The potential of jamu to relieve clinical symptoms and reduce the tumor size of patients with Fibro Adenoma Mammae (FAM) at Rumah Riset Jamu (RRJ) Hortus Medicus Tawangmangu: a pilot study

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Abstract. Fibro Adenoma Mammae (FAM) is a benign tumor that sometimes causes clinical symptoms like pain. Not all women who suffer from FAM in Indonesia are willing to undergo surgery and choose to drink jamu. In fact, scientific evidence regarding jamu efficacy is limited. This study aims to determine the effect of jamu consumption on the size and clinical symptoms of FAM patients. A total of 26 women with FAM who came to RRJ Hortus Medicus and met the inclusion and exclusion criteria participated in this study until finish. Subjects were asked to drink boiled water of 8 plants Simplicia with a certain dose every day for 16 weeks. A breast ultrasound to determine tumor size was performed at baseline and day-112. Clinical symptoms were assessed at baseline and every 2 weeks. The result showed that the tumor average size was decreased from 13.89±6.47mm to 11.79±5.74mm (paired t-test p<0.001). About 88.46% of the subjects experienced a decrease in tumor size. The pain subsided and disappeared in 69.23% and 30.77% of subjects, respectively. The itching that was complained by one subject subsided since week 6. The administration of jamu for 16 weeks has the potential to reduce tumor size and clinical symptoms.

1. Introduction
Fibroadenoma mammae (FAM) is a benign breast tumor that usually affects women between 15 and 35 years [1]. A global prevalence reaching 10% of the female population [2]. The FAM has components of glands (epithelium) and connective tissue (stroma) that are round in shape, encapsulated, solid, easy to move, and well-demarcated with the surrounding tissue [3]. These tumors can be found single or multiple in one or both breasts with varying sizes [3]. The exact cause of FAM is not known yet, but it is thought to be related to the hormone estrogen, an increase in the sensitivity of breast tissue to the hormone estrogen [4]. Recent studies suggest the involvement of the Mediator complex subunit 12 (MED12) gene in the pathophysiology of FAM [5]. The FAM diagnosis is established by performing three assessments. First, anamnesis and physical examination lead to the characteristics of FAM as mentioned above and the history of the lump. Second, imaging examinations, such as breast ultrasound. Third, histopathological examination of tumor tissue samples obtained from fine-needle aspiration biopsy (FNAB), core biopsy, or total tumor removal surgery [1,6]. However, several recent studies have stated that it is safe not to perform a biopsy in patients aged less than 29 years if the clinical examination and breast ultrasound were entirely consistent with FAM [1,7,8].

Once the diagnosis of FAM is established, management can be done conservatively and interventional. Close observation with breast ultrasound examination every 6 months or once a year is considered safe for FAM with small sizes (< 5 cm) and asymptomatic, while surgery is performed when the tumor enlarges, causes pain, changes the shape of the breast, and if it persists or occurs after age
Unfortunately, not all women with FAM are willing and brave to perform surgery. Other treatments that less invasive are Vacuum-assisted percutaneous therapeutic excisional biopsy (VAB), percutaneous ultrasound- or stereotactic-guided, radiofrequency-assisted excision, percutaneous cryoablation, percutaneous thermal ablation, high intensity focused ultrasound (HIFU), percutaneous microwave ablation (MWA)[2]. However, these minimally invasive procedures are not commonly performed in Indonesia yet. All intervention therapies to remove FAM still left the possibility of lumps regrowth with the lowest recurrence rate in open surgery procedures [1].

In Indonesia, FAM sufferers often drink herbs or jamu to heal. The herbs they get from composing themselves, buying at herbal medicine shops, going to Traditional Chinese Medicine (TCM) practitioners, herbal medicine clinics, or Traditional medicine practitioners (BATRA)[10,11]. The use of herbs for tumors, especially benign breast tumors is based on empirical experience, which is passed down from generation to generation [10]. According to our knowledge, clinical trials of herbal formulas for benign breast tumors, especially FAM, have never been conducted in Indonesia. This is a pilot study to determine the efficacy of the jamu formula developed by B2P2TOOT on the size and clinical symptoms of FAM.

2. Material and Methods

2.1. Design and site of the study

This study is a clinical trial with pre-post design conducted at the Rumah Riset jamu (RRJ) Hortus medicus Tawangmangu, a service-based research clinic aimed at developing jamu belonging to the B2P2TOOT Ministry of Health of the Republic of Indonesia. Ethical approval for this study was issued by the Ethics Committee for Health Research, Ministry of Health Republic of Indonesia (number: LB.02.01/5.2/KE.456/2013).

Eligible patients were given 14 packs of herbal ingredients for 2 weeks. Subjects were asked to come back to the RRJ every 2 weeks for 16 weeks for a physical examination, anamnesis related to the symptoms, and the administration of jamu. At the 4th (week 8) and 8th (week 16) follow-up, an ultrasound examination of the breasts was performed.

2.2. Jamu material and preparation

The simplicia that composed the jamu formula prepared and packaged by the post-harvest laboratory team of B2P2TOOT. The package for one day consists of Curcuma mangga tubers 15 grams, Camellia sinensis leaves 7 grams, Scurulla sp herb 8 gram, Kaempferia rotunda tubers 10 grams and Merremia mammosa tubers 5 grams. All the simplicia used in this study had passed the quality control process. Each subject was asked to boil 1 pack of jamu in 800 ml of boiling water in the morning for approximately 15 minutes, filter the remaining water, divide it into 2 glasses, and drink one glass each in the morning and evening for 16 weeks.

2.3. Inclusion and exclusion criteria

Subjects were declared eligible if they met the inclusion criteria: female patients with FAM diagnosis confirmed with physical examination performed by RRJ medical doctor (MD), breast ultrasound (performed by radiology specialist), and histologic examination of fine-needle aspiration biopsy (FNAB) performed by pathologist, age between 17-50 years old, willing to follow the schedule of follow-up study and willing to signed informed consent and did not meet the exclusion criteria: history of hypersensitive to any of the components of the jamu Formula, taking drugs or other herbs with the similar function, pregnant and lactation (based on recognition), complications of severe disease, such as heart failure NYHA III and IV, severe gastritis, acute myocardial infarction.

2.4. Outcomes parameter
Tumor size as the primary outcome in this study was assessed based on breast ultrasound examination performed at baseline, week 8 and 16 by the same radiology specialist. The clinical symptoms felt by subject regarding the tumor were assessed based on the doctor's anamnesis at baseline and every 2 weeks during follow-up.

2.5. Data analysis
Data were analyzed descriptively and using statistical tests (paired t-test). Statistical analysis with IBM SPSS statistics 25.

3. Results and discussion
A total of 30 eligible female patients attending RRJ Hortus Medicus participated in this study. Only 26 subjects completed the study. One subject dropped out due to pregnancy at week 7, one subject did not want to continue the study at week 4. Two subjects decided to undergo surgery before the study was completed (figure 1).

![Consort diagram](image)

**Figure 1.** Consort diagram.

3.1. Subjects Characteristics
Demographic and clinical characteristics data includes all eligible subjects (N=30). About 66.67% of subjects have ages between 20-40 years with the highest number of cases in the 20-30 years age category. This is in line with the previous studies [9,12]. FAM mostly affects young adult women where menstruation and estrogen hormone fluctuations still occur [2]. Most of the subjects are married, only three subjects are unmarried. This is consistent with the results of Rangaswamy and Rubby research that FAM is more common in married women, possibly due to early marriage and pregnancy [2,13]. During pregnancy, FAM tends to proliferate because of the increased production of female reproductive hormones [5]. More than 50% of the subjects had high education. FAM patients with higher education are more active in seeking treatment for their disease [14] (Table 1).
Table 1. Demographic characteristics.

| Variables                             | Number of subjects (N=30) | Percentage (%) | Mean± SD  |
|---------------------------------------|---------------------------|----------------|----------|
| Age                                   |                           |                |          |
| 20-30 y.o                             | 11                        | 36.67          | 35.1± 9.17 |
| 31-40 y.o                             | 9                         | 30             |          |
| 41-50 y.o                             | 10                        | 33.33          |          |
| Marital status                        |                           |                |          |
| Married                               | 27                        | 90             |          |
| Not-married                           | 3                         | 10             |          |
| Education                             |                           |                |          |
| Low (Elementary and Junior High School) | 8                         | 26.67          |          |
| High (Senior High School and Bachelor) | 22                        | 73.33          |          |
| House wife                            | 14                        | 46.67          |          |
| Working                               | 16                        | 53.33          |          |

In this study half of the subjects (50%) have normal BMI. Abbas et al examined the characteristics of 200 women with breast lump in Pakistan and found out that BMI between 19-25 kg/m² was the risk factor for all types of breast tumor [15]. However, the effect of BMI on FAM is unclear. Some studies show high BMI increases the risk of FAM while other studies show a low BMI affects the occurrence of FAM [16]. Based on their review, Lee and Soltanian noticed that more than 70% of FAM are single lump similar to this study result that shows 60% of subjects had a single lump[4]. FAM usually only affects one breast [1]. Our findings support this fact, which only 23.33% of the subjects had lumps in both breasts (Table 2).

In this study, the incidence of FAM in the right breast is slightly higher than in the left breast. Gupta and Agarwal also Rangaswamy and Rubby both from India reported a higher incidence of FAM in the right breast[12,13]. Mostly of fibroadenoma located in the upper outer quadrant of the breast [2]. Unfortunately, we do not have data about the location of the lump in this study. More than half of subjects (63.33%) have a history of using hormonal contraception in this study. The previous studies declared that the use of oral contraception contains a combination of progesterone and estrogen could reduce the premenopausal risk of FAM, the risk decline with the duration of oral contraception consumption [14]. Unfortunately, we do not have data on what type of hormonal contraception the subjects used and for how long. In this study, 66.67% of the subjects have suffering FAM for more than 1 year and 3 subjects have a history of previous breast lump surgery. About 90% of the subjects admitted to avoiding surgery as the reason for choosing treatment with jamu. In this study, 43.33% of subjects have a family history of breast tumors. Based on a cohort study conducted by Johansson et al, the presence of breast tumor in family history, especially breast cancer, has a significant effect on the occurrence of benign tumors, including FAM [14] (Table 2).

Table 2. Clinic Characteristics.

| Variables    | Number of subjects (N=30) | Percentage (%) | Mean± SD (kg) |
|--------------|---------------------------|----------------|--------------|
| BMI          |                           |                |              |
| Underweight  | 5                         | 16.67          | 22.46± 4.49  |
| Normoweight  | 15                        | 50             |              |
| Overweight   | 8                         | 26.67          |              |
| Obese        | 2                         | 6.66           |              |
| Number of lump |                        |                |              |
| Single       | 18                        | 60             |              |
| Multiple     | 12                        | 40             |              |
| The affected breast |                |                |              |
| Right        | 12                        | 40             |              |
3.2. Clinical symptoms
A total of 26 subjects complained of pain and one subject complained of itchy at the affected breast. Decreased pain perceived by 21 subjects began the second week of treatment with jamu. At week 6, all subjects felt their breast pain subsided. At the end of the study, 8 subjects had no pain anymore, while 18 subjects still felt the pain that sometimes occurs just before menstruation. Complaints of itchy disappear in weeks 8 and did not reappear until the end of the study (Table 3). Pain is a common symptom of FAM that usually follows the menstrual cycle[4]. Itching in the affected breast is not a usual symptom of FAM and is more commonly found in Paget's disease[17]. However, the subject with breast itching in this study had undergone examinations to exclude a possibility of breast cancer or inflammatory b. The ability of jamu to reduce and even eliminate pain and itching due to FAM is inseparable from the anti-inflammatory, analgesic, and anti-allergic content in the constituent plants[18–22].

Table 3. Clinical symptoms felt by subjects.

| (Week) | Number of subjects (N=26) | Tumor Pain | Tumor Itches |
|--------|---------------------------|------------|-------------|
|        |                           | Constant   | Diminish    | Disappear/no pain | Constant | Diminish | Disappear/no itches |
| 0      | 26                        | -          | -           | -                  | 1        | -        | 25 |
| 2      | 6                         | 20         | -           | -                  | 1        | -        | 25 |
| 4      | 5                         | 21         | -           | -                  | 1        | -        | 25 |
| 6      | -                         | 26         | -           | -                  | 1        | -        | 25 |
| 8      | -                         | 20         | 6           | -                  | -        | -        | 26 |
| 10     | -                         | 20         | 6           | -                  | -        | -        | 26 |
| 12     | -                         | 19         | 7           | -                  | -        | -        | 26 |
| 14     | -                         | 18         | 8           | -                  | -        | -        | 26 |
| 16     | -                         | 18         | 8           | -                  | -        | -        | 26 |

3.3. Tumor or lump size
There was a decrease in the average tumor size after 16 weeks of intervention (Table 4). The limitation of this study is that no placebo group can confirm the efficacy of jamu. Another limitation is we did not
have data regarding the possibility of any supplements consumed by subjects or traditional therapies other than herbs that the subject receives, such as acupressure or acupuncture. Not all subjects experienced a decrease in the size of the tumor, 3 subjects experienced an increase in the size of the tumor. The increase was as follows: 14.2 mm to 14.4 mm, 11.17 mm to 11.57 mm, and 18.2 mm to 19.3 mm. Previous limited studies have also shown that the use of herbs as an alternative therapy in FAM patients did not always work. Shukla et al conducted an open-label single-arm observational study of the administration of homeopathic (herbal) therapy in patients with FAM. A total of 64 FAM-confirmed women participated in this study. Evaluation of pain and clinical symptoms was performed every month while breast ultrasound every 6 months. The result showed that of 12 subjects suffering from breast pain, 9 patients no longer felt pain and 3 felt less pain. The lump disappeared in 23 (35.93%) subjects, significantly smaller in 22 subjects (34.37%) while 19 (29.69%) subjects did not experience improvement/status quo. The plants considered as the most useful remedy were *Conium maculatum* and *Phytolacca decandra* [23]. Chang et al reported an enlarged breast tumor in a 16-year-old woman who had a 3-year history of drinking Shi Wu Tang (SWT), Chinese herbal medicine consisting of 4 plants: *Ligusticum chuanxiong* (chuan xiong) Rhizoma, *Paeoniae alba* (bai shao yao) Radix, *Angelica sinensis* (dang gui) Radix, and *Rehmanniae preparata* (shu di huang) Radix. Histopathological examination during surgery revealed that the tumor was a giant aneuploid fibroadenoma. A cohort study showed that stopping SWT intake for 3 months reduced the average FAM size significantly compared to the placebo group. The SWT decoction is well-known in China for treating female diseases such as menstrual pain and pre-menopausal syndrome. These findings lead to a warning that the recommendation and consumption of herbal medicines in patients with breast tumors should be carried out by competent complementary and alternative (CAM) practitioners [24].

The jamu in this study was composed of plants that have been used empirically by the community, especially in Java island to treat tumors. Scientifically, the plant parts have antiproliferative and cytotoxic activities [25]. The dose of herbal medicine used in this study was the empirical dose used in the community and adjusted to the literature study. Related to how jamu works against FAM could not be explained with certainty. When associated with the pathophysiology of FAM, the flavonoid content in the jamu that is phytoestrogen may play a biphasic role, inhibit and induce the proliferation of breast tumors [26,27]. Therefore, we agree with Chang et al that the administration and use of jamu or other herbs by patients with FAM must be supervised by a competent health worker.

**Table 4. Average of Tumor Size.**

| Tumor size          | Baseline (Day-0) (millimeter/mm) | After (Day-112) (millimeter/mm) | P     |
|---------------------|----------------------------------|---------------------------------|-------|
|                     | 13.89± 6.47                      | 11.79±5.74                      | <0.001* |

*confidence interval 95%

During this study, no serious side effects were found. Based on laboratory parameters, the average values of Hemoglobin (Hb), White Blood Cell Count (WBC), Platelet count, Hematocrite (Hct), Alanine Transaminase (ALT), Aspartate AminoTransferase (AST), blood urea, and creatinine at the beginning and end of the study were within the normal range (Table 5). Acute toxicity test on rats showed no signs of toxicity or death up to 14 days after administration of jamu with a pseudo-LD50 value >5000mg/dl. Subacute toxicity test showed that the administration of jamu for 90 days did not cause any signs of toxicity or death in the rats. The average of ALT, AST, blood urea, and creatinine were not significantly different between the beginning and the end of the study and there was an increase in average body weight indicating good health condition [28].
Table 5. Average of Safety Parameter.

| Parameter          | Baseline (Day-0) | After (Day-112) | Normal value (female) |
|--------------------|------------------|-----------------|-----------------------|
| Hb (gram/dl)       | 11.92±1.32       | 11.83±1.28      | 12-16                 |
| WBC (x10^3)        | 6.946±1.68       | 9.473±1.38      | 4-10                  |
| Platelet Count (x10^6) | 253.962±63.44  | 240.731±58.20  | 150-450               |
| Hct (%)            | 36.53±4.04       | 36.03±3.54      | 37-47                 |
| ALT (U/L)          | 22.92±10.74      | 19.65±7.34      | <40U/L                |
| AST (U/L)          | 16.77±7.77       | 19.38±7.83      | <35U/L                |
| Blood urea (mg/dl) | 21.5±4.22        | 19.96±2.96      | 13-43                 |
| Creatinine (mg/dl) | 0.90±0.22        | 0.79±0.14       | 0.5-0.9               |

4. Conclusion

The administration of jamu for 16 weeks has the potential to reduce tumor size and clinical symptoms. Jamu formula must be given by a medical doctor accompanied by observation during administration.

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