THE STABILITY STUDY OF CLINACANTHUS NUTANS OR PRAYAYOR CREAM DECLARED IN NATIONAL LIST OF ESSENTIAL MEDICINES B.E.2560

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ABSTRACT

Abstract- Thailand has its own identity of traditional medicine called "Thai Traditional medicine" (TTM). It was believed that it originated during or event before the Sukhothai period (1238-1377) as the means of community health care until the early 20th century. However the migration of modern medicine from the Western world to the East, leading to the dramatically declined in the practice of traditional medicine in Thailand. The consequence of modern medicine invasion had taken over TTM and became Thai mainstream health-care system. TTM was neglected for over 60 years until the revival of TTM began in the late 1970s. Herbal medicines that have been (scientifically) developed not only for Primary Health care but also medical tourism Industry. Various dosage forms of single herbal medicines from the following five medicinal plants were selected, namely: Turmeric for dyspepsia,*Senna alata* for constipation, *Andrographis paniculata* for pharyngotonsillitis and diarrhea, *Zingiber cassumunar* for bruises and muscle sprains and finally *Clincanthus nutans* for herpes simplex and herpes zoster infection of the skin, cold sores, skin rash, hives and itching. However there is still a certain issues, for example the stability of the *Clinacanthus nutans* cream or Prayayor cream declared in National List of essential Medicines B.E. 2560(NLEM 2560). This objective of this paper is to study the stability problem of the *Clincanthus nutans* cream declare in National List of essential Medicines B.E. 2560 and propose the solution to resolve this problem to sustain and develop "Thai Traditional medicine" not only for the primary health care but also the medical tourism industry.

Key words: Stability problem, Clincanthus nutans cream

Introduction

According to past history shows that Thai people began to use herbal medicine for health care for the treatment of various symptoms and illness during or before the Sukhothai period or before 1238 A.D. During the same period, the stone inscription of King Chaivoraman, the Khmer Kingdom indicated that 102 Arogaya Sala, the indigenous hospitals were built to serve people throughout that Kingdom, including the northeastern part of today's Thailand confirmed the wide spread used and popularity of Traditional medicine knowledge in this Era.

During the Ayutthaya period (1350-1767) , there were a number of community TTM stores for the general public as well as royal dispensary in the royal palace. During the reign of King Narai the Great (1656-1688) , the king traditional practitioners was ordered to compile a National Recipe called King Narai's medicinal recipe or Tumra Phra Osod Phra Narai, which was the first official TTM recipes.

After devastation Ayutthaya in 1767 by Burma, Thailand's new capital city was re-established in Thonburi and later in Bangkok in the Rattanakosin Era in 1782. Kings Rama I, II and III of the present Chakri Dynasty played an important role in the revival of TTM. Over thousands of recipes and the body of knowledge of TTM regarding the illness and their treatments were gathered and inscribed on marble and placed on the walls of two temples, named Wat Po and Wat Raja Oros. The marble inscriptions also included the principle of Thai traditional massage and stretch exercise called "Ruesi Dud Ton", the explanations of the symptoms or illness and how to treat and/or heal.The purposes of the Kings' orders were to compile and renew the collective knowledge of TTM that had been partly lost or destroyed during the war. The knowledge became the health education to the Thai people so that they could take the TTM knowledge for their own health care.

During the reign of King Rama III, the Western medicine has been introduced into Thailand by the group of missionaries and Western physicians, gradually Increased and become well accepted. However, during the

reign of King Rama V (1868-1910), there was the effort to promote the TTM for example, the medical recipe "Tumra Paetsart Sonkrau" and "Tumra Vejasuksa" were introduced and became the first Thai national formulary called "Tumra Paetsart Sonkhrau Chabub Luang" and "Tumra Vejasuksa", the first TTM textbook for medical students during that time.

In 1888, King Rama V established the Siriraj Hospital, the first Western-style hospital and medical school. At the beginning, both TTM and modern medical services were provided. The medical school also taught both TTM and modern medical principles.

However, in 1916 the teaching of TTM and the provision of TTM services at Siriraj Hospital were discontinued with the reasons that the two principals were considered incommensurable and confusing to medical students. TTM was viewed as inconsistent and variable depending on a doctor's opinion rather than empirical evidence and the teaching curriculum were based on only a few classical textbooks that must be learned by exchanging the tacit knowledge rather than the explicit knowledge which was believed as unscientific and unacceptable knowledge.

The systematic teaching of TTM in the medical school had declined in acceptance, especially among well educated people. The status of TTM practitioners in health-care system became worse when the "Medical Act B.E. 2466" and the "Control of the Practice of the Art of Healing Act B.E. 2479" were promulgated in 1923 and 1936 respectively.

As a consequence of the laws and the misinterpret of the TTM philosophy, the majority of TTM practitioners at that time became illegal. TTM practitioners could only practice TTM privately in their own clinics and their role in the provision of health care for the Thai people was therefore limited to only the poor living in rural areas where modern medicines were not easily accessible. [2]

The resurrection of Thai traditional medicine

Almost 70 years after the cessation of TTM services and TTM education at Siriraj Hospital, The revival of TTM began around 1978 after the proclamation of the Alma-Ata Declaration. [1] As the World Health Organization (WHO) urged its member countries to include medicinal plants in their primary health care (PHC) programme. According to Thailand, Ministry of Public Health responded to WHO's recommendation by including such a policy to promote the use of medicinal plants in PHC since the time of the Fourth Health Development Plan (1977-1981). Government policy regarding the promotion of the use medicinal plants and Thai traditional medicine in the country's health-care system has continued until today as stated in the Fifth to Ninth (current) National Economic and Social Development Plans (2002-2006). [1,2,3]

In 1979, there was a meeting on "Thai traditional medicine" among TTM practitioners, modern medical doctors and university professors held at Siriraj Hospital to discuss ways to revive TTM and improve the role of TTM in the health system. In 1986, the Division of Health Planning and the Collaborating Centre of Medicine and Health held national seminars on the "Development of Thai Traditional Medicine". However, no clear-cut development plans or projects could be effectively formulated or implemented. One of the conclusions from both seminars was the suggestion to the Ministry to establish an office to play an active role in the revival of TTM.

According to the conclusions from both seminars, an office was established in 1989, initially as the "Collaborating Centre for the Development of Thai Traditional Medicine and Pharmacy" under the Office of the Permanent Secretary. This Centre was later upgraded to division level in 1993 as the "Institute of Thai Traditional Medicine" (ITTM) under the Department of Medical Services [4]. Through the years, the Institute has organized several activities to develop TTM in various aspects, until the Bureaucratic Reform Act, the "Department for the Development of Thai Traditional and Alternative Medicine" (DTAM) was established as a new department under the Ministry in October 2002, comprising ITTM, the Division of Alternative Medicine and the Office of the Secretary [5]. Therefore, the commitment of the government to promote TTM as another means of health care for Thai people was more or less established [6].

In addition to the Ministry, non-governmental organizations (NGOs) have also played a role in the revival and development of TTM. In 1980, Professor Dr. Ouay Ketusingh, a renowned senior medical professor of Siriraj Hospital who appreciated the value of TTM for enhancing Thai people's health and for reducing the cost of health care, made an announcement on the establishment of the "Foundation for the Promotion of Thai Traditional Medicine", which was officially registered in 1982. The main objectives of the Foundation were to revive TTM knowledge, improve educational standards and the medical practice of TTM and promote TTM education [7]. In 1987, the Ministry issued the Control of the Practice of the Art of Healing Act B.E. 2530, allowing the graduates from the Ayurvedh Vidhayalai (Jevaka Komarapaj) college who passed the licensing examination to become licensed applied-TTM practitioners. They are thus legally allowed to use some medical equipment, e.g., stethoscope, sphygmomanometer and thermometer, for

physical examination of patients in order to diagnose the patients better and to determine whether or not modern medical therapy is needed. However, they can prescribe only traditional medicines and use traditional therapies to treat their patients [8].

Recently, Thailand was declared as the top travel destination medical tourism of the world by Bloomberg in 2015.Therefore Thai herbal medicine should be one of the key success factors of the medical tourism Industry[9].The development of thai herbal medicine should be considered as priority.

The role of Thai traditional medicine in health promotion and Tourism industry.

The revival of TTM in 1978, various aspects and practices of TTM have been promoted for the health promotion of the Thai people with hope to fully integrate into the National Health Service system for example

- Medicinal plants and traditional medicines
- Thai massage or Nuad Thai
- Hot herbal compresses and herbal steam baths

The development of herbal medicines were not only for health promotion but also in Tourism industry. The promotion of the use of medicinal plants in PHC was the first movement in the revival of TTM because it was stated in the national policy as a result of the Alma Ata Declaration. However, in order to sustain Thailand as the the top travel destination, the Thai Herbal medincines and Thai massage or Nuad Thai could serve as one of the key services for Tourism industry.

According to the development of herbal medicines and medicinal plants and their role in health promotion 57 medicinal plants were selected and recommended for the treatment and relief of 19 groups of common minor symptoms and diseases [10,11]. PHC has increased the use of medicinal plants by the public, an attempt has also been made to increase the use of herbal medicines in hospitals in place of modern medicines, where appropriate, by including some herbal medicines on the National List of Essential Drugs (List of Herbal Medicinal Products), as follows

- *Curcuma longa L.* or Turmeric for dyspepsia
- *Senna alata* for constipation
- *Andrographis paniculata* for pharyngotonsillitis and diarrhoea
- *Zingiber cassumunar* for bruises and muscle sprains
- *Clincanthus nutans* for herpes simplex and herpes zoster infection of the skin, skin rash and itching.

The cream dosage form of *Clincanthus nutans* was selected to study the stability of the cream according to the suggested formulation in National List of essential Medicines (NLEM) [11].

Materials and Method

Collection and identification - The leaves of *Clinacanthus nutans* were purchased from the local market, Lumlukka District, Pathumthanee, Thailand and identified by Microscopic determination of the leaf.

Extraction-The fresh leaves of Clinacanthus nutans were washed thoroughly with distilled water to remove and clean the adhering dust particles. Then the leaves were left in clean tray until dry.

50 g of fresh dried leaves of Clinacanthus nutans were extracted by using 1.0 L of 95% ethanol as a solvent and shake regularly 3-4 times a day for 7 days. The ethanoic extract of Clinacanthus nutans leaves was filtered and concentrated on the water bath under controlled temperature 60-70 ^{o}C until the final weight of the primary *Clinacanthus nutans* ethanolic extract is 4 gm. and stored at 4 ^{o}C in a refrigerator till further use.

Preparation of Secondary *Clinacanthus nutans*- Ethanolic extract - The 100 gm of primary Clinacanthus nutans ethanolic extract was added with Tween 20, 5 gm and stirs until homogeneous.

Preparation of cream base - The 100 gm. cream base formulation is as follows

Part A.	Cetostearyl alcohol	25 gm.
	Tween 60	2.5 gm
	Tween 80	2.5 gm.

Part B. Sodium EDTA 0.1 gm
Sodium metabisulfite 0.1 gm.
Water qs. 100 gm.

Heat part A and part B in water bath until reach 72 ºC. Pour part A to part B, stir until the mixture become homogeneous and then cool down to 42 ºC to be ready for adding the primary or secondary Clinacanthus nutans ethanolic extract.

Preparation of the 4% *Clinacanthus nutans* ethanolic extract cream - Pour the 4 gm of primary or secondary Clinacanthus nutans ethanolic extract into 42 ºC cream base and stir until the mixture become homogenous. The two preparations were used to compare the stability regarding to the Physicochemical properties, pH value and % label amount of total flavonoids.

Quantitative Phytochemical Analysis-

The total flavonoids of the ethanoic extract of the fresh leaves of *Clinacanthus nutans* limit is not less than 1.0 percent and the total flavonoids of *Clinacanthus nutans* cream is not less than 10 mg%.

Determination of Total Flavonoids - Leaf extract of *Clinacanthus nutans* (1 mL) was added to 10-ml volumetric flasks containing 4 ml methanol. $NaNO_2$ solution (1:5, w/v, 0.3 mL) was added to the flasks and allowed to stand for 6 min at room temperature. After 6 min, 0.3 ml AlCl3 solution (1:10, w/v) was added to the flasks, mixed well and kept for 6 min at room temperature. At last 2.0 ml. NaOH 1 M solution was added and kept for 10 min at room temperature. The absorbance was measured at 510 nm by spectrophotometer (Shimadzu, Japan).Quercetin was used as a standard for the calibration curve.

Stability Evaluation

The stability evaluation of the 4 % primary *Clinacanthus nutans* ethanolic extract cream (Formulation1) compare to 4 % secondary *Clinacanthus nutans* (Formulation2) ethanolic extract cream as follows

Stability Study					
DAYS	**STORAGE CONDITION**	**FORMULATION**	**APPEARANCE**	**VISCOSITY (cps)**	**TOTAL FLAVONOID (mg %)**
0	**Ambient**	**1**	**Dull greenish nonhomogeneous cream.**	**52,000**	**35**
		2	**Bright greenish homogenous cream**	**98,000**	**40**

Table 1: The approximate 6 month (180 days) stability study of the 4 % primary *Clinacanthus nutans* ethanolic extract cream (Formulation1) compare to 4 % secondary *Clinacanthus nutans* (Formulation2) ethanolic extract cream in ambient condition.

180	**Ambient**	**1**	**Dark greenish separated cream.**	**80**	**Not detected**
		2	**Bright greenish homogenous cream**	**88,000**	**35**

Results and Discussion

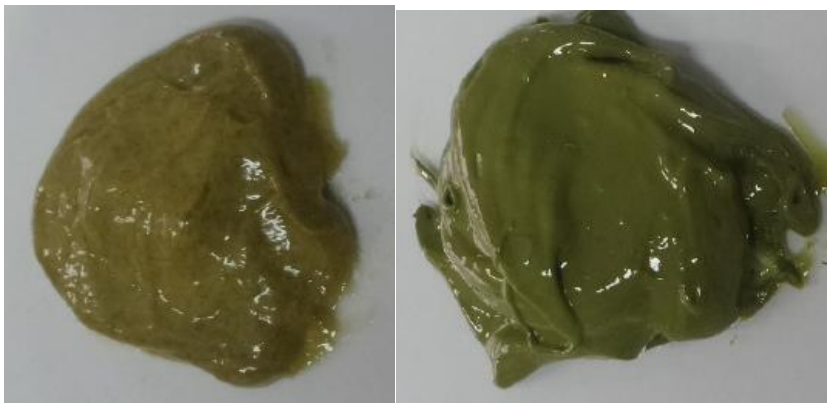
Clincanthus nutans is an asean herb, roots contain betulin, lupeol,b-sitosterol, and stigmasterol. The leaves contain lupeol, b-sitosterol, stigmasterol, phenolic acids and flavonoid compound [13] . It demonstrated good free radical scavenging activity when measured by different methods. For high pharmaceutical quality, *Clincanthus nutans* should be harvested 6 months after planting because of the high accumulation of flavonoids and phenolic acids at this growth stage. This might be due to increased translocation of the polyphenols into the buds from other parts of the plant or biosynthetic enzyme activities [14] . The primary Clinacanthus nutans ethanolic extract is mainly comprised of oil soluble resinous compounds which is translocated from the *Clincanthus nutans* fresh herb to ethanolic extracting solution. The resinous compounds will not dissolve in aqueous part during the preparation of the cream, therefore the primary *Clinacanthus nutans* ethanolic extract cream (Formulation1) is not homogenous and finally become separated and loss its viscosity after the approximate 6 month (180 days) storage in ambient condition.

To resolve this problem, the Tween 20, 5 gm is added into the primary *Clinacanthus nutans* ethanolic extract as the solubilizer to form the secondary homogenous *Clinacanthus nutans* ethanolic extract. The secondary homogenous Clinacanthus nutans ethanolic extract is now readily to dissolve in aqueous part during the preparation of the cream, therefore the secondary *Clinacanthus nutans* ethanolic extract cream(Formulation2) become homogenous(see figure1) and the stability of the cream is much more stable than the primary Clinacanthus nutans ethanolic extract cream(Formulation1) (see Table1)

The formulation1 after 180 days storage at ambient condition, the total flavonoids content is not detectable, while the formualtion2, the total flavonoids content slightly lower, however its total flavonoids content is still in specification limit. The steep reduction of the total flavonoids content in formulation1 is expected from the rapid hydrolysis of the flavonoids which is exposed directly to the in aqueous part of the nonhomogeneous cream (Formulation1).

According to the stability study the proposed solution to resolve this problem is to add a suitable solubilizer in the ethanolic plant extract before incorporate the ethanolic plant extract into a cream base. This technique will not only prevent the decomposition of the active components in the extract but also could stabilize the cream base in long term storage condition.

In this stability case study, the proposed solution will be able to sustain and develop "Thai Traditional medicine" *Clinacanthus nutans* or Prayayor cream not only for the primary health care but also medical tourism industry regarding to the "Thai Traditional medicine" national policy recently announced by Thai government.



(a) (b)

Figure 1

(a) 4 % primary *Clinacanthus nutans* ethanolic extract cream (Formulation1) and (b) 4 % secondary Clinacanthus nutans ethanolic extract cream (Formulation2) . Obviously,the 4 % secondary *Clinacanthus nutans* ethanolic extract cream(Formulation2) is bright greenish homogenous cream (b) while 4 % primary *Clinacanthus nutans* ethanolic extract cream(Formulation1) is pale dull greenish nonhomogenous cream(a).

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