Available online on www.ijppr.com
International Journal of Pharmacognosy and Phytochemical Research 2015; 7(6); 1244-1250

ISSN: 0975-4873

Research Article

Clinacanthus nutans (burm. F.) Lindau: An Useful Medicinal Plant of South-East Asia

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Available Online:30th November, 2015

ABSTRACT

The present paper outlines the traditional use, pharmacological and phytochemical aspects of a very popular medicinal plant *Clinacanthus nutans* (Burm. f.) Lindau (Family-Acanthaceae), primarily used in South East Asian countries. Owing to its antiviral properties, the extracts of this plant is used in many hospitals in Thailand for treating herpes simplex virus and herpes zoster virus. The plant has been included in 'Thai Herbal National Essential Drug List' and promoted for the treatment of herpes simplex, herpes zoster, and skin pruritis in primary health care programmes. A complete review involving the traditional uses, phytochemical constituents and pharmacological properties of *C. nutans* has been made using published papers, databases and books. The plant contains terpenoids, flavonoids, C-glycosyl flavones, sulfur-containing glucosides and glycoglycerolipids which contribute to the pharmacological activities. Pharmacological studies revealed that *C. nutans* possesses antiviral, anticancer, antioxidant, antidiabetic, immunomodulatory, wound healing, anti-inflammatory and analgesic activities. Clinical trials of the creams containing extracts of *C. nutans* in the treatment of *Herpes genitalis* and *Herpes zoster* infection showed successful results. Few isolated compounds are reported to possess anti-herpes simplex activity. Acute and subacute toxicity studies revealed *C. nutans* is non toxic when used at the recommended doses. Further research on this plant is needed to isolate the active components for rationalizing its use in therapy.

Keywords: *Clinacanthus nutans*, traditional uses, phytochemical, pharmacological

INTRODUCTION

The use of medicinal plants in the treatment of diseases and ailments dates back to the earliest recorded human history. In spite of tremendous advances made in the discovery of many synthetic drugs in recent years, medicinal plants have still retained their therapy in the literature. A vast majority of the world population still rely upon plants and their extracts for their primary health care needs[1]. The World Health Organization estimates that around 80% of the world population in developing countries use plant-based products in need[2-4]. Several medicinal plants have shown to possess significant pharmacological activities and offered several novel phytoconstituents for medical research. The ethnomedical information on medicinal plants has a great potential for researchers in providing scientific basis for their properties. The increasing cost of modern medicines paved the way to the rural practitioners to rely upon medicinal plants based on their traditional information. *Clinacanthus nutans* (Burm. f.) Lindau (Acanthaceae), is one of such medicinal plants that have been initially used to treat poisonous snake bites, but later identified to possess potential antiviral properties. The plant is still used in many hospitals in Thailand for treating herpes simplex virus and herpes zoster virus. A through literature survey available from all possible scientific sources revealed sufficient scope to do further research on this plant. This review provides an updated status on the phytochemistry, pharmacology and traditional uses of the plant that will be helpful to the future investigators in rationalizing its use as a potential antiviral candidate to treat herpes infection.

Botany and Taxonomy

The family Acanthaceae consisting of about 250 genera and 2500 species belongs to a taxon of dicotyledonous flowering plants and are mostly tropical herbs, shrubs while some of them are epiphytes. The genus *Clinacanthus* belongs to the family Acanthaceae and comprises of two species *Clinacanthus nutans* (Burm. f.) Lindau and *Clinacanthus siamensis* Bremek[5]. Both the species are found throughout South East Asia[6,7].

C. nutans is a tall, erect herbaceous perennial shrub, growing up to 1 m in height and found distributed throughout the tropical regions including Southeast Asia and China. This plant is primarily indigenous to Thailand, Indonesia and Malaysia[8,9]. It is widely grown in tropical Asia and has been used as important medicinal herb in China, Thailand and Malaysia[10]. In Malaysia, the plant is popularly known as "Sabah snake grass" in English since it is found in Sabah of East Malaysia. The slightly curved stem supporting the leaves resembles the curve of an elephant's trunk and therefore it is also named as Daun

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Belalai Gajah (elephant's trunk) in Bahasa Malaysia language[11]. However, in Thailand the plant is popularly known as Saled Pangpon Tua Mea (saliva of female mongoose)[12] or Phaya-Yor or Phaya Plong Thong[13].

Description

The taxonomic classification and nomenclature of *Clinacanthus nutans* is as follow:

Kingdom: Plantae
Phylum: Magnoliophyta
Class: Magnoliopsida
Order: Lamiales
Family: Acanthaceae
Genus: *Clinacanthus*
Species: *nutans*- Lindau
Scientific name: *Clinacanthus nutans* (Burm. f.) Lindau

The stems are terete, striate and glabrescent. The leaves are simple, opposite, narrowly elliptic-oblong or lanceolate 2.5-13 cm long, and 0.5-1.5 cm wide with apex acute or acuminate; dentate or subentine margins. The leaf base are cuncate, obtuse rounded or truncate; often oblique. Petiole 0.3-2 cm long, sulcate, bifariously pubescent. The flowers are present in dense cymes at the top of branches, covered with 5-alpha cymules, and combined into a large lax, leafy panicle. The ovary is compressed into two cell and each cell having two ovules in each cell. Capsule is oblong, basally contracted into a short, solid stalk 4-seeded. Seeds are 2 mm in diameter[14]. The cylindrical stem turns into yellow when it becomes dry[12].

Traditional uses

Traditionally, only the leaves are used medicinally. The leaves are consumed as raw vegetable or mixed with other juices (apple, sugarcane or green tea) or served as fresh drink or refreshing beverage in Thailand[11]. The decoction of the dried leaves is applied on the affected part to treat herpes infection[15]. The fresh leaves are used for the treatment of envenomation (Naja Naja Siamensis). About 20-25 leaves are chewed for internal consumption and pounded leaves are applied on the site of the snake bite[16, 17]. The infusion or decoction of dried leaves and stem is recommended for hepatitis infection[18, 19]. The fresh leaves are used for relieving of insect bites and skin rashes in primary health care[5, 20, 21]. Recently, this plant has gained high popularity among Malaysians for its high medicinal value in treating cancer[22]. However, its effectiveness has yet to be proven scientifically and more research need to be carried out before it could be taken as an alternative treatment for cancer patients. The method of consuming Sabah snake grass was introduced by blending the leaves of the grass and drink as normal juice. It has created a fast growing market in Malaysia for herbal-based products such as 'Sabah snake grass tonic'.

The leaf extracts are also used for the treatment of varicella-zoster virus (VZV) lesions[7]. It has been used traditionally as antivenom, anti-inflammatory, analgesic, antidiabetic, antirheumatism, antiviral and antioxidant[5, 23]. In traditional medicine, fresh leaves of *C. nutans* has been suggested to be effective in treating poisonous snake and insect bites, burns and allergic reactions[24].

The dried leaves are used to treat fever, diarrhea and dysuria[11, 25]. Recently, there are many products available in the market in the form of herbal tea, capsules, tablets and concentrated plant extracts. However, formulations are less popular in Peninsular Malaysia due to lack of information among common people[11].

Herpes genitalis, also known as genital herpes is a sexually transmitted disease caused by the herpes simplex virus (HSV). *C. nutans* has long been traditionally used in herpes simplex virus (HSV) treatment in Thailand. Clinical trial reports indicated that the fresh leaves were effective in herpes simplex virus and used in primary health care[5, 20, 21]. Reports of clinical trials have further indicated that the topical preparations containing *C. nutans* extracts were effective in the treatment of HSV-2 infections[26]. In Thailand, typical *C. nutans* products are commonly being used as the replacement of topical acyclovir for the treatment of HSV and herpes zoster virus in many hospitals[27].

C. nutans is commonly used in traditional Malaysian medicine for its nourishing and antioxidant properties. Recently, the leaf extracts have been used extensively as primary sources of complementary and alternative healthcare or as economical in-house regimens for cancer patients[11, 25]. Patients have claimed that they have recovered from cancer illness after consuming the leaves over a certain period of time. In Thailand, it has been categorized as principal medicinal plant for primary health care by the Thai Ministry of Public Health (National Drug and Committee, 2006), for treatment of insect and snake bites, skin rashes, herpes simplex virus (HSV) and varicella zoster virus (VZV) lesions[13, 28].

Phytochemistry

Present knowledge on phytochemistry about this species is still limited. However, some researchers have contributed towards isolation of some novel constituents and their activity. Majority of the phytochemicals reported from this plant includes triterpenes, C-glycosyl flavones and sulfur-containing glucosides. Previous studies revealed presence of lupeol and β-sitosterol in the stem[29], betulin, lupeol and β sitosterol in dried rhizomes[30]. Presence of six known C-glycosyl flavones namely, schaftoside, vitexin, isovitexin, orientin, isoorientin and isomollupentin -7-O- β-D-glucoside have been reported in the dried leaves and stem[18]. The butanol soluble fraction of the methanol extract of leaves and stem yielded five sulfur-containing glucosides namely, clinacoside A, clinacoside B, clinacoside C, cycloclinacoside A1 and cycloclinacoside A2 respectively[19]. In 2001, Satakhum et al[31] reported the isolation of two glycoglycerolipids namely, 1,2-Odilinolenoyl-3-O-β-D-galactopyranosyl-glycerol and 1-O-palmitoyl-2-Olinolenoyl-3-O-[α-D-galactopyranosyl-(1" 6')-O-β-D-galacctopyranosyl]-glycerol from the leaves of *C. nutans*. A mixture of nine cerebrosides and a monoacylmonogalatosylglycerol from the ethyl acetate soluble fraction of the ethanol extract of the leaves has been reported (Tuntiwachwuttikul, *et al*., 2004). The structures of the cerebrosides were characterized as 1-*O*-b-D-glucosides of phytosphingosines, which comprised a

common long-chain base, (2*S*, 3*S*, 4*R*, 8*Z*)-2-amino-8(*Z*)-octadecene-1,3,4-triol with nine 2-hydroxy fatty acids of varying chain lengths (C16, C18, C20-26) linked to the amino group. The glycosylglyceride was characterized as (2*S*)-1-*O*-linolenoyl-3-*O*-b-D-galactopyranosylglycerol.

Sakdarat et al[32] reported isolation of eight compounds related to chlorophyll a and chlorophyll b. The compounds were identified as 13^2-hydroxy-(13^2-*S*)-phaeophytin a, 13^2-hydroxy-(13^2-*R*)-phaeophytin a, phaeophorbide a, 13^2-hydroxy-(13^2-*S*)-chlorophyll b, 13^2-hydroxy-(13^2-*R*)-chlorophyll b, 13^2-hydroxy-(13^2-*S*)-phaeophytin b, 13^2-hydroxy-(13^2-*R*)-phaeophytin b and purpurin-18- phytyl ester respectively.

Pharmacology

Clinical trials

The effectiveness of creams containing extracts of *C. nutans* in the treatment of *Herpes genitalis* and *Herpes zoster* infection was examined from a randomised clinical trial consisting of 151 patients. The results demonstrated that *C. nutans* cream is efficacious for the treatment of *H. genitalis*. The findings of the study further revealed the efficacy of the cream in *H. genitalis* with HSV-2 infection. The use of the cream resulted better '3 day-full crusting' and '7 day-complete healing' compared to placebo[15]. As regards to the activity on HSV, it was postulated that *C. nutans* cream may possess synergistic effect when used in combination with acyclovir where the later interferes with the viral DNA polymerase inside the infected cells, while the extracts prevent HSV from entering the host cells. On the other hand, the mode of action on VZV still remains unclear but suggested that the preparations containing *C. nutans* extract could be considered as alternatives in treatment of *H. zoster* infection[33]. Significant effects on *C. nutans* cream against HSV-2 for '3 day-full crusting' and '7 day-complete healing' were also reported in two other studies[27, 34].

In another clinical trial, 5% *C. nutans*, 5% acyclovir (Zovirax®) or placebo creams were applied four times daily for up to 10 days in 77 patients with early genital herpes lesions. According to the study, the virological and haematological testing of the samples from the participants performed on 4, 7 and 14 day of the trial. There was a significant healing of lesions with the patients treated with either *C. nutans* or acyclovir creams when compared to the placebo cream[35, 36].

Another report of randomised clinical trial comprising of 60 participants, suffering from herpes zoster infections also revealed similar outcomes. The participants were advised to apply *C. nutans* or placebo creams five times daily for 7–14 days. More rapid crusting and healing of lesions was observed in the group treated with *C. nutans* cream[36, 37]. Similar results were recorded in a double-blind random clinical trial with 120 herpes zoster patients who applied cream three times per day until lesions were completely healed[38].

Toxicity studies

The acute oral toxicity studies of the methanol extract of the leaves in mice is reported. The study was performed according to OECD 423 guidelines. At the end of the experiment, the results revealed no mortality in the animals of the treatment groups even at the acute exposure of 1.8 g/kg of the extract. Further, the study suggested the oral LD_{50} of the extract is greater than 1.8 g/kg bw in male mice[25].

The sub acute toxicity studies of the methanol extracts from the leaves in young male Sprague Dawley rats was reported by P'ng et al[22]. The toxicity was assessed after a 14 day oral treatment of the methanol extract at 0.3, 0.6 and 0.9 g/kg to different groups of animals. The results revealed no significant changes in the biochemical parameters.

In another study, the methanol extract of the leaves was studied for free radical scavenging activity using DPPH assay. The extract was further studied for its effects on liver and kidney function parameters in normal female Sprague Dawley rats at a single oral dose of 2 g/kg and monitored for 14 days. The blood samples were analysed on

day-15 for biochemical parameters. Results of the study revealed dose-dependent free radical scavenging activity with IC50 value of 1.33 ± 0.001 mg/ml. There were no toxic signs or death in rats with no significant changes in the biochemical parameters[39].

Antiviral activity

The effect of ethyl acetate extract of from the leaves was tested on HSV type 1 strain F (HSV-1F) using plaque reduction assay. The extract completely inhibited the HSV-1F plaque formation with IC_{50} value of 7.6 µg/ml. The study further suggested that the antiviral mode of action of the crude extract may be due to the virucidal activity through inhibition of the viral attachment or the penetration[40].

Direkbusarakom and his co-workers[41] studied the antiviral activity of the ethanol extract of *C. nutans* on yellow-head rhabdovirus (YRV) in black tiger shrimp *(Penaeus monodon).* The results showed that the extract inhibited YRV in *vitro* with a minimum concentration of 1µg/ml suggesting that *C. nutans* extract (1g/kg) mixed with pallet feed could be ideal to control YRV infection in shrimps.

Kunsorn and his co-workers[5] studied the difference between *C. nutans* and *C. siamensis* by assessing characteristics, molecular aspect through genomic DNA extraction and evaluation of their anti-herpes simplex virus (HSV) type 1 and type 2 activities. The antiviral activity of n-hexane, dichloromethane and methanol extracts was performed using plaque reduction assay and their cytotoxicity was studied on Vero cells through MTT assay. The results indicated that the combination of macroscopic, microscopic and biomolecular methods will be helpful for their identification and both the plants were found to possess anti HSV activity against type 1 and type 2 virus.

Antioxidant effects

The ethanol extract of the dried leaves was tested for antioxidant activity through DPPH, FRAP and the intracellular antioxidant activity assays. The protective effect of the extract on rat RBC against 2,2″-azobis(2-amidinopropane) hydrochloride (AAPH) was also studied. The results of the study revealed significant

antioxidant activity of the extract. Further, the extract protected RBCs against AAPH-induced hemolysis with an IC_{50} of 359.38±14.02 mg/ml, suggesting that *C. nutans* may protect oxidative damage to cell components in diseased conditions[42]. In another experiment, the antioxidant activity of different extracts of *C. nutans* was also reported[43].

Yuan and his coworkers[10] studied the ethanol extract of the leaves for antioxidant activity and its protective effects on the integrity of plasmid DNA in *Escherichia coli*. The results revealed better retention of the integrity of super-coiled plasmid DNA under riboflavin photochemical treatment when compared with the extracts of green tea.

Cytotoxicity activity

The aqueous extract of the leaves is reported to possess cytotoxicity effect on vero cell cultures with a CD_{50} of 2828 mcg/ml[44].

The in vitro cytotoxic, antioxidant and antimicrobial activities of the petroleum ether, ethyl acetate and methanol extracts and semi-fractions of *C. nutans* leaves were studied against HeLa and K-562 cell lines by MTT assay and antioxidant activity by DPPH assay. The sub fractions collected from ethyl acetate extract were tested against

Bacillus cereus, Escherichia coli, Salmonella enterica Typhimurium and *Candida albicans*. The results revealed strongest cytotoxic activity of the petroleum ether extract against HeLa and K-562 cells with IC50 of 18.0 and 20.0 µg/mL respectively and highest radical scavenging activity among other extracts. In MIC assay, all the extracts and fractions showed inhibition against all tested microorganisms[9].

Anticancer activity

The antiproliferative effects of chloroform, methanol, and aqueous extracts of the leaves of *C. nutans* were performed on HepG2, IMR32, NCL-H23, SNU-1, Hela, LS-174T, K562, Raji, and IMR32 cancer cells using MTT assay. The chloroform extract exerted the highest antiproliferative effect on all cell lines in a concentration-dependent manner except on IMR-32 cells[43].

Na-Bangchang et al[45] investigated the anticancer and immunostimulating activities of one of the most popular Thai folkloric remedies for treatment of cancer. The remedy consisted of a mixture of parts from five different plants (namely whole part of *Polygala chinensis, Ammania baccifera*, stems and leaves of *C. nutans*, rhizomes of *Canna indica* and *Smilax corbularia*), and five animals (namely scales of *Manis javanica*, spines of *Hystrix brachyuran, Damonia subtrijuga* and sternums of *Trionyx cartilajineus*) respectively. The decoction of the remedy was investigated for the activities. The cytotoxic activity was investigated *in vitro* in KB cells and *in vivo* in mammary cancer-bearing rat (induced by 7, 12 DMBA at a single oral dose of 150 mg/kg body weight) and in cervical cancer xenograft nude mouse models. Acute and subacute toxicity tests were performed following intraperitoneal and/or oral dose administration. The results of the study revealed that the remedy was well tolerated in both acute and subacute toxicity tests and possess significant anticancer activity and activated NK cell activity.

Thongrakard and Tencomnao[46] reported the modulatory effects of ethanol extract of C. nutans on IFN-γ/TNF-α caused HaCaT apoptosis and correlate with the natural phenolic contents. Results revealed that the extract (1 and 100 µg/ml), significantly inhibited the IFN-γ/TNF-α induced HaCaT apoptosis but these findings might not be directly correlated with its natural phenolic content.

Anti-inflammatory and analgesic effects

The possible anti-inflammatory activities of methanol extracts of *Barleria lupulina* and *C. nutans* was studied through two neutrophil-dependent acute inflammatory models (carrageenan-induced paw oedema and ethyl phenylpropiolate-induced ear oedema) in rats. The study was further extended to investigate the effects of the test extracts on human neutrophil responsiveness, in order to elucidate underlying cellular mechanisms. The results revealed significant inhibitory dose-dependent effects in both the models with a significant inhibition of myeloperoxidase (MPO) activity in the inflamed tissues. The anti-inflammatory activity of the extracts is believed to be associated with reduced neutrophil migration[28]. The significant anti-inflammatory and analgesic activities of the butanol extracts of the leaves is also reported[47].

Antidiabetic effects

Wong and coworkers[48] reported the antioxidant and anti-glucosidase activities of six tropical medicinal plants including *C. nutans*. Results of the study revealed that *C. nutans* possesses antioxidant and α-glucosidase inhibitory activity.

Wound healing effects

Roeslan and co-workers[49] performed *in vitro* wound healing assay through migration rate of human gingival fibroblast (HGF) supplemented with hexane and chloroform extracts of *C. nutans*. The results revealed that the extracts did not give any effect on HGF proliferation, but enhanced the migration rate, suggesting the potential therapeutic effect on periodontal disease.

Immunomodulatory effects

The immunomodulatory capabilities of the ethanol extract of the leaves of *C. nutans* were investigated on cell-mediated immune response (CMIR) through its effects on lymphocyte proliferation, natural killer (NK) cell activity and cytokine production of human peripheral blood mononuclear cells. The findings of the study indicated that the lymphocyte proliferation was significantly increased with decrease in activity of NK cells and increase in the level of IL-4. Further, the findings suggested that the effect of the extract on human CMIR may be partially due to the release of IL-4 from peripheral blood mononuclear cells[24]. Another study reported the Interleukin-1-beta (IL-1β) release inhibition of the ethanol extract of the leaves when tested on human blood[50].

Pharmacological activities of isolated metabolites

On the basis of the discovery of antiviral β-galactosyl diglycerides from

C. nutans leaves, 19 monoglycosyl diglycerides were synthesized and examined for inhibitory effect on HSV-1 and HSV-2. The structure–activity relationships study of the synthetic monoglycosyl diglycerides indicated that the fatty acyl moieties were critical for inhibitory action with higher activity displayed as the acyl groups became more olefinic in character. The sugar moiety was also important for anti-HSV action; however, the type of sugar (glucose or galactose) did not affect activity. The stereochemistry at C-2 of the glycerol backbone displayed no significant effect on anti-HSV activity. Among the compounds synthesized, 1,2-*O*-dilinolenoyl-3-*O*-β-D-glucopyranosyl-*sn*-glycerol showed the highest inhibitory activity against HSV-1 and HSV-2 with IC_{50} values of 12.5±0.5 and 18.5±1.5 µg/ml, respectively[51].

Three chlorophyll derivatives (phaeophytins) with structures related to chlorophyll a and chlorophyll b namely 13(2)-hydroxy-(13(2)-R)- phaeophytin b, 13(2)-hydroxy-(13(2)-S)-phaeophytin a and 13(2)-hydroxy-(13(2)-R)-phaeophytin a were isolated from the leaves of *C. nutans* and screened for anti-herpes simplex activity. The compounds exhibited anti-HSV-1F activity at subtoxic concentrations. The compounds inactivate the virus before entry to the host cells by interfering with the virion envelops structure or a mask viral glycoprotein, which involved in host cell adsorption and penetration[13].

Miscellaneous Studies

The changes in the synthesis of secondary metabolites and overall pharmaceutical quality of *C. nutans* in relation to plant age were reported. The activity of the key enzyme chalcone synthase, which governs flavonoid production, was measured at different intervals of time. The results revealed significant differences in total flavonoid and total phenolic contents in 6-month-old buds. There was a significant increase in the production of phenolic acids in the plants when they are 1 to 6 months old. However, after 6 months up to 1 year of age, the production of phenolic acids significantly decreased indicating that early harvesting of the plant up to 6-month-old may provide good quality plant material[52].

The macroscopic and microscopic features of *C. nutans* and *C. siamensis* are reported in order to distinguish the differences between these species. The stomatal number, stomatal index and palisade ratio of the leaves were evaluated and documented[5].

CONCLUSION AND PERSPECTIVES

In Thai folk medicine, the plant has been esteemed as a remedy for snake bite but there is no research evidence to support this claim[29, 53]. However, *C. nutans* has attracted much public interest recently due to its purported high medicinal values for the treatment of cancer, inflammation and various skin problems including herpes simplex virus (HSV) and varicella-zoster virus (VZV) lesions. Clinical trials have reported the successful use of a *C. nutans* preparation (cream) for treatment of genital herpes and varicella-zoster lesions in patients. The plant has been included in 'Thai Herbal National Essential Drug List' and promoted for the treatment of herpes simplex, herpes zoster, and skin pruritis in the primary health care programmes[54]. The plant extracts are reported to possess potential anticancer, antioxidant, antidiabetic, immunomodulatory, wound healing, anti-inflammatory and analgesic activities. A few of the isolated compounds are also reported to possess anti-herpes simplex activity. Toxicity studies has revealed that *C. nutans* is non toxic when used at the recommended doses. The need of the hour is to study the molecular mechanisms underlying the pharmacological activities and further isolate other active components for rationalizing its use in therapy.

REFERENCES

1. Dangarembizi R, Erlwanger KH, Moyo D, Chivandi E. Phytochemistry, Pharmacology and Ethnomedicinal uses of Ficus thonningii (Blume Moraceae): A review. Afr J Trad Compl Alter Med 2013;10(2): 203-212.
2. Salatino A, Faria Salatino ML, Negri G. Traditional uses, Chemistry and Pharmacology of Croton species (Euphorbiaceae). J Braz Chem Soc 2007;18(1): 11-33.
3. Hassan A, Rahman S, Deeba F, Mahmud S. Antimicrobial activity of some plant extracts having hepatoprotective effects. J Med Plants Res 2009;3(1): 20-23.
4. Ziblim IA, Timothy KA, Deo-Anyi EJ. Exploitation and use of medicinal plants, Northern Region, Ghana. J Med Plants Res 2013;7: 1984-1993.
5. Kunsorn P, Ruangrungsi N, Lipipun V, Khanboon A, Rungsihirunrat K. The identities and anti-herpes simplex virus activity of *Clinacanthus nutans* and *Clinacanthus siamensis.* Asian Pac J Trop Biomed 2013;3: 284-290.
6. Smitinand T. Thai Plant Names (Botanical Names-Vernacular Names). Bangkok: Royal Forest Department;1980.
7. Tuntiwachwuttikul P, Pootaeng-on Y, Phansa P, Taylor WC. Cerebrosides and a monoacylmonogalactosylglycerol from *Clinacanthus nutans.* Chem Pharm Bull 2004; 52(1): 27-32.
8. Nesheim I, Dhillion, SS, Stolen KA. What happens to Traditional knowledge and use of natural resources when people migrate? Human Ecol 2006;34: 99-131.
9. Arullappan S, Rajamanickam P, Thevar N, Kodimani CC. In vitro screening of cytotoxic, antimicrobial and antioxidant activities of *Clinacanthus nutans* (Acanthaceae) leaf extracts. Tropical J Pharm Res 2014;13(9): 1455-1461.
10. Yuann JMP, Wang JS, Jian HL, Lin CC, Liang JY. Effects of *Clinacanthus nutans* (Burm.f) Lindau leaf extracts on protection of plasmid DNA from riboflavin photoreaction, MC-Transaction on Biotech 2012;4: p.e5.
11. Shim SY, Aziana I, Khoo BY. Perspective and insight on *Clinacanthus nutans* Lindau in traditional medicine. Int J Int Biol 2013;14(1**):** 7-9.
12. Watson R, Ronald RW, Victor RP. Botanical Medicine in Clinical Practice. 3rd edition. Cambridge: CAB International; 2008.

13. Sakdarat S, Shuyprom A, Pientong C, Ekalaksananan T, Thongchai S. Bioactive constituents from the leaves of *Clinacanthus nutans* Lindau. Bioorg Med Chem 2009;17(5): 1857-1860.
14. http://www.eFloras.org. Flora of China. Vol. 19, p. 442. Available from http://www.eFloras.org
15. Kongkaew C, Chaiyakunpruk N. Efficacy of *Clinacanthus nutans* extracts in patients with herpes infection: systematic reviews and meta-analysis of randomised clinical trials. Compl Ther Med 2011;19: 47-53.
16. Thongharb C, Tejasen P. The effect of Slaed pang porn (*Clinacanthus nutans*) on Thailand cobra venom (Naja Naja Siamensis). Thai J Pharm Sci 1977;2: 1057-1063.
17. Tejasen P, Thongthaap T. The antagonistic effect against cobra envenomization comparison of medicinal plants, corticosteroid and antivenine anti. Chieng Mai Med Bull 1978;17: 159-168.
18. Teshima KI, Kaneko T, Ohtani K, Kasai R, Lhieochaiphant S, Picheansoonthon C, Yamasaki K. C-glycosyl flavones from *Clinacanthus nutans*. Nat Med 1997;51(6): 557-560.
19. Teshima KI, Kaneko T, Ohtani K, Kasai R, Lhieochaiphant S, Picheansoonthon C, Yamasaki. Sulfur-containing glucosides from *Clinacanthus nutans*. Phytochemistry 1998;48(5): 831-835.
20. Wirotesangthong M, Rattanakiat S. Anti-herpes simplex virus Type 2 activities of some Thai medicinal plants. Thai J Pharm Sci 2006; 30: 19-27.
21. Wirotesangthong M, Nagai T, Yamada H, Amnuoypol S, Mungmee C. Effects of Clinacanthus siamensis leaf extract on influenza virus infection. Microbiol Immunol 2009;53: 66-74.
22. P'ng XW, Akowuah GA, Chin JH. Evaluation of the sub-acute oral toxic effect of methanol extract of *Clinacanthus nutans* leaves in rats. J Acute Disease 2013; 29-32.
23. Senny O. Anti-cancer and anti-inflammation herbs Sabah snake grass, [cited 2009 Nov 28]. Available from http://sennyong.blogspot.com/2009/11/anticancer-
24. herbs-and-anti-inflammation.html
25. Sriwanthana B, Chavalittumrong P, Chompuk L. Effect of *Clinacanthus nutans* on Human cell-mediated immune response *in vitro*. Thai J Pharm Sci 1996;20(4): 261-267.
26. P'ng XW, Akowuah GA, Chin JH. Acute oral toxicity study of *Clinacanthus nutans* in mice. Int J Pharm Sci Res 2012;3(11): 4202-4205.
27. Vachirayonstien T, Promkhatkaew D, Bunjob M, Chueyprom A, Chavalittumrong, P, Sawanpanyalert P. Molecular evaluation of extracellular activity of medicinal herb *Clinacanthus nutans* against herpes simplex virus type-2. Nat Prod Res 2010;24(3): 236-245.
28. Sangkitporn S, Polchan K, Thawatsupa P, Bunchob M, Chawalitthumrong P. Treatment of recurrent Genital herpes simplex virus infection with *Clinacanthus nutans* extract. Bull Depart Med Serv 1993;18: 226-231.
29. Wanikiat P, Panthong A, Sujayanon P, Yoosook C, Rossi AG, Reutrakul V. The anti-inflammatory effects and inhibition of nutrophil responsiveness by *Barleria lupulina* and *Clinacanthus nutans* extracts. J Ethnopharmacol 2008;116(2): 234-244.
30. Dampawan P, Huntrakul C, Reutrakul V, Raston CL, White AH. Constituents of *Clinacanthus nutans* and the crystal structure of Lup-20(29)-ene-3-one. J Sci Soc Thailand 1977;3(1): 14-26.
31. Lin J, Li HM, Yu JG. Studies on the chemical constituents of Niu xu hua (*Clinacanthus nutans*). Chung Ts'ao Yao 1983;14(8): 337-340.
32. Satakhun S, Suwanborirux K, Lipipun Y, Suttisri R, Pummangura S. Chemical constitutents of *Clinacanthus nutans* leaves. Thai J Pharm Sci Suppl 2001;25: 38.
33. Sakdarat S, Shuyprom A, Na Ayudhya TD, Waterman PG, Karagianis G. Chemical composition investigation of the *Clinacanthus nutans* Lindau leaves. Thai J Phytopharm 2006;13(2): 13-24.
34. Thawaranantha D, Balachandra K, Jongtrakulsiri S, Chavalittumrong P, Bhumiswasdi J, Janyavasu C. In vitro antiviral activity of *Clinacanthus nutans* on varicella-zoster virus. SirirajHosp Gaz 1992;44: 285-291.
35. Jayavasu C, Dechatiwongse T, Balachandra K. The virucidal activity of *Clinacanthus nutans* Lindau extract against Herpes simplex virus type-2: an *in vitro* study.Bull Dept Med Sci 1992;34: 153-158.
36. Jayavasu C, Balachandra K, Sangkitporn S, Maharungraungrat A, Thavatsupa P, Bunjob M, Chavalittumrong P, Dechatiwongse N, Ayudhaya T, Sittisomwong N. Clinical trial in the treatment of genital herpes patients with *Clinacanthus nutans* extract. Communicable Disease J 1992;18(3)**:** 152–161.
37. Martin KW, Ernst E. Antiviral agents from plants and herbs: a systematic review. Antiviral Therapy 2003;8:77-90.
38. Sangkitporn S, Chaiwat S, Balachandra K, Na-Ayudhaya TD, Bunjob M, Jayavasu C. Treatment of herpes zoster with *Clinacanthus nutans* (bi phaya yaw) extract. J Med Asso Thailand 1995;78(11)**:** 624–627.
39. Charuwichitratana S, Wongrattanapasson N, Timpatanapong P, Bunjob M. Herpes zoster: Treatment with *Clinacanthus nutans* cream. Int J Dermatol 1996;35(9): 665-666.
40. P'ng TW, Wen PX, Han CJ, Akowuah GA. Effect of methanol extract of *Clinacanthus nutans* on serum biochemical parameters in rats. J App Pharm 2014;6: 77-86.
41. Thongchai S, Ekalaksananan T, Pientong C, Aromdee C, Seubsasana S, Sukpol C, Kongyingyoes B. Anti-herpes simplex virus Type 1 activity of crude ethyl acetate extract derived from leaves of *Clinacanthus nutans* Lindau. J Sci Technol 2008;27(4): 318-326.

42. Direkbusarakom S, Ruangpan L, Ezura Y, Yoshimizu M. Protective Efficacy of *Clinacanthus nutans* on Yellow-head disease in Black Tiger Shrimp *(Penaeus monodon).* Fish Pathol 1998;33(4): 401-404.
43. Pannangpetch P, Laupattarakaseem P, Kukongviriyapan V, Kukongviriyapan U, Kongyingyoes B, Aromdee C. Antioxidant activity and protective effect against oxidative hemolysis of *Clinacanthus nutans* (Burm.f) Lindau. Songklanakarin J Sci Technol 2007;29(1): 1-9.
44. Yong YK, Tan JJ, Teh SS, Mah SH, Ee GCL, Chiong HS, Ahmad Z. *Clinacanthus nutans* extracts are antioxidant with antiproliferative effect on cultured human cancer cell lines. Evidence-Based Complementary and Alternative Medicine 2013. (Article ID 462751, 8 pages, http://dx.doi.org/10.1155/2013/462751 Hindawi Publishing Corporation).
45. Yoosook C, Bunyapraphatsara N, Boonyakiat Y, Kantasuk C. Anti-herpes simplex virus activities of crude water extracts of Thai medicinal plants. Phytomedicine 2000; 6(6): 411-419.
46. Na-Bangchang K, Ketsa-ard K, Wiwatwittaya S, Thongprasert S, Vongsakul M, Picha P, Karbwang J. Anticancer activity and immunostimulating effect on NK-cell activity of a well-known Thai folkloric remedy. Int Res J Pharm Pharmacol 2012;2(10): 254-264.
47. Thongrakard V, Tencomnao T. Modulatory effects of Thai medicinal plant extract on proinflammatory cytokines-induced apoptosis in human keratinocyte HaCaT cells. African J Biotech 2010;93(1)**:** 4999-5003.
48. Satayavivad J, Bunyapraphatsara N, Kitisiripornkul S, Tanasomwang W. Analgesic and anti-inflammatory activities of extract of *Clinacanthus nutans* (Burm.f.) Lindau. Thai J Phytopharm 1996;3(1): 7-17.
49. Wong F, Yong A, Ting EP, Khoo S, Ong H, Chai T. Antioxidant, metal chelating, anti-glucosidase activities and phytochemical analysis of selected tropical medicinal plants. Iranian J Pharm Res 2014;13(4): 1409-1415.
50. Roeslan MO, Na Ayudhya TD, Koontongkaew S. Characteristics of *Clinacanthus nutans* extraction from Thailand and Indonesia (Preliminary study). Sci-Health 002 (2012) (Available from www. http://www.tu.ac.th/org/research/GS-NETT2012/GS-NETT-2012%20Web-%20proceedings_files/fullpaper/Sci-Health%20002.pdf)
51. Thamaree S, Rugrungtham K, Ruangrungsi N, Thaworn N, Kemsri W. The inhibitory effects of andrographolide and extracts of some herbal medicines on the production of proinflammatory cytokines by LPS-stimulated human blood cells. Chulalongkorn Med J 2001;45(8): 661-670.
52. Janwitayanuchit W, Suwanborirux K, Patarapanich C, Pummaguram S, Lipinun V, Vilaivan T. Synthesis and anti-herpes simplex viral activity of monoglycosyl diglycerides. Phytochem 2003;64(7):1253-1264.
53. Ghasemzadeh A, Nasiri A, Jaafar HZE, Baghdadi A, Ahmad I. Changes in phytochemical synthesis, chalcone synthase activity and pharmaceutical qualities of Sabah Snake Grass (*Clinacanthus nutans* L.) in relation to plant age. Molecules 2014;19(11): 17632-17648.
54. Levery HA. Toxicity of the venom of the sea-snake, *Laticauda colubrina*, with observations on a Malay 'folk cure'. Toxicon 1969;6(4): 269-276.
55. Oppamayun Y, Suwannakaesawong W, Kaewpaneukransri W, Sripirom P. Safety monitoring of Thai Herbal National Essential Drug Lists. Planta Med 2007;73: 608.