# Preliminary Efficacy and Safety of Oral Suspension SH, Combination of Five Chinese Medicinal Herbs, in People Living with HIV/AIDS ; the Phase I/II Study

Mayura Kusum MD*, Virat Klinbuayaem MD**,
Malee Bunjob Msc in Pharm***, Somchai Sangkitporn MD****

* Department of Medical Sciences, Ministry of Public Health
** Sanpatong Hospital, Sanpatong District, Chiang Mai
*** Medicinal Plant Research Institute, Department of Medical Sciences
**** National Institute of Health, Department of Medical Sciences

*Objective :* *To evaluate the preliminary efficacy and safety of the mixture of drug extracts from 5 Chinese medicinal herbs (SH), in the treatment of Human Immunodeficiency Virus (HIV) infection among people living with HIV/AIDS (PLWHA).*

*Design :* *Open-label study.*

*Setting :* *Sanpatong Hospital, Chiang Mai, Thailand.*

*Subjects :* *HIV-1 infected adults with a CD4 cell count of more than 200 cell/mm³ and HIV-1 RNA > 20,000 copies/ml.*

*Material and Method :* *Patients received an oral suspension of SH, a combination of 5 Chinese medicinal herbs namely Glycyrrhiza glaba L., Artemisia capillaris Thumb., Morus alba L., Astragalus membranaceus(Fisch.) Bge., Carthamus tinctorius L., 5 g or 30 ml, in 3 divided doses after meals, plus sulfamethozaxole/trimethoprim, 400/80 mg tablet, once daily after breakfast for 12 weeks. During the treatment and the follow up period, the absolute CD4 cell count and the plasma HIV-1 RNA were monitored. Adverse events were observed.*

*Results :* *Of the 28 enrolled patients, the number of positive response patients with reduction of plasma HIV-1 RNA more than 0.5 log during the treatment and follow up period were 4-10 (14.2-35.7%) while the number of negative response patients who had plasma HIV-1 RNA rising at least 0.5 log were 2-4 (0-14.2%). The means viral load at week 0 (baseline), 12 and 20 were 4.94, 4.83 and 4.76 log copies/ml, which were slightly declined. Whilst, the mean absolute CD4 cell count of week 0 (baseline), 4, 8, 12, and 20 fluctuated within the baseline, range of 382.1, 404.2, 359.4, 404.1, 360.2 cell/mm³, respectively. All subjects had good compliance without any serious adverse events.*

*Conclusion :* *Under the condition used, SH drug therapy is safe. Satisfactory positive response, by decreased viral load of more than 0.5 log, was found in 14%-35% of HIV-positive patients. However, the immunologic response, an increase of CD4 cell count was not clearly demonstrated. The clinical benefit of SH needs more thorough scientific support before being prescribed as adjunctive therapy for treating PLWHA.*

*Keywords :* *Efficacy, Safety, SH, Chinese medicinal herbs, People living with HIV/AIDS*

Human immunodeficiency virus (HIV) infection induces a chronic, progressive, immune dysfunction rendering those infected susceptible to opportunistic infections, malignancies, wasting disease, neurologic sequelae, and early death. Although much is known about the HIV and numerous agents that inhibit HIV-1 replication in vitro have been developed, the therapeutic goal has still not been achieved yet. The goal of anti HIV therapy is to

*Correspondence to : Kusum M, Department of Medical Sciences, Ministry of Public Health, Nonthaburi 11000, Thailand.*

eradicate HIV or, if that is not possible, to stop the disease progression while preserving or improving the quality of life for the afflicted is also desired[1].

To treat HIV infection, the drug should decrease the viral load (preferably to < 20 copies/mL) as long as possible which can halt disease progression and prevent or reduce resistant variants. It was noted that CD4 response is often good with partial viral suppression, and opportunistic infections (OIs) are uncommon with a viral load < 5,000 copies/ml[2]. However, partially suppressive regimens are less durable and lead to the emergence of drug-resistant virus. The anti HIV drugs should at least maintain or stimulate the immune reconstitution, that means quantitative CD4 cell count is in the normal range with qualitative pathogen-specific immune response.

There have been great advances in the management of patients with HIV infection in the past decade. Introduction of highly active antiretroviral therapy (HAART) has decreased HIV-related deaths. However, long term use of HAART may develop viral resistance and drug - relate toxicity with new clinical entities such as lipodystrophy and immune reconstitution illnesses[3]. Treatment strategies need to take into account these limits to better target those HIV-infected patients who could benefit the most from antiretroviral therapy.

Many international research institutes have increased publications of unconventional therapies (UT)[4,5], otherwise called: alternative, traditional, complementary; terms often used as synonyms[6]. Some researches showed that 31-91%, according to studies and nations where they have been conducted on people living with HIV/AIDS (PLWHA), use UT[7-10].

The use of UT alone or in conjunction with antiretroviral treatment appears to have high prevalence in PLWA individuals and to be associated with the debilitating and chronic nature of HIV disease. The researches of herbal medicine are needed to identify the complementary medicinal herbs that may be used as adjunctive therapy. SH drug, a herbal preparation composed of 5 Chinese medicinal plant extracts was developed by the Kunming Institute of Botany (KIB) in Kunming, China, which has been used as tonic solution among Chinese people and PLWA for more than 10 years. As a part of the collaborative program between the Ministry of Public Health, Thailand (MoPHT) and KIB, a long term toxicity study of SH drug in rats was performed, by the Medicinal Plant Research Institute (MPRI), Department of Medical Sciences (DMSc), MoPHT. In this study, both sex Wistar rats were orally given the SH drug suspension in 1% tragacanth at the dose of 100, 500 and 2,500 mg/kg body weight for 28 days. These doses were equivalent to 1, 5 and 25 times of the therapeutic dose. The highest dose group reduced food intake and body weight, but not beyond the normal range as well as the change of several hematological parameters in female rats. The serum alanine aminotransferase (ALT), was also higher than the control group without pathological change. It was suggested that the 1 and 5 times of the therapeutic dose was safe in animal studies[11].

The present study aimed to assess the preliminary efficacy and safety of the SH drug in the treatment of HIV infection. The authors hypothesized that more minimizing of the viral replication and/or increasing the CD4 cell count could be a good candidate for anti HIV drug as UT.

## Material and Method
### Preparation of SH suspension
The crude extracts of Glycyrrhiza glabra L., Artemisia capillaris Thumb., Morus alba L., Astragalus membranaceus (Fisch.) Bge., Carthamus tinctorius L., were mixed thoroughly in 1:1:2:1:1 part by weight and formulated in a suspension form by MPRI. Sulfamethoxazole/trimetroprim 400/80 mg tablets were from Roche Thailand, Ltd.

### Study design and patients
This was a simple preliminary trial conducted in Sanpatong Hospital, Chiang Mai province, Thailand. The patients were recruited from the outpatient department during March to December 2000. The inclusion criteria were individuals 18 years old or older who had HIV-1 infection with a CD4 cell count not lower than 200 cell/ml or HIV-1 RNA more than 20,000 copies/ml, no prior AIDS-defining illness, Karnofsky Performance Score at least 70 points. Exclusion criteria included pregnancy, breast-feeding, unwilling to avoid pregnancy for the duration of the trial, allergy to sulfamethoxazole/trimetroprim, and having ARV medication within 6 months of entry or planning to have it during the study. The protocol and informed consent were approved by the national ethical committee and institutional review board of the trial center.

The subjects were prescribed 12 weeks of SH suspension 5 g or 30 ml orally in 3 divided doses after meals plus a tablet of sulfamethozaxole/trimethoprim, 400/80 mg once daily after breakfast for the

prophylaxis of pneumocystis carrinii pneumonia. After the treatment period, these patients were followed up until 20 weeks. The disease progression was prospectively observed by the investigators. Adverse events were reported according to the number of patients who experienced them. If a patient reported a specific event more than once, only the one worst severity was included. The relationship of the adverse events to the drugs were evaluated by the investigators.

### Laboratory study

Absolute number of CD4 lymphocyte counts were checked by flow cytometry on real-time basis, and plasma HIV-1 RNA load was determined by batch testing at Faculty of Medical Technology, Chiang Mai University. The viral load assays were performed using the Amphicor HIV monitor assay (Roche Diagnostic), with a limit of quantitative of 400 copies per ml[12].

### Statistics and HIV markers

The primary end point of the study was the effect on plasma HIV-1 RNA load over the time of treatment and follow-up visits at the weeks 0, 2, 4, 6, 8, 10, 12 and 20; and CD4 cell counts at week 0,4,8,12 and 20. The plasma HIV-1 RNA loads were log transformed. The result was considered satisfactory when there was at least 0.5 log decrease of plasma HIV-1 RNA after commencing the drug. The average measurement change from baseline at admission was used for primary analysis. Compliance was assessed based on patient-reported missed doses, as recorded in the case report form. Failure to take at least 20% of medications was defined as noncompliance in this analysis.

## Results
### Characteristics of the study patients

Of the 90 subjects screened, 28 met the criteria and were enrolled in the study. Twenty-two of 28 cases or 78.5 % were females. The mean age was 34 years (SD=11.8). Karnofsky Performance Score 100 and 90 were 16 and 12 cases respectively. At admission, the mean CD4 cell count was 382.1 cell/mm$^3$, and the mean HIV-1 RNA was 4.94 log copies/ml. The baseline admission characteristics are shown in Table 1.

### Virologic effect and Immunologic effect

The means viral load of week 0 (baseline), 2, 4, 6, 8, 10, 12 and 20 were 4.94, 4.79, 4.78, 4.76, 4.66, 4.82, 4.83 and 4.76 log copies/ml, respectively. As

**Table 1.** Baseline admission characteristics

| | |
|---|---|
| mean age, years (SD) | 34 (11.8) |
| female/total cases (%) | 22/28 (78.5) |
| Karnofsky score, cases (%) | |
| 100 | 16 (57.1) |
| 90 | 12 (42.9) |
| baseline CD4 cell count, cell/mm$^3$ | |
| mean | 382.1 |
| range | 213-928 |
| baseline HIV-1 RNA, log copies/ml | |
| mean | 4.94 |
| range | 4.35-5.56 |

shown in Fig. 1, a reduction in plasma HIV-1 RNA of the baseline were -0.15, -0.16, -0.18, -0.28, -0.12, -0.11 and -0.18 log copies/ml by the week 2, 4, 6, 8, 10, 12 and 20, respectively. During treatment and follow up period the mean absolute CD4 cell count of week 0, 4, 8, 12, and 20 fluctuated within the baseline of 382.1, 404.2, 359.4, 404.1, 360.2 cell/mm$^3$ respectively which was no significant change.

### Response categories of treatment

The results of the treatment from week 2 to 20 can be categorized by mean logarithmic change of plasma HIV-1 RNA into three groups: 1) positive response, reduction of mean logarithmic change at least 0.5 log copies/ml or more; 2) partially positive and negative response, reduction or raising of mean logarithmic change less than 0.5 log copies/ml; 3) negative response, raising of mean logarithmic change at least 0.5 log copies/ml or more.

The majority of patients were in the partially positive and negative response group, which were 22 (78.5%), 19 (67.8%), 18 (64.2%), 16 (57.1%), 23 (82.1%), 21 (75%) and 18 (64.2%) at week 2, 4, 6, 8, 10, 12 and 20 respectively. During the same period, the number of positive response groups were 6 (21.4%), 5 (17.8%), 7
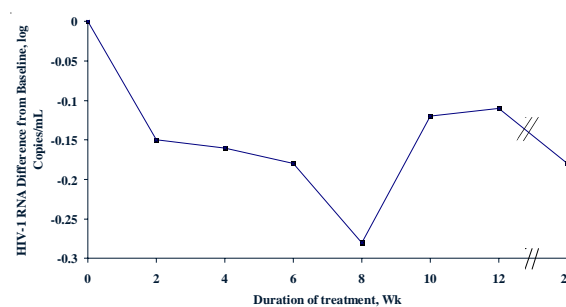


**Fig. 1** Mean logarithmic change in Human immunodeficiency virus type 1 (HIV-1) from admission baseline for all patients

(25%), 10 (35.7%), 4 (14.2%), 4 (14.2%), 8 (28.5%) while the number of negative response groups were 0 (0%), 4 (14.2%), 3 (10.7%), 2 (7.1%), 1 (3.5%), 3 (10.7%) and 2 (7.1%) respectively (Fig. 2).

### Adverse Events

During the study, a number of subjects reported the concomitant symptoms and signs of: myalgia 5 (17.6%), allergic rhinitis 4 (14.2%), insomnia 4 (14.2%), upper respiratory tract infection 4 (14.2%), weakness 3 (10.7%), peptic ulcer 3 (10.7%), dizziness 2 (7.1%), diabetes mellitus 2 (7.1%), conjunctivitis 2 (7.1%), goiter 2 (7.1%), asthma 2 (7.1%), tonsillitis 2 (7.1%), and back pain 2 (7.1%). The least proportion, of 1 (3.5%), had reported the conditions such as sinusitis, tenia cruris, hypertension, typhoid fever, irregular menstruation, breast tenderness, headache, and loose stool. The chronic conditions were recognized as follows: dermatitis 5 (17.8%), oral ulcers 2 (7.1%), oral candidiasis 2 (7.1%), and oral hairy leukoplakia 1 (3.5%).

The adverse events that may possibly be related to the studied drug are presented in Table 2. The most frequent reported side effect, feeling warm in the stomach, as well as drowsiness could be due to the ethanol content in the SH suspension. Most of the adverse events were not serious and appeared over a short period. The patients had good compliance because there was no report a missed dose.

### Discussion

The Community Forum, which took place at the same time as the XI International Conference on AIDS, held in Vancouver in 1996, has expressly turned an invocation for a greater commitment also with

**Table 2.** Adverse events possible related to the study drugs

| Adverse Events | Number (%) |
| --- | --- |
| Feeling warm in the stomach | 10 (35.7%) |
| Anorexia | 5 (17.8) |
| Nausea /vomiting | 4 (14.3) |
| Drowsiness | 3 (10.7) |
| Feeling warmth in the throat | 1 (3.6) |
| Hyperthermia | 1 (3.6) |
| Bloating | 1 (3.6) |
| Chest pain | 1 (3.6) |
| Hepatitis* | 1 (3.6)* |
| Fatigue | 1 (3.6) |
| Anemia | 1 (3.6) |

* subsequent serum was positive for HBV Ag.
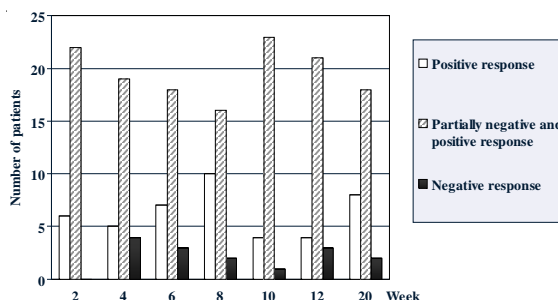


**Fig. 2** Response categories of the treatment from week 2 to week 20

respect to UT experimentation and availability. Many researches showed that a high proportion of PLWHA use UT. Some of the most important world's HIV and AIDS researchers clearly expressed the need to look for natural therapies to combat HIV and AIDS. The use of UT is yet too conditioned by anecdotal, incomplete and contradictory knowledge. It is necessary to conduct clinical studies about the efficacy of UT for HIV and AIDS. The MoPHT committed to launch the national policies with the purpose of fully involving UT based therapies in 1997. Many pilot researches, using Thai and/or Chinese medicinal herbs, have been performed. The in vitro results are backed up by clinical studies on PLWHA. The clinical pharmacotherapies have been evaluated.

Although the ideal clinical trial should be blind, randomized and placebo-controlled, in herbal medicine, placebo-controlled studies may not be possible in some cases, especially in herbal medicine with prominent flavor or strong taste[13]. This phase I/II study is a prospective open label study without placebo control since it was impossible to find a suitable placebo. For the efficacy and safety of SH suspension in the treatment of HIV-1, the SH drug is safe in terms of adverse reactions and side effects. During the study period, the subjects reported several but mild adverse events some of which may have been caused by the disease itself. Most side effects such as warm in the throat and stomach or hyperthermia or drowsiness were possibly the effect of ethanol component in SH suspension. However, for good compliance in long term therapy the appropriate combinations of suspension should be concerned and improved.

Many laboratory markers have been used to evaluate the progression in patients with HIV infection but in practice, at least two markers should be used for disease monitoring[14]. Prognosis of HIV infected

persons is more accurately defined by a combination of plasma HIV 1 RNA and CD4 lymphocyte[15] while absolute number of circulating CD4 has been suggested as the single best predictor of AIDs onset[16]. In the present study, the authors used plasma HIV-1 RNA and absolute CD4 cell counts as the markers for efficacy evaluation. The target level of HIV-1 RNA after treatment is undetectable or less than 5000 copies/ml while minimal decrease in HIV-1 RNA which indicate the antiviral activity is less than 0.5 log decrease[15,17]. The present study relatively showed the positive results of the Chinese medicinal herbs in the treatment of HIV-1 infection among PLWHA. Fourteen to thirty five percent of the subjects had a decreased viral load of more than 0.5 log. However, the immunologic response as seen by the number of CD4 cells was not observed. The present result challenged and warranted further clinical trials of SH drugs in a larger number of HIV infected subjects in conjunction with other antiretroviral agents for a longer treatment period. The Thai-Chinese project on UT research is an example of bilateral collaboration, and the integrated tasks among MoPHT, research institutes, universities, and public health services, realization of a rigorous scientific research finalized to the optimization of potential effects by these remedies on PLWHA.

### References

1. Schnittman SM, Pettinelli CB. Strategies and progress in the development of antiretroviral agents. In: De Vita VT, Hellman S, Rosenberg SA, Curran J, Essex M, Fauci As. AIDS: Etiology, Diagnosis, Treatment and Prevention, 4th ed. Lippincott-Raven, Philadelphia, 1997: 467-87.
2. Deeks SG, Barbour JD, Martin JN, Swanson MS, Grant RM. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with human immunodeficiency virus infection. J Infect Dis 2000; 181: 946-53.
3. Kingston MA, Bowman CA. The investigation of patients with HIV infection: 10 years of progress. Int J STD AIDS. 2001; 12: 1-7.
4. Fisher P, Ward A. Complementary medicine in Europe. BMJ 1994; 309: 107-10.
5. Eisemberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. Unconventional medicine in the United States. Prevalence, costs, and pattern of use. N Engl J Med 1993; 328: 246-52.
6. Joyce CR. Placebo and complementary medicine. Lancet 1994; 344: 1279-81.
7. Bates BR, Kissinger P, Bessinger RE. Complementary therapy use among HIV-infected patients. AIDS Patient Care STDS 1996; 10: 32-6.
8. Ostrow MJ, Cornelisse PG, Heath KV, et al. Determinants of complementary therapy use in HIV-infected individuals receiving antiretroviral of anti-opportunistic agents. J Acquir Immune Defic Syndr Hum Retrovirol 1997; 15: 115-20.
9. Anderson W, O'Cornor BB, MacGregor RR, Schwartz JS. Patient use and assessment of conventional and alternative therapies for HIV infection and AIDS. AIDS 1993; 7: 561-5.
10. Sparber A, Wotton JC, Bauer L, et al. Use of complementary medicine by adult patients participating in HIV/AIDS clinical trials. J Altern Complement Med 2000; 6: 415-22.
11. Chavalittumrong P, Chivapat S, Chuthaputti A, Rattanacharasroj S, Punyamong S, Butraporn R. Subacute toxicity of SH drug in rats. Medicinal Herb Research Institute Report, Department of Medical Sciences, Ministry of Public Health, Thailand, 2000.
12. Mulder J, McKinney N, Christopherson C, Sninsky J, Greenfield L, Kwok S. Rapid and simple method for extracting human immunodeficiency virus type 1 RNA from plasma, enhanced sensitivity. J Clin Microbiol 1997; 35: 1278-80.
13. World Health Organization. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. Geneva World Health Organization, 2000.
14. Gupta V, Gupta S. Laboratory markers associated with progression of HIV infection. www.ijmm.org/issues/jan04/reviewarticle.htm.
15. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4 lymphocytes as prognostic markers of HIV1 infection. Ann.Intern Med 1997; 126: 946-54.
16. Fahley JL, Taylor JMD, Detels R, et al. The prognostic value of cellular and serologic markers in infection with human immunodeficiency virus type 1. N Engl J Med 1990; 322: 166-72.
17. Saag MS, Holodniy M, Kuritzkes DR, et al. HIV viral load markers in clinical practice. Nature Med 1996; 2: 625-9.

## การศึกษาเบื้องต้นเกี่ยวกับประสิทธิภาพและความปลอดภัยของยาน้ำผสมสมุนไพรจีน 5 ชนิด SH ในผู้ป่วยและผู้ติดเชื้อ HIV : การศึกษาระยะ 1/2

**มยุรา กุสุมภ์, วิรัตน์ กลิ่นบัวแย้ม, มาลี บรรจบ, สมชาย แสงกิจพร**

**วัตถุประสงค์** : เพื่อประเมินประสิทธิผลและความปลอดภัยเบื้องต้นของสารสกัดสมุนไพรจีน 5 ชนิด (SH) ในการรักษาผู้ติดเชื้อ HIV

**วิธีการ** : เป็นการศึกษาแบบปลายเปิด

**สถานที่** : โรงพยาบาลสันป่าตอง จังหวัดเชียงใหม่

**กลุ่มตัวอย่าง** : เป็นผู้ติดเชื้อ HIV ที่มี จำนวน CD4 มากกว่า 200 เซลล์/มม$^3$ และมี HIV-1 RNA มากกว่า 20,000 copies/ml

**วิธีการ** : ผู้ป่วยได้รับยาน้ำแขวนตะกอน SH ซึ่งมีส่วนผสมสมุนไพรจีน 5 ชนิดคือ Glycyrrhiza glaba L., Artemisia capillaris Thumb., Morus alba L., Astragalus membranaceus (Fisch.) Bge., Carthamus tinctorius L. รับประทานวันละ 5 กรัม หรือ 30 มล. แบ่งให้ 3 เวลาหลังอาหาร ร่วมกับยาเม็ด sulfamethoxazole-trimetroprim 400/80 มก. รับประทานวันละ 1 ครั้งหลังอาหารเช้า เป็นเวลา 12 สัปดาห์ ตรวจนับจำนวน CD4 และ HIV-1 RNA ในระหว่างให้ยาและหลังจากหยุดยา พร้อมกับสังเกตอาการไม่พึงประสงค์ และอาการข้างเคียงของยาในระยะเวลาดังกล่าว

**ผลการศึกษา** : มีผู้เข้าร่วมการศึกษาทั้งสิ้น 28 คน ผู้ติดเชื้อที่มีการเปลี่ยนแปลงในทางบวกคือมี HIV-1 RNA ลดลงมากกว่า 0.5 log ในการตรวจทุก 2 สัปดาห์มีจำนวน 4-10 คน (14.2%-35.7%) ผู้ติดเชื้อที่เปลี่ยนแปลงในทางลบคือมี HIV-1 RNA เพิ่มขึ้นมากกว่า 0.5 log มีจำนวน 2-4 คน (7.1%-14.2%) ค่าเฉลี่ยของจำนวนไวรัสเปรียบเทียบระหว่างเมื่อเริ่มโครงการคือสัปดาห์ที่ 0 เมื่อสิ้นสุดการรักษาคือสัปดาห์ที่ 12 และหลังการรักษาในสัปดาห์ที่ 20 พบว่าลดลงเล็กน้อยคือ 4.94, 4.83 และ 4.6 log copies/ml ค่าเฉลี่ยของจำนวน CD4 ในสัปดาห์ที่ 1, 4, 8, 12 และ20 เปลี่ยนแปลงในช่วงแคบ ๆ คือ 382.1, 404.2, 359.4 และ 404.1 เซลล์/มม$^3$ ผู้ป่วยทุกรายให้ความร่วมมือรับประทานยาตามที่สั่ง พบอาการที่ไม่พึงประสงค์และอาการข้างเคียงเล็กน้อย

**สรุป** : การรักษาด้วย SH มีความปลอดภัย ผลการรักษาพบว่าประมาณ 14-35% ของผู้ติดเชื้อ ตรวจพบจำนวนไวรัสลดลงมากกว่า 0.5 log แต่ไม่พบการเปลี่ยนแปลงด้านภูมิคุ้มกันคือ CD4 ไม่เพิ่มขึ้น บ่งชี้ว่า SH อาจจะช่วยในการรักษาผู้ติดเชื้อ HIV แต่จะต้องมีการศึกษาเพิ่มเติมอีกมากกว่านี้