciparum* in vitro and *P. berghei* in vivo. Several isolated compounds from this plant exhibited antimalarial activity (Hidayati, 2003; Utomo, 2003; Ernawati, 2005). One of the isolated compound identified as heteroflavon C, a prenylated flavone, have a higher antimalarial activity than chloroquine (Widyawaruyanti et al., 2007). Standarized ethanol extract of *A.champeden* stembark (EEAC) also exhibited potent antimalarial activities against *P. falciparum* in vitro and *P. berghei* in vivo, Therefore, it is potential to develop EEAC as antimalarial phytopharmaceutical product. As phytopharmaceutical product, that requires consistency in the efficacy, safety, and effectivity (Widyawaruyanti et al., 2007; Widyawaruyanti, 2008).

The research was conducted to develop tablet formulation of EEAC and to evaluate the effectivity as antimalarial drug.

MATERIALS AND METHODS

Materials

The stembark of *A. champeden* were collected from Mugirejo, Samarinda East Kalimantan, Indonesia on October 2009. The tablet excipients used were lactose monohydrate, amilum manihot as filler, colloidal silicon dioxide (Cab-o-Sil) as absorbent and glidant, microcrystalline cellulose (Avicel PH 101) and sodium starch glycolate (primogel) as disintegrant and magnesium stearate as lubricant.

Preparation of extract

10 kg powdered cempedak stembark was macerated with ethanol solvent 80% during 2 hour with warm-up at temperature 40°C. Then it was filtered The residue dried

and re-macerated with the same solvent for three times. Extract collected and evaporated to obtain concentrate EEAC.

Preparation of EEAC tablets

The tablet formulation containing EEAC were prepared according to the formula given in table 1. Tablets were prepared by wet granulation method. Extract was dissolved in ethanol for homogenization then mixed with lactose monohydrate, amilum manihot, Cab-O-Sil, Avicel PH101 and Primogel (internal phase disintegrant). The moist mass was granulated by passing them through a 12 mesh sieve (2,100 pm) then dried at 40°C. After the drying process, the granules obtained were re-sieved through a 18 mesh sieve (1,400 pm). Then the granules were mixed with sodium starch glycolate (external phase disintegrant) and Mg stearate. The granules were compressed into tablets (final weight 430 mg) by means of spherical punch (1.0 mm in diameter) using laboratory single-punch tablet pump for 1 second with loads of 2 tons. The tablets were evaluated for physical characteristics including tablet hardness, weight uniformity, friability and disintegration time. Then were determined for its antimalarial activity.

Tablet organoleptic and weight uniformity

Tablets were evaluated for their physical appearance visually and also for its higroscopicity. For tablet weight uniformity, 20 tablets were weighed individually by using O'Hauss miligram balance.

Crushing Strength and Friability Tests

The load (kP) required to diametrically break each tablet was determined at room temperature using Erweka Hardness tester. Ten tablets were used for its determination. The friability of the tablets were evaluated for 20 tablets using Erweka Friability Tester which operated at 50 rotation per minute for 10 minutes.

Disintegration Test

The disintegration time of tablets were determined in distilled water at 37±0.5°C using an Erweka disintegration testing apparatus.

Evaluation of Tablet Properties

a. Physical appearance, tablets were evaluated for their physical appearance visually and also for higroscopicity.

b. Tablet hardness, it was determined for l0 tablets using Erweka Hardness Tester.

c. Tablet weight uniformity, 20 tablets were weighed individually by using O'Hauss miligram balance. The result should fulfill the requirements.

In vivo antimalarial test

Antimalarial activity of EEAC tablet was determined by modification of the "4-days Supressived Test" originally described by Peters (1980). For each experiment, mice were randomly assigned to a given treatment group (five mice in each group). The day of infection is termed D0, and succeeding day of infection was termed Dl, D2, etc. EEAC tablet was suspended in CMC-Na (0.5%) and was given to mice once a day at dose 100 mg/kg body weight (as single dose) and twice a day 10 mg/kg body weight (as multiple dose). While untreated group received CMC-Na (0.5%) solution. Thin blood smears were made from the tail blood every day. The level of parasitemia in mice, as seen in Giemsa-stained smears, were assessed.

RESULT AND DISCUSSION

Result of Formulation Study of EEAC Optimation formula of EEAC tablet

EEAC tablets have been successfully prepared and evaluated The tablets were evaluated for uniformity of weight hardness friability, and disintegration time. The results of physical appearance of EEAC tablet prepared using wet granulation method shows good physical appearance and relatively non higroscopic. The result indicate that the tablets fulfill the requirement (398.3 – 462.9 mg) which have range of tablet weight between 424.8 – 435.0 mg. A good degree of uniformity of weight was achieved for all of tablet prepared. The percent deviation did not exceed 5%, indicating excellent uniformity of weight in the tablet formulations prepared (table 2). The tablet exhibited good mechanical properties with regard to both hardness and friability (Tables 3 and 4). The crushing strength test results interval value of tablets hardness between 9.0 - 12.27 kP with an average is 10.78 kP. In the friability studies, weight loss values of the tablet was less than 1%. The result of disintegration time of EEAC tablet shows the time required for all tablets to break up into small particle is 11 minutes 56 seconds.

This is less than traditional medicine requisite which stated time of disintegration should be less than 20 minutes.

In vivo antimalarial test

Antimalarial activity test result from various therapy models of EEAC tablets showed at figure 1. The result showed that EEAC tablet given as single dose and multiple dose can inhibit the growth of parasite, compare with the untreated group. Three day after the treatment ended, the inhibition percentage for EEAC tablet as single dose was 83.32% and multiple dose was 73.88%. The dosage of EEAC tablet given twice a day is five times than given once a day. It concluded that multiple dose (twice a day, 10 mg/g body weight) more effective than single dose (once a day, 10 mg/kg body weight).

CONCLUSION

The formula of EEAC tablet that composed: EEAC 150 mg, lactose 140 mg, cab-o-sil 5%, amilum 46 mg, avicel PH 101 7%, primogel 5%, and Mg stearat 1% was active as antimalarial drug. Oral administration of EEAC tablet at dose of 10 mg/kg body weight multiple dose (twice a day) more potential than 100 mg/kg body weight single dose (once a day).

ACKNOWLEGEMENT

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