RESEARCH ARTICLE

Treatment of Acne with Topical Patch Containing *Tacca Chantrieri* Extract: an Open-Label Study

Shisanupong Anukanon, Chaiyong Rujjanawate

School of Medicine, Mae Fah Luang University, Chiang Rai, Thailand

Abstract

Tacca chantrieri André is a perennial plant with a cylindrical rhizome. Previous pre-clinical studies revealed that an ethanolic extract of this plant's rhizome exerts many pharmacological actions, including anti-inflammatory and antimicrobial activities, which make it suitable for acne treatment. In this study, a topical patch incorporating 2% w/w of ethanol extract of *Tacca chantrieri* André's rhizomes was evaluated for clinical efficacy and safety, in 30 participants with non-inflammatory or inflammatory acne. An open-label, without a comparator study, was conducted for a period of 6 weeks. The results showed that participants with all grades of Acne Global Severity Scale (AGSS) had a reduction in the severity of their acne. The success rate of treatment was 65.52%. There were no adverse reactions in any of these participants. Our data showed that a topical patch containing an ethanol extract of *Tacca chantrieri* André's rhizome can be a useful treatment of acne.

Keywords: Topical patch, *Tacca chantrieri*, acne, inflammation, clinical trial

Address correspondence and reprint request to: Shisanupong Anukanon, School of Medicine, Mae Fah Luang University, Chiang Rai 57100, Thailand. E-mail address: shisanupong.anu@mfu.ac.th.

การรักษาสิวด้วยแผ่นแปะผิวหนังที่มีสารสกัดจากเนระพูสีไทย (*Tacca Chantrieri*): การศึกษาแบบเปิด

ชิษณุพงษ์ อนุกานนท์, ไชยยง รุจจนเวท

สำนักวิชาแพทยศาสตร์ มหาวิทยาลัยแม่ฟ้าหลวง จังหวัดเชียงราย

บทคัดย่อ

เนระพูสีไทย (*Tacca Chantrieri* André) เป็นไม้ยืนต้นอายุหลายปี มีเหง้ายาวเป็นทรงกระบอก โดยส่วนเหง้าของเนระพูสีไทยมีการศึกษาฤทธิ์ทางเภสัชวิทยา โดยเฉพาะสารสกัดจากเอทานอลซึ่งมีฤทธิ์ต้านการอักเสบและต้านเชื้อจุลชีพได้ จึงมีแนวคิดในการพัฒนาให้อยู่ในรูปแบบแผ่นแปะภายนอกเพื่อใช้การรักษาสิว การศึกษาในครั้งนี้เป็นการนำตำรับแผ่นแปะที่มีสารสกัดเอทานอลจากเนระพูสีไทยความเข้มข้นร้อยละ 2 โดยน้ำหนักของตำรับมาศึกษาประสิทธิภาพในอาสาสมัคร 30 คนที่เป็นสิวทั้งสิวอักเสบ หรือสิวไม่อักเสบ การศึกษาเป็นการวิจัยแบบเปิด ไม่มีกลุ่มควบคุม ระยะเวลาในการทดสอบ 6 สัปดาห์ ผลการศึกษาพบว่าความรุนแรงของสิวลดลงในอาสาสมัครทุกคน โดยพบว่ามีอาสาสมัครที่ประสบความสำเร็จในการรักษาสิวร้อยละ 65.52 และไม่มีรายงานเหตุการณ์ไม่พึงประสงค์จากการใช้แผ่นแปะดังกล่าวตลอดการศึกษา ผลจากการศึกษานี้แสดงให้เห็นว่า แผ่นแปะรักษาสิวที่มีสารสกัดเอทานอลของเหง้าเนระพูสีไทยมีส่วนช่วยในการรักษาสิวได้

คำสำคัญ: แผ่นแปะ, เนระพูสีไทย, สิว, การอักเสบ, การศึกษาในมนุษย์

Introduction

Acne vulgaris is a common skin condition involving obstruction, infection and inflammation of hair follicles and sebaceous glands. It affects all ages of men and women, especially teenagers, who have more acne than any other age group.[1] Principally, acne can be divided into 2 types, inflammatory and non-inflammatory acne. Inflammatory acne in teenagers requires treatment, because of its impact on physical appearance and perceived attractiveness.[2,3] Adolescents with acne vulgaris often use anti-acne products to speed up acne healing[4]. Although acne will eventually heal on its own without any treatment, it takes a long time to heal completely. The urge to scratch or squeeze lesions can lead to scar formation and an uneven skin surface, causing long term significant impacts relating to psychosocial consequences to each individual, including low self-esteem, social withdrawal and anxiety.[2-5]

At the present time there are several anti-acne products with proven effective outcomes, either topical or systemic treatments. Systemic treatment for acne, including oral antimicrobials, vitamin A derivatives and hormonal agents, are prescribed for moderate to severe inflammatory acne.[6] The major limitations in the use of these treatments are systemic side effects, for example, antimicrobial resistance for oral antimicrobials[7,8], teratogenicity for oral vitamin A derivatives[9] and irregular menstruation with hormonal agents.[10]

Topical products are therefore preferred to treat this condition because of less systemic side effects and convenience of use. The active ingredients in the topical preparations are localized within the skin to enhance the local effect, and so are useful in the treatment of non-inflammatory acne or mild to moderate inflammatory acne.[6] On the other hand, the conventional topical products can cause local side effects, including skin irritation and allergy.[11,12] Moreover, long term exposure of topical antimicrobials agents is also limited because of the development of antimicrobial resistance.[8]

Medicinal plants are natural remedies that are increasingly being used as an alternative or add-on treatments in Thailand. This increased market is due to failure of treatment, intolerance to systemic side effects, or denial of conventional therapy.[13] Furthermore, the Thai government is promoting and supporting the use of medicinal plants, as Thailand has natural resources of herbs.[14] *Tacca chantrieri* Andre (Nera phusi thai) is an interesting plant that has the possibility to be effective in the treatment of these acne disorders.

T. chantrieri Andre (family Dioscoreaceae) is an indigenous perennial herb, with a cylindrical rhizome, which can be found in rain forests regions, such as South East Asia, South China and India.[15] A decoction prepared from this plant's rhizome is used for the treatment of muscle aches and gastric pain, and as an antidote for food poisoning. The rhizome extracts of this plant have several pharmacologic effects, both anti-inflammatory[16,17] and antimicrobial effects[17], which are known to be suitable for the treatment of acne in a topical preparation. In previous studies, the topical products, containing this rhizome's extract, were formulated to include gel product.[18] They were developed and have been shown to be effective in the treatment of acne in a concentration of 2% w/w of *T. chantrieri* rhizome's extract. This study examines an interesting way to add market value, by incorporating this extract into

a topical patch and determining its efficacy in the treatment of acne vulgaris of the face of study participants.

Materials and Methods

Plant material and extraction

The rhizomes of *T. chantrieri* were collected from within Chiang Rai province in February 2016. The plant was authenticated by one of the authors (Dr. Rujjanawate) and the voucher specimen (no. 167-F) was deposited at the school of Medicine, Mae Fah Luang University, Thailand. The dried powdered rhizome of this plant was macerated with 95% ethanol overnight and then filtered. The filtrate was evaporated under reduced pressure using a vacuum rotary evaporator. The ethanol extract from the rhizomes of *T. chantrieri* was then lyophilized, this preparation, which from now is referred as "TCE", was used.

Gas chromatography-mass spectrometer (GC-MS) analysis

GC-MS analysis of the TCE was carried out using an Agilent model 7890A gas chromatograph (GC) (Agilent Technologies, CA, USA)[19] fitted with a DB-5MS column (30m × 0.25 mm ID × 0.25 µm film thickness). The GC oven temperature was programmed from 50°C, then held for 5 min, and then raised to 200°C at 10°C/min. Then the temperature was increased to 250°C at 5°C/min and held for 10 min. The injection temperature was 250°C; and the flow rate of carrier gas (helium) was at 1.5 mL/min; 5:1 split ratio. The GC was coupled to a mass selective detector (model 5975C, Agilent Technology, CA, USA). The MS operating parameters were as follows: ion source temperature, 230°C. Identification of the TCE components was performed by compared the relative retention times and mass spectra with those in the W8N08.L database (John Wiley and Sons, Inc., NY, USA).

Preparation of TCE topical patch

The type of topical patch used in our research is a matrix-type or drug-in-adhesive topical patch. The method of preparation of topical patch containing 2% w/w of TCE was performed according to the method reported by Shisanupong and Chaiyong.[20] Briefly, the composition of the matrix layer is a mixture of polyvinyl-pyrrolidone and polyvinyl alcohol (in the ratio of 3:1); propylene glycol; dimethyl sulfoxide and TCE were used as matrix polymer, plasticizer, skin penetration enhancer, and active ingredient respectively (unpublished results). Purified water was used as a vehicle. The solvent from dispersion was evaporated using a hot air oven at 40°C overnight. After drying, the patches were peeled and cut into squares (1.5×1.5 cm^2). The dry patches were packed in laminated foil packaging until used.

Participants

The protocol of this study was approved by the Human Research Ethics Committee of Mae Fah Luang University (document no. 088/2559 dated on June 10, 2016) and each participant signed an informed consent before starting the study. Thirty participants (including both men and women) between 18 to 25 years old, with facial acne, who met all inclusion and exclusion criteria, were enrolled. Inclusion criteria required participants to be healthy and to have non-inflammatory

or inflammatory facial acne. Excluded from the study were those who were receiving systemic medication, including all hormonal contraceptives, within one month prior to the beginning of the study.

Study design, efficacy and safety assessment

The study was designed as an open-label study, without a comparator, to determine the efficacy and safety of the product, over a 6 week period. Prior to the beginning of the study, investigators manually scored the facial acne for each participant by using the Acne Global Severity Scale (AGSS) which is approved by the US Food and Drug Administration.[21] A scale of 0 to 5 was used for grading (0, clear skin; 1, almost clear; 2, some non-inflammatory lesions are present, with few inflammatory lesions; 3, non-inflammatory lesions predominate, with multiple inflammatory lesions; 4, inflammatory lesions are more apparent; and 5, highly inflammatory lesions predominate).

All participants were instructed to attach a topical patch containing TCE on the affect area of the face once daily before bedtime and then to remove the patch in the morning. The topical patches were changed every day for 6 weeks. They were advised to attend, to be re-scored, at week 7 of the study. Front facing and bilateral facial view photographs of each participant were taken at the beginning and the end of the study. The images were taken using a Canon EOS 700D camera, under the same conditions (temperature, lighting and distance) by the investigator. The photographs (at baseline and weeks 7) were assessed by another investigator who was blinded to the "before" and "after" treatment groups. Assessment of the clinical efficacy was performed using the acne score reduction, post-treatment pre-treatment acne lesions were compared.

The investigators also recorded adverse drug reactions caused by this formulation. The participants were interviewed at week 7 of the study for the presence of skin irritation, allergy, and other possible side effects occurring during the study, using Naranjo's algorithm. Only those reactions rated as probably or definitely drug related were included in the report.

Satisfaction test by questionnaire

After finishing of the study, participants were randomly questioned about their product satisfaction. The questionnaire was based on a five-point Likert-type scale, that included responses from 1, strongly disagrees, to 5, strongly agrees, on topical patch use. The questions used were related to the product appearance (colors and smells), patch flexibility in use, comfort in use, residual sticky feeling after use and overall satisfaction.

Statistical analysis

The data was analyzed using SPSS version 16.0 (SPSS v16.0 for Windows, SPSS Inc., Chicago, IL, USA). Wilcoxon signed rank tests were used to compare the differences in median acne grade between pre-treatment and post-treatment. Logistic regression was used to estimate the association between successful treatment of acne (success is defined as "clear", grade 0 or "almost clear", grade 1, at the end of the study[21]) and also independent variables including age, gender and acne score baseline. Statistical significance was set at less than 0.05 of *p*-value.

A sample size of 30 participants was required to detect the difference of AGSS, before and after treatment, to give 80% power with a 2-sided Type I error rate of 0.05.[21]

Results

Gas chromatography-mass spectrometry (GC-MS) analysis

The GC-MS fingerprint of TCE demonstrated that it contains 21 identified compounds (unpublished results). The five most abundant constituents were linoleic acid ethyl ester (16.46%); palmitic acid ethyl ester (14.30%); palmitic acid (5.21%); ethyl linolenate (4.23%) and (Z, Z)-9, 12-octadecadienoic acid (3.85%).

Efficacy and safety assessment

The study included 30 participants (5 men, 25 women) with a mean age of 20.4±1.4 years old. There was a participant withdrawal (3.33%) in this study (due to non-adherence). The remaining 29 participants completed the 6 weeks of the study period. According to the AGSS scoring, there were 12 participants with grade 2, 10 participants with grade 3 and 7 participants with grade 4 acne at baseline (Table 1).

Table 1. Demographic characteristics of participants (n =30).

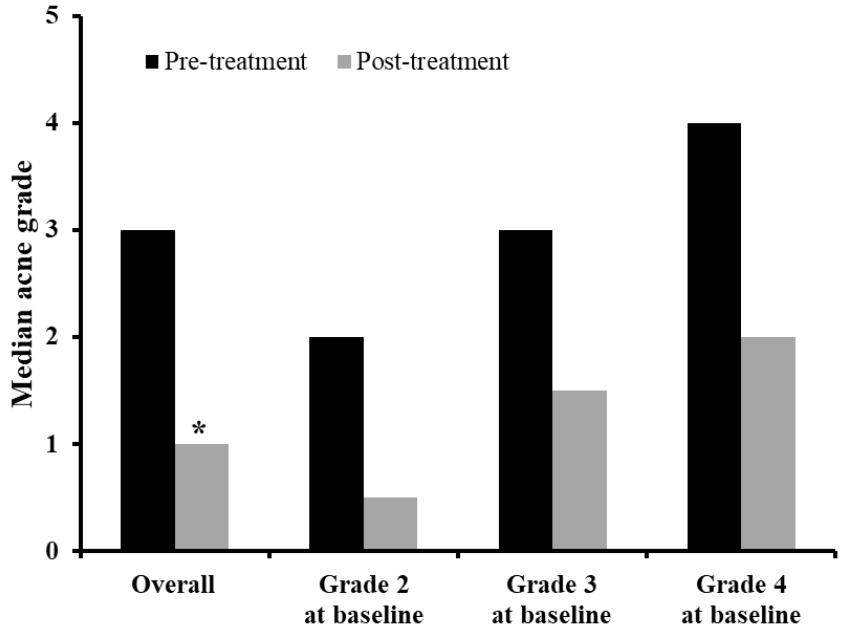
Description	Number (%)
Age, years	
< 19 years	7 (23.3%)
20-22 years	19 (63.3%)
> 23 years	4 (13.3%)
Sex	
Male	5 (16.7%)
Female	25 (83.3%)
Education background	
High school or lower	1 (3.3%)
Diploma	28 (93.3%)
Bachelor degree or higher	1 (3.3%)
Acne score baseline	
Grade 2	12 (40.0%)
Grade 3	10 (33.3%)
Grade 4	8 (26.7%)

After finishing of the study, there were reductions in acne severity in all participants (Table 2 and Figure 1). In grades 2, 3 and 4 acne at baseline, there was an 83.3%, 50.0% and 57.1% reduction in AGSS, respectively. In addition, the number of participants with successful treatment of acne (clear or almost clear of acne) was 19 (65.52%). Most of them had acne score baseline of grade 2 at the outset of the study (Table 2).

Table 2. Clinical response of participants after topical patch treatment stratified by AGSS grading (n = 29).

Acne score baseline	Number of participant 6 week after treatment (% of acne score baseline)			
	Grade 3	**Grade 2**	**Grade 1**	**Grade 0**
Grade 2	-	-	4 (33.3%)	8(66.7%)
Grade 3	-	5 (50.0%)	5 (50.0%)	-
Grade 4*	1 (12.5%)	4 (50.0%)	1 (12.5%)	1 (12.5%)

* There was a participant withdrawal in this study.



Figures 1. Clinical response to acne treatment in all participants (overall, n = 29) and participants stratified by AGSS grading at baseline (grade 2, grade 3 and grade 4). *Significant response to treatment measured using Wilcoxon signed-rank test, $p < 0.05$.

The logistic regression analysis was not statistically significant, comparing the successful treatment of acne and all independent variables, including age, gender and acne score baseline (data not shown). Moreover, there were no significant adverse drug reactions reported related to the use of the TCE topical patches.

Satisfaction test by questionnaire

The results of the questionnaire, relating to the product appearance (colors and smells), patch flexibility in use, comfort in use, residual sticky feeling after use and overall satisfaction are summarized in Table 3. Most participants were very satisfied with the products appearance and its flexibility in use. The average overall satisfaction score was 3.8.

Table 3. Percentage of participant' satisfaction score by the questionnaire (n = 29).

Participants satisfaction	Number of participants (%)				
	Score 1	Score 2	Score 3	Score 4	Score 5
Colors of topical patch	-	1 (3.4%)	2 (6.9%)	18 (62.1%)	8 (27.6%)
Smells of topical patch	-	-	6 (20.7%)	10 (34.5%)	13 (44.8%)
Patch flexibility in use	-	2 (6.9%)	9 (31.0%)	12 (41.4%)	6 (20.7%)
Comfortable in use	-	3 (10.3%)	6 (20.7%)	12 (41.4%)	8 (27.6%)
Residual sticky feeling after used	-	4 (13.8%)	13 (44.8%)	8 (27.6%)	4 (13.8%)
Overall satisfaction	-	1 (3.4%)	7 (24.1%)	18 (62.1%)	3 (10.3%)

* Score; 1, strongly disagree to 5, strongly agree.

Discussion

The results revealed that the topical patch containing 2% w/w of TCE can be a useful treatment of acne, especially of the face. These findings support previous research regarding the clinical efficacy of the use of a topical gel of the same concentration.[18]

In the GC-MS fingerprint of this TCE, there were no major chemical constituents, similar to those reported in previous studies. The chemical composition of *T. chantrieri* included diarylheptanoides[22], diarylheptanoide glycosides[22], spirostan glycosides[23], furostan glycosides[24], pseudofurostan glycosides[24], pregnane glycosides[25], ergostane glycosides[24,26], and withanolide glycosides.[27] It is likely that the high temperatures at GC-MS conditioning may have caused the breakdown of the chemical structures, explaining their absence in the GC-MS analysis.

It is possible that the clinical efficacy of TCE topical patch in the treatment of acne is related to its anti-inflammation and antimicrobial activity. There are several pharmacological studies of the extract from *T. chantrieri*, which suggests that this plant has an important role in anti-inflammatory[16,17], analgesic[16,17], antimicrobial[17] and antitumor[28-31] effects. In term of anti-inflammatory effects, it was reported that TCE works via inhibition of cyclooxygenase-2 (COX-2), a key enzyme responsible for the production of inflammatory and pain mediators, such as prostaglandins.[17] In animal model studies, it also possesses effects, which are mediated via inhibition of prostaglandin biosynthesis.[16]

The pathophysiology of acne incudes inflammation and also microorganism infection. *Propionibacterium acnes,* a gram-positive bacterium, is the most common causative agent of acne vulgaris infection. It contributes to the progression of inflammatory acne by metabolism of triglycerides in the sebaceous glands into free fatty acids, which attract immunocompetent cells to the affected area and contribute to inflammation.[32,33] Also there are bacteria inhabiting the surface of the skin and the pilosebaceous ducts, which also play a pathophysiological role in inflammatory acne. These include *Staphylococcus aureus*[34] and *Staphylococcus epidermidis.*[35] A previous *in vitro* study reported that TCE had antimicrobial activity, the most sensitive gram-positive bacteria strain was *S. aureus.*

A topical patch preparation can protect acne affected skin from the surrounding environment, especially hand touching, and promote the absorption of the TCE active ingredients into the affected skin. It also prevents the acne from drying out and hasten the healing time of acne. Because of the high level of satisfaction and safety after use, this topical patch is a promising product that can be used as an alternative herbal medication in the treatment of acne.

The clinical efficacy of this study confirmed that the TCE topical patch is an effective acne treatment in all of the participants, although there is controversy about the incomplete study design. First, this study did not set exclusion criteria for participants who were using other topical preparations. This may be a confounding factor that could affect our results. Second, this clinical study, without comparators (placebo or active control), was not able to show a reduced lesion resolution time for this formulation. Finally, the follow-up process of this study was limited because of budget limitations, creating difficulties in the ability to adequately follow-up and measure clinical efficacy. We recommend that a double-blind, placebo-controlled study should be conducted to further assess the efficacy of TCE topical patch for acne treatment, with continuous weekly follow-up.

Conclusion

This research work revealed preliminary results that a topical patch containing 2% w/w of ethanol extract from *T.chantrieri* Andre rhizome may cause effective reduction in acne severity after 6 weeks of treatment. It can reduce both non-inflammatory and inflammatory types of acne with safety, and so is a further promising product to add to the market.

Acknowledgements

This study was financially supported by Mae Fah Luang University, Chiang Rai, Thailand. English Language support was provided by Dr. Roger Callaghan, School of Medicine, Mae Fah Luang University.

References

1. Cunliffe WJ, Gould DJ. Prevalence of facial acne in late adolescence and in adults. Br J Dermatol. 1979;1:1109-10.
2. Koo J. The psychosocial impact of acne: patient's perceptions. J Am Acad Dermatol. 1995;32:S26-S30.

3. Hazarika N, Archana M. The psychosocial impact of acne vulgaris. Indian J Dermatol. 2016;61(5):515-20.
4. Rubinow DR, Peck GL, Squillace KM, Gantt GG. Reduced anxiety and depression in cystic acne patients after successful treatment with oral isotretinoin. J Am Acad Dermatol. 1987;17:25-32.
5. Tan JK. Psychosocial impact of acne vulgaris: evaluating the evidence. Skin Therapy Lett. 2004;9:1-3
6. Whitney KM, Ditre CM. Management strategies for acne vulgaris. Clin Cosmet Investig Dermatol. 2011;4:41-53.
7. Adler BL, Kornmehl H, Armstrong AW. Antibiotic resistance in acne treatment. JAMA Dermatol. 2017;153(8):810-1.
8. Swanson JK. Antibiotic resistance of *Propionibacterium acnes* in acne vulgaris. Dermatol Nurs. 2003;15(4):359-62.
9. Bérard A, Azoulay L, Koren G, Blais L, Perreault S, Oraichi D. Isotretinoin, pregnancies, abortions and birth defects: a population-based perspective. Br J Pharm. 2007;63:196-205.
10. Trivedi MK, Shinkai K, Murase JE. A review of hormone-based therapies to treat adult acne vulgaris in women. Int J Womens Dermatol. 2017;3(1):44-52.
11. Dominguez J, Hojyo MT, Celayo JL, Domínguez-Soto L, Teixeira F. Topical isotretinoin vs. topical retinoic acid in the treatment of acne vulgaris. Int J Dermatol. 1998;37:54-5.
12. Sagransky M, Yentzer BA, Feldman SR. Benzoyl peroxide: a review of its current use in the treatment of acne vulgaris. Expert Opin Pharmacother. 2009; 10:2555-62.
13. Gilani AH, Rahman AU. Trends in ethnopharmocology. J Ethnopharmacol. 2005;100(1-2):43-9.
14. Daengprasert S, Sutanthavibul N, Chandrachai A. Development process for Thai traditional medicines. JOMB. 2012;1(1):11-3.
15. Phengklai C. Taccaceae. In: Smitinand T, Larsen K. Flora of Thailand volume six part one. Bangkok: Royal Forest Department; 1993:1-7.
16. Keardrit K, Rujjanawate C, Amornlerdpison D. Analgesic, antipyretic and anti-inflammatory effects of *Tacca chantrieri* Andre. J Med Plants Res. 2010; 4(19):1991-5.
17. Sudtiyanwimon S, Niwatananun W, Yotsawimonwat S, Okonogi S. Phyto-chemical and biological activities of *Tacca chantrieri*. J Min Met Mat S. 2010;20(3):179-83.
18. Rujjanawate C, inventor. Anti-inflammatory gel containing *Tacca chantrieri*'s extract. Thailand, Petty patent number 9613. 2008 Nov 26.
19. Rujjanawate C. Treatment of tinea corporis with *Tacca chantrieri*'s extract. SNRU J Sci Technol. 2016;8(1):115-21.

20. Anukanon S, Rujjanawate C. Formulation and evaluation of topical patch containing *Tacca Chantrieri*'s extract. In: Janvanichyanont U, editor. Proceeding of the 5th National and international academic conference: research to serve society; 2017 May 26; Huachiew Chalermprakiet University. Samutprakarn: Huachiew Chalermprakiet University; 2017. p. HSI46-55.
21. US Food and Drug Administration. Draft guidance for industry acne vulgaris: developing drugs for treatment [Internet]. Rockville, MD: US Department of Health and Human Services; 2005 [updated 2005; cited 2017 Oct 4]. Available from: https://www.fda.gov/ohrms/dockets/98fr/2005d-0340-gdl0001.pdf
22. Yokosuka A, Mimaki Y, Sakagami H, Sashida Y. New diarylheptanoids and diarylheptanoid glucosides from the rhizomes of *Tacca chantrieri* and their cytotoxic activity. J Nat Prod. 2002;65:283-9.
23. Yokosuka A, Mimaki Y, Sashida Y. Spirostanol saponins from the rhizomes of *Tacca chantrieri* and their cytotoxic activity. Phytochemistry. 2002;61:73-8.
24. Yokosuka A, Mimaki Y. New glycosides from the rhizomes of *Tacca chantrieri*. Chem Pharm Bull (Tokyo). 2007;55(2):273-9.
25. Yokosuka A, Mimaki Y, Sashida Y. Steroidal and pregnane glycosides from the rhizomes of *Tacca chantrieri*. J Nat Prod. 2002; 65:1293-8.
26. Yokosuka A, Mimaki Y, Sakuma C, Sashida Y. New glycosides of the campesterol derivative from the rhizomes of *Tacca chantrieri*. Steroids. 2005; 70(4):257-65.
27. Yokosuka A, Mimaki Y, Sashida Y. Chantriolides A and B, two new withanolide glucosides from the rhizomes of *Tacca chantrieri*. J Nat Prod. 2003;66:876-8.
28. Peng J, Jackson EM, Babinski DJ, Risinger AL, Helms G, Frantz DE, et al. Evelynin, a cytotoxic benzoquinone-type retro-dihydrochalcone from *Tacca chantrieri*. J Nat Prod. 2010;73(9):1590-2.
29. Sparg SG, Light ME, Staden J. Biological activities and distribution of plant saponins. J Ethnopharmacol. 2004;94(2-3):219-43.
30. Peng J, Risinger AL, Fest GA, Jackson EM, Helms G, Polin LA. Identification and biological activities of new taccalonolide microtubule stabilizers. J Med Chem. 2011;54(17):6117-24.
31. Risinger AL, Mooberry SL. Taccalonolides: novel microtubule stabilizers with clinical potential. Cancer Lett. 2010;291(1):14-9.
32. Zouboulis CC. Is acne vulgaris a genuine inflammatory disease? Dermatology. 2001;203(4):277-9.
33. Webster GF, McGinley KJ, Leyden JJ. Inhibition of lipase production in *Propionibacterium acnes* by sub minimal inhibitory concentrations of tetracycline and erythromycin. Br J Dermatol. 1981;104:453-7.
34. Fanelli M, Kupperman E, Lautenbach E, Edelstein PH, Margolis DJ. Antibiotics, acne, and *Staphylococcus aureus* colonization. Arch Dermatol. 2011;147(8):917-21.
35. Wang Y, Kuo S, Shu M, Yu J, Huang S, Dai A. *Staphylococcus epidermidis* in the human skin microbiome mediates fermentation to inhibit the growth of *Propionibacterium acnes*: implications of probiotics in acne vulgaris. Appl Microbiol Biotechnol. 2014;98(1):411-24.