Efficacy and safety of *Vernonia cinerea* (L.) Less. and *Boesenbergia rotunda* (L.) Mansf. oral sprays in light cigarette smokers with behavioral counseling for smoking cessation: A preliminary study

Supaporn Pitiporn* Uraiwan Chotigeat** Siriporn Poonsub *Pisit Chaiprasertsud*
Jiraporn Trakarnjunsiri* Wachiraporn Tong-on*** Krittika Wilai*** Naraporn Sanguanjai***
Phanpatchanun Wongprakob*** Kuaina Rongso*** Pakakrong Kwankhao****

วันที่รับบทความ : 01/03/2562
วันแก้ไขบทความ : 29/04/2562
วันตอบรับบทความ : 30/05/2562

Abstract

Vernonia cinerea (L.) Less. (VC) and *Boesenbergia rotunda* (L.) Mansf. (BR) are supposed to be effective for ceasing cigarette smoking, but systematic investigation is lacking. Objective of this study was to primarily assess the efficacy and safety of two oral spray formulations, one with VC extracts alone and another with combined extracts of VC and BR compared to placebo. The randomized, placebo-controlled trial was conducted at the outpatient department of Chao Phya Abhaibhubejhr Hospital, Prachinburi Province, Thailand. Smokers were randomly assigned to three groups to receive oral sprays with the extracts of VC (n=22), VC combined with BR (n=23), or placebo (n=22) together with a counseling program. Descriptive statistics were employed to analyze baseline characteristics while non-parametric inferential statistics were used to compare among the groups.

Results: By the sixth week, the percentages of reduction of cigarette smoking was in the groups with VC spray (n=18), VC combined with BR spray (n=21), and the placebo (n=17) compared to the first week 67.09% vs. 28.19%, 73.90% vs. 35.97%, and 46.65% vs. 26.20%, respectively. The reduction in the intervention groups compared to the placebo group was significantly higher since the second week ($p<0.05$). There were no significant differences in the abstinence status ($p>0.05$) among three groups. The Fagerstrom Test For Nicotine Dependence (FTND) score before and after the study in all groups was significantly decreased. Both active spray formulations were well-tolerated similar to placebo. No serious adverse events were observed. Both oral spray formulations appear to be promising to support smoking cessation. Further studies with larger group of heavy smokers and longer duration of the interventions are needed to provide robust data about the issue.

Keywords: *Vernonia cinerea* (L.) Less., *Boesenbergia rotunda* (L.) Mansf, smoking cessation, oral spray

*Chao Phya Abhaibhubejhr Hospital, Prachinburi Province, Thailand.

**Queen Sirikit National Institute of Child Health, Bangkok, Thailand.

***Research and Development Department, Chao Phya Abhaibhubejhr Hospital Foundation, Prachinburi Province, Thailand.

****Abhaibhubejhr College of Thai Traditional Medicine, Prachinburi Province, Thailand,

Email:pakakrong2@gmail.com

การศึกษาประสิทธิผลและความปลอดภัยเบื้องต้นของสเปรย์หญ้าดอกขาวในการเลิกบุหรี่

สุภาภรณ์ ปิติพร* อุไรวรรณ โชติเกียรติ** ศิริพร พูลทรัพย์* พิสิฎฐ์ ชัยประเสริฐสุด*
จิราพร ตระการจันทร์สิริ* วชิราภรณ์ ทองอ่อน*** กฤติกา วิไล*** นราพร สงวนใจ***
พรรณพัชนันท์ วงษ์ประกอบ*** กูไอนะ รงโซะ*** ผกากรอง ขวัญข้าว****

บทคัดย่อ

หญ้าดอกขาว (*Vernonia cinerea* (L.) Less (VC)) และกระชาย (*Boesenbergia rotunda* (L.) Mansf. (BR) เป็นพืชสมุนไพรที่มีรายงานการใช้ประโยชน์ในผู้ที่สูบบุหรี่ วัตถุประสงค์เพื่อประเมินประสิทธิผลและความปลอดภัยของสเปรย์พ่นในช่องปาก 2 สูตร คือ สูตรที่มีส่วนผสมของสารสกัด VC และสูตรผสมของสารสกัด VC และสารสกัด BR โดยศึกษาเปรียบเทียบกับยาหลอก การศึกษาดำเนินการที่แผนกผู้ป่วยนอก โรงพยาบาลเจ้าพระยาอภัยภูเบศร โดยศึกษาในผู้สูบบุหรี่ที่เข้าร่วมโปรแกรมเลิกบุหรี่ด้วยการปรับเปลี่ยนพฤติกรรม ซึ่งแบ่งเป็น 3 กลุ่มด้วยวิธีสุ่ม ได้แก่ กลุ่มที่ 1 VC (n=22), กลุ่มที่ 2 VC และ BR (n=23) และกลุ่มที่ 3 ยาหลอก (n=22) วิเคราะห์โดยใช้สถิติพรรณนาและอนุมานเพื่อเปรียบเทียบความแตกต่างของกลุ่มตัวอย่าง

ผลการวิจัย: ที่ 6 สัปดาห์ พบร้อยละของจำนวนบุหรี่ที่ลดลง ในกลุ่มที่ VC (n=18), กลุ่มที่ VC และ BR (n=21) และกลุ่มที่ได้รับยาหลอก (n=17) เมื่อเปรียบเทียบกับสัปดาห์แรก เท่ากับ 67.09% และ 28.19%, 73.90% และ 35.97% และ 46.65% และ 26.20% ตามลำดับ อัตราการลดลงของมวนบุหรี่ในทั้งสองกลุ่มมีนัยสำคัญทางสถิติ ($p<0.05$) ตั้งแต่สัปดาห์ที่สอง แต่ไม่มีความแตกต่างอย่างมีนัยสำคัญทางสถิติ ($p>0.05$) กับยาหลอก ผลคะแนน Fagerstrom Test For Nicotine Dependence (FTND) ช่วงก่อนและหลังการศึกษามีค่าลดลงอย่างมีนัยสำคัญทางสถิติในทุกกลุ่มตัวอย่าง สเปรย์ทั้งสามชนิดมีความปลอดภัยดี สเปรย์พ่นในช่องปากที่มีส่วนผสมของสมุนไพรทั้ง 2 สูตรมีความเป็นไปได้ที่จะใช้เสริมการเลิกบุหรี่ ทั้งนี้ควรมีการศึกษาในกลุ่มผู้สูบบุหรี่จำนวนมากขึ้นและขยายช่วงระยะเวลาการศึกษาให้นานขึ้น

คำสำคัญ: หญ้าดอกขาว (*Vernonia cinerea* (L.) Less) กระชาย (*Boesenbergia rotunda* (L.) Mansf. การเลิกบุหรี่ สเปรย์พ่นในช่องปาก

*โรงพยาบาลเจ้าพระยาอภัยภูเบศร จังหวัดปราจีนบุรี
**สถาบันสุขภาพเด็กแห่งชาติมหาราชินี จังหวัดกรุงเทพมหานคร
***ฝ่ายวิจัยและพัฒนา, มูลนิธิโรงพยาบาลเจ้าพระยาอภัยภูเบศร จังหวัดปราจีนบุรี
****วิทยาลัยการแพทย์แผนไทยอภัยภูเบศร จังหวัดปราจีนบุรี, Email: pakakrong2@gmail.com

Introduction

Tobacco smoking is one of the most important risk factors of various diseases including cancer.[1] Smoking cessation is, therefore, a particularly important preventive measure that deserves serious attention from healthcare professionals and smokers alike.

Smoking cessation guidelines normally recommend two steps of treatment, including counseling for behavioral modification and pharmacotherapy. Having a strong intention is the first step towards quitting smoking. The second step, pharmacotherapy, is also significant to alleviate the nicotine withdrawal symptoms, including anxiety, irritability, restlessness, and others.[2] Two major options of the pharmacological approaches are nicotine replacement therapy (NRT) using nicotine patch and nicotine gum, and non-nicotine medications such as varenicline, bupropion, clonidine and nortriptyline.[3] Today, some evidence and traditional wisdom have supported using of medicinal plants as supplements in this purpose, for example *Vernonia cinerea* (L.) Less. (VC),[4] *Acorus calamus* L.,[5] *Eugenia aromaticum* O. Berg and *Astragalus membraneceus* (Fisch.) Bunge.[6] VC tea are included in the National List of Essential Medicine (NLEM) for smoking cessation.[7]

In ancient times, VC has been used to relieve cough, fever, stomachache, flatulence and dysuria.[8-9] It contributes to smoking cessation by making the tongue numb from its high content of nitrate. It also makes cigarettes smelling unpleasantly and disturbs the sense of taste. In addition, VC relieves withdrawal symptoms because itself also contains nicotine[9]; it's effect on smoking cessation has been frequently investigated.[4,9-18]

Boesenbergia rotunda (L.) Mansf. (BR) is a Thai traditional medicine with antiflatulent, diuretic and tonic effects.[19] A study showed that BR can reduce the accumulation of dental plaque and biofilm, which are the causes of caries and halitosis.[20,21] Cigarette smokers may develop halitosis and periodontal problems.[22] BR would help relieving these symptoms and as a result smokers may feel more comfortable. This effect may also enhance the effectiveness of pharmacotherapy.

The above-mentioned properties of VC and BR have made them the leading candidates for alternative pharmacotherapy for smoking cessation, hence the oral spray was developed to improve patients' adherence by combining the extracts of these two medicinal plants. This preliminary study aims to assess the efficacy and safety of new oral spray formulations compared to a placebo in light cigarette smokers.

Methodology

Subjects

Male 'light' smokers aged 18-50 years living in Prachinburi Province and determined to quit smoking were enrolled in this study. 'Light smoking was defined by smoking at least 3

cigarettes daily in the last one month. Exclusion criteria were relevant co-morbidity, such as heart diseas, cancer, hepatic or renal abnormalities, depression, using other tobacco products such as cigars, pipes, baraku, being used to narcotics such as amphetamine, amphetamine derivatives, marijuana, and heroin. In addition we excluded individuals already using alternative anti-smoking medication, such as NRT, varenicline, bupropion, clonidine, nortriptyline or medicinal plants, as well as those not being able to communicate in Thai language, or participating in other studies. All subjects signed informed consent forms before the experiment.

The sample size was estimated to accomplish a power of 80% at the alpha level of 0.05. The average percentage reductions of cigarettes smoked in the treatment group, 59.52% and the control group, 14.04% were used for effect size in the calculation.[14] The calculated n was 17 for each group. To account for the possible dropout rate of 20%, however, the sample size was adjusted to 21 for each group.

The oral Sprays

The oral sprays of VC, VC extract combined with BR extract and the placebo were manufactured by Chao Phya Abhaibhubejhr Hospital Foundation. In brief, the active ingredient of the VC oral spray was extracted from 20 grams of the dried crude plants. For the oral spray of VC combined with BR, the concentrated extract of VC was mixed with the volatile oil of BR. Quality control of raw materials and finished products were done according to Thai Herbal Pharmacopeia.

Study Design

The randomized, placebo-controlled trial was conducted at the Outpatient Department of Chao Phya Abhaibhubejhr Hospital, Prachinburi Province, Thailand.

Data Analysis

Descriptive Statistics were used to illustrate the baseline characteristics and the smoking history. Discrete data were presented as numbers and percentages. Continuous data were presented as mean and standard deviation (mean ± SD). Nonparametric inferential statics were employed for the data with abnormal distribution. The analysis was conducted using SPSS software 22.0. The statistical differences were significant at $p < 0.05$.

Results

Baseline characteristics and smoking history

Sixty-seven smokers participated in this study. Twenty-two subjects were randomly assigned to receive the VC oral spray, 23 for the combined VC and BR oral spray, and 22 for the placebo. Eleven subjects dropped out of the study: 4 subjects, 2 subjects, and 5 subjects form the above-mentioned groups, respectively so that the final numbers of participants for analysis were 18, 21, and 17, respectively. Baseline characteristics and smoking history of the participants are shown in Table 1. There were no

statistically significant differences among groups of the participants for any characteristic. Most subjects were single and either senior high school or vocational school graduates. None had underlying diseases as mentioned in method.

Table 1 Baseline characteristics and smoking history of the participants

Characteristics	VC oral spray n = 18	combined VC and BR oral spray n = 21	placebo oral spray n = 17	p
Age (years)	29.89 ± 6.38	33.19 ± 7.26	32.59 ± 5.79	0.270
Marital status				
Single	7(38.89)	7 (33.33)	6 (35.30)	0.940
Married	11(61.11)	14 (66.67)	11 (64.70)	
Education levels				
Junior high school	5 (27.78)	2 (9.52)	6 (35.30)	0.153*
Above Junior high school	13 (72.22)	19 (90.48)	11 (64.70)	
Underlying diseases				
No underlying diseases	18 (100)	21 (100)	17 (100)	
Average age at 1st time smoking, years	19.06 ±4.12	17.95±5.41	19.59±2.89	0.321
Smoking duration, years	10.83 ± 6.75	15.24 ± 7.68	13.00 ± 5.61	0.141
Cigarettes smoked/day				
<10 cigarettes/day	13(72.22)	11(52.38)	12(70.59)	
10-20 cigarettes/day	4(22.22)	8(38.10)	5(29.41)	0.276*
>20 cigarettes/day	1(5.56)	2(9.52)	0(0.00)	
Attempt to quit smoking, times	1.72±1.13	2.05±1.66	1.82±1.01	0.734
FTND score	2.11 ± 1.41	3.67 ± 2.58	2.88 ± 2.69	0.120

***** p-value from Fisher's Exact test

Age, 1st time smoking age, smoking duration, attempt to quit smoking and FTND score are expressed as mean ± SD while other characteristics are expressed as number (%).

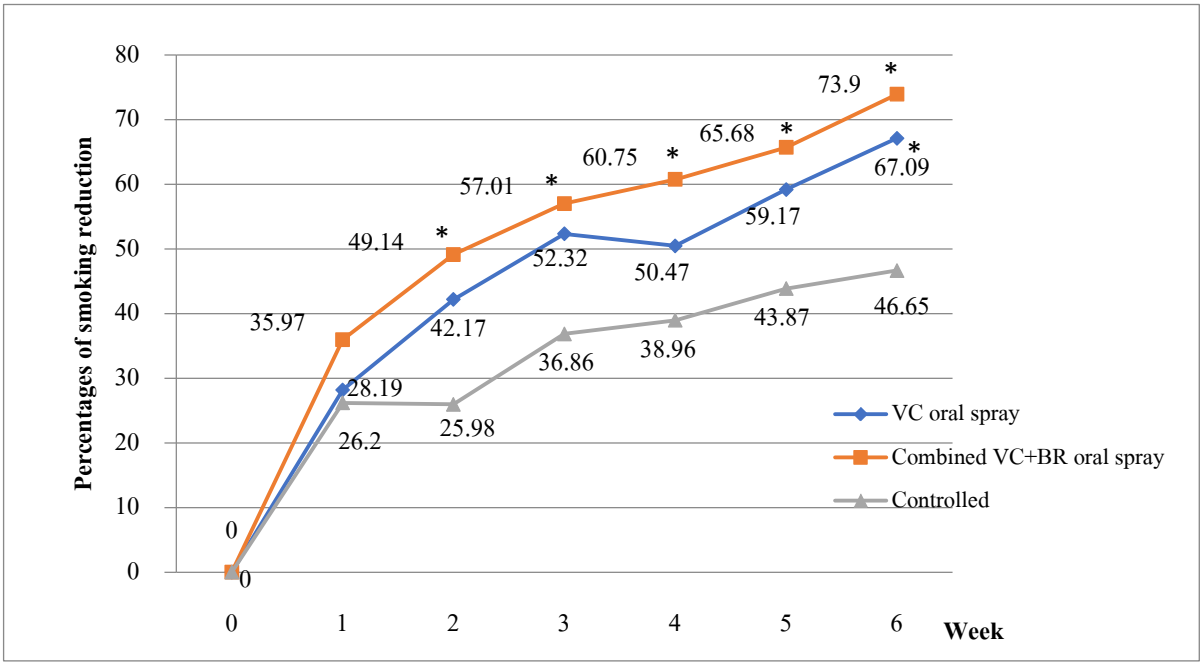
Fagerstrom Test for Nicotine Dependence (FTND) score is a standard instrument for assessing the intensity of physical addiction to nicotine. The test was designed to provide an

ordinal measure of nicotine dependence related to cigarette smoking. The FTND scoring evaluation: ≤ 4 is low dependence on nicotine, 5 is moderately dependence on nicotine and ≥ 6 is high dependence on nicotine.[23]

Smoking history of the groups VC oral spray, the combined VC and BR oral spray did not differ significantly including the average age for the first smoking with 19.06, 17.95 and 19.59 years, respectively. The smoking durations were 10.83, 15.24 and 13.00 years, respectively. Most subjects smoked less than 10 cigarettes daily. The number of attempts to quit smoking were 1.72 times, 2.05 times, 1.82 times, respectively. Most subjects had low level of nicotine dependence.

Efficacy of oral sprays

The percentages of reduction in smoking for each week are shown in Figure 1. In the first week, the percentages of reduction in smoking did not differ significantly. However, there were significant differences between those for week 2-6. As for the percentages of reduction in the sixth week were 67.09, 73.9 and 46.65, respectively, both formulas of oral spray could reduce the numbers of cigarettes smoked.



* = significant at p < .05

Figure 1 Percentages of smoking reduction during the six-week period

At the end of Week 6, when 56 subjects were regrouped into the VC group (n = 39) and the placebo (n = 17). Five subjects (12.82%) in the former and 2 subjects (11.76%) in the latter were found to have successfully quit smoking (number of cigarette equal to zero at 6th week). These percentages as shown in Table 2, however, there was not statistical difference.

Table 2 Subjects' smoking status at the end of the sixth week

Smoking status	**VC oral sprays** **n = 39**	**Placebo oral spray** **n = 17**	**p**
Abstinence	5 (12.82)	2 (11.76)	0.152
No abstinence	34 (87.18)	15 (88.24)	

Values are expressed as number (%).

FTND scores before and after the studied period are shown in Table 3. After participating in the study, all subjects' nicotine dependence significantly decreased.

Table 3 FTND scores before and after participating in the study

	VC oral spray **n = 18**	**Combined VC *and* BR oral spray n = 21**	**Placebo oral spray** **n = 17**
Before	2.11 ± 1.41	3.67 ± 2.58	2.88 ± 2.69
After	0.78 ± 0.94	1.57 ± 1.63	1.18 ± 1.70
p-value	0.002	0.001	0.002

FTND scoring evaluation : $\leq$ 4 = low dependence on nicotine, 5 = moderately dependence on nicotine, $\geq$ 6 = Highly dependence on nicotine

Safety of oral sprays

The adverse events noticed in each group of the participants are shown in Table 4. The number of adverse events did not significantly differ among the three groups. No serious adverse events occurred in any groups.

Table 4 Safety of oral sprays reported by participants

Adverse events	VC oral spray n = 18	combined VC *and* BR oral spray n = 21	placebo oral spray n = 17	p
Dry mouth	12 (66.67)	10 (47.62)	11 (64.71)	0.409
Tongue numbness and inability to taste food	10 (55.56)	8 (38.10)	7 (41.18)	0.518
Gastrointestinal disturbances	2 (11.11)	4 (19.05)	3 (17.65)	0.780
Nausea and vomiting	1 (5.56)	1 (4.76)	0 (0.00)	0.631
Dizziness	2 (11.11)	0 (0.00)	0 (0.00)	0.112
Sore throat	0 (0.00)	0 (0.00)	1 (5.88)	0.311
Aphthous ulcer	1 (11.11)	0 (0.00)	0 (0.00)	0.341
Having sputum	1 (11.11)	1 (4.76)	1 (5.88)	0.987

Values are expressed as number (%).

Discussion

The major findings of this randomized, placebo-controlled trial disclosed the significant efficacy of the oral sprays of VC extract and VC extract combined with BR extract on reduction in the number of cigarettes smoked more than a placebo. This results are in accordance with findings of several studies.[4,10-16]

As compared to previous researches, it seems that VC oral sprays were very effective as the daily dose of VC consumed by volunteers was low (data not shown). For example, this research needed average dose of VC between 0.31-0.38 g/day. Whereas herbal tea[4,14,17-18] and capsule[15] needed dose of VC 4-10.71 g/day and 3 g/day respectively to reach the goal.

The most common adverse events found in all groups were dry mouth, tongue numbness, decreased ability to taste foods, and gastrointestinal disturbances. There were no significant differences among the groups. This is consistent with the findings of another study, which showed no serious adverse events[4,13,15].

As for the satisfaction with the oral sprays (data not shown), the spray of VC extract combined with BR extract was found to be the most efficient product, probably due to the taste and the fact that BR could reduce plaque and biofilm accumulation, which is the causes of caries and halitosis.[19-20]

The abstinence status, however, did not significantly differ from placebo. This may result from the small number of subjects and the

short duration of the study. An oral spray, nevertheless, is more convenient to use because of its small size and readyness to use.

For further study, objective data such as urine nicotine or breath carbon monoxide should be assessed to crosscheck with subjective data. Moreover, heavy smokers should be included in future studies to find out effects on cigarette abstinence.

Conclusion and suggestion

The oral sprays of VC extract and *V. cinerea* extract combined with *B. rotunda* extract could reduce the number of cigarettes smoked, but did not significantly increase smoking cessation rates. Further studies with more subjects with heavy smoking behavior and for a longer duration are needed.

References

1. Bonnie RJ, Stratton K, Kwan LY, editors. Committee on the public health implications of raising the minimum age for purchasing tobacco products; board on population health and public health practice. Institute of Medicine. Washington (DC): National Academies Press (US); 2015.
2. Ward MM, Swan GE, Jack LM. Self-reported abstinence effects in the first month after smoking cessation. Addict Behav. 2001;26(3):311-27.
3. Aubin HJ, Luquiens A, Brelin I. Pharmacotherapy for smoking cessation: Pharmacological principles and clinical practice. Br J Clin Pharmacol. 2013;77(2):324-36.
4. Wongwiwatthananukit S, Benjanakaskul P, Songsak T, Suwanamajo S, Verachai V. Efficacy of Vernonia cinerea for smoking cessation. Journal of Health Research. 2009;23(1):31-6.
5. Nisaa ZU, Zafar A, Zafar F. Efficacy of a smoking cessation intervention using the natural agents. Int J Collab Res Intern Med Public Health. 2018;10(2):809-15.
6. Lee HJ, Lee JH. Effects of medicinal herb tea on the smoking cessation and reducing smoking withdrawal symptoms. Am J Chin Med. 2005;33(1):127-38.
7. National Drug System Development Committee. National list of essential medicine. Bangkok: Agricultural Cooperation Community Thailand; 2018. (in Thai).
8. Bunyapraphatsara N. Medicinal plants indigenous to Thailand**.** 5th ed. Bangkok: Department of Pharmacognosy, Faculty of Pharmacy, Mahidol University; 2005. (in Thai).
9. Lhieochaiphant S. A Phytochemical study of Vernonia cinera Less [Thesis]. Chiang Mai: Chiang Mai University; 1985. (in Thai).
10. Ketsuwan N, Leelarunggrayub J, Kothan S, Singhatong S. Antioxidant compounds and activities of the stem, flower, and leaf extracts of the anti-smoking Thai medicinal plant: Vernonia cinerea less. Drug Des Devel Ther. 2017;11:383–91.

11. Leelarungrayub D, Pratanaphon S, Pothongsunun P, Sriboonreung T, Yankai A, Bloomer RJ. Vernonia cinerea Less. Supplementation and strenuous exercise reduce smoking rate: Relation to oxidative stress status and beta-endorphin release in active smokers. J Int Soc Sports Nutr. 2010;7:21.
12. Jitpukdeebodintra S, Jangwang A. Coffee for smoking cessation. J Food Agric Environ. 2009;7(34):130-3.
13. Kitphaiboontawee S. Efficacy of Vernonia cinerea lozenge as an adjunct to pharmacist counseling on smoking abstinence rate: A randomized controlled trial [Thesis]. Songkhla: Prince of Songkla University; 2012. (in Thai).
14. Chaisawad S, Makanuntachote M. A study of smoking cessation therapy model using Vernonia cinerea Less and natural cure at Theng hospital, Chiangrai, Thailand. Nonthaburi: Office of The Alcohol Beverage and Tobacco Committee, Department of Disease Control; 1996. (in Thai).
15. Traipopsakul W, Sittiphun C. Efficacy of Vernonia cinerea for smoking cessation in Thai active smokers. Bangkok: Tobacco Control Research and Knowledge Management Center and Thai Health Promotion Foundation; 2011. (in Thai).
16. Yamashita HSS, inventor; Müller-Boré Partner Patentanwälte, assignee. Filter for cigarette, and cigarette. European patent EP 1491103A1. 2004 Dec 29.
17. Duangchorn C, Somwang U, Thanakhwang K, Kwanchainon C, Nutda W, Rodklang N, et al. Comparison on the effectiveness of Vernonia cinerea Less and placebo for smoking cessation. Suphan Buri: U-thong Hospital; 1994. (in Thai).
18. Boonyaratphan M, Chuencheam P, Somwatsan S. The effectiveness of Vernonia on smoking cessation compared to Chinese tea. Chonburi Hospital Journal. 2009;34(3):133-40.
19. Eng-Chong T, Yean-Kee L, Chin-Fei C, Choon-Han H, Sher-Ming W, Li-Ping CT, et al. Boesenbergia rotunda: From ethnomedicine to drug discovery. Evid Based Complement Alternat Med. 2012:473637. doi: 10.1155 /2012/473637.
20. Limsuwan S, Voravuthikunchai SP. Boesenbergia pandurata (Roxb.) Schltr., Eleutherine americana Merr. and Rhodomyrtus tomentosa (Aiton) Hassk. as antibiofilm producing and antiquorum sensing in Streptococcus pyogenes. FEMS Immunol Med Microbiol. 2008;53(3):429-36.
21. Taweechaisupapong S, Singhara S, Lertsatitthanakorn P, Khunkitti W. Antimicrobial effects of Boesengergia pandurata and Piper sarmentosum leaf extracts on planktonic cells and biofilm of oral pathogens.Pak J Pharm Sci. 2010;23 (2):224-31.
22. Rech RS, Santos KW, Maahs MA, Vidor

DC. Masticatory changes as a result of oral disorder in smokers. Int Arch Otorhinolaryngol. 2014;18(4):369-75.

23. Heatherton TF, Kozlowski LT, Frecker RC, Fagerstrom KO. The Fagerstrom Test for nicotine dependence: A revision of the Fagerstrom Tolerance Questionnaire. Br J Addict. 1991;86(9):1119-27.