

# The Efficacy and Side Effects of Oral *Centella asiatica* extract for Wound Healing Promotion in Diabetic Wound Patients

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**Objective:** To study clinical efficacy and side effects of the oral *Centella asiatica* extract capsule in the diabetic wound healing. And to study the side effects of *Centella asiatica* extract capsule.

**Material and Method:** This prospective randomized control study enrolled two hundred diabetic patients in the department of Surgery, Thammasat University Hospital. The exclusion criterion were low immune patients, oral steroid intake, age more than 80 year and less than 18 years, serum albumin less than 3.0 gm/dl, uncorrected peripheral arterial diseased patients, and uncontrolled infective wound. The termination criterion were patient refusal, wound infection, delayed primary sutured wound, secondary healing wound. The patients were divided into two groups randomly, group A was *Centella asiatica* extract capsule group and group B was placebo group. *Centella asiatica* extract capsule and placebo were prescribed in each group under the random sheet. The administration was 2 capsules after meal, three times a day (50 mg of extracted asiaticoside / capsule in group A). The general symptoms, wound characteristics, wound size and depth were examined at day 7, day 14 and day 21 by the same investigator. The demographic data of the sample were analyzed by student t test and comparative wound characteristics were analyzed by Pearson Chi-Square test.

**Results:** Wound contraction in the study group is better than placebo group but granulation tissue forming is better in the placebo group. No serious adverse reaction in both groups.

**Conclusion:** *Centella asiatica* extract capsule is the Thai herb preparation capsule that effective in the wound healing promotion and also suppress the scar in diabetic wound patients. There was no demonstrable serious side effect of the *Centella asiatica* extract capsule group. *Centella asiatica* extract capsule can shorten the course of diabetic wound and can be prescribed to the diabetic patients safely.

**Keywords:** *Centella asiatica*, Wound healing, Diabetic wound

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The crucial mechanisms involving wound healing process are angiogenesis, collagen formation, epithelialization and wound contraction. There are several factors promote wound healing which include physical factors, chemical factors and also pharmacological factors. Some previous studies confirmed the pharmacologic action of the *centella asiatica* in the wound healing process. The active ingredients of *centella asiatica* are triterpenoid compounds that is asiatic acid, madecassic acid, asiaticoside and

madecassodie which stimulate collagen synthesis. So the possible pharmacologic action of the *centella* is wound healing promotion. Both Alcohol *centella* cream and oral form increase wound healing in mice by stimulate DNA and collagen synthesis and stimulate maturation and collagen crosslinking<sup>(1)</sup>. There was the study showed the increase of the enzymatic and non enzymatic antioxidants in new tissue of the mice<sup>(2)</sup>. There were studies in diabetic guinea pig by applying 0.4% asiaticoside cream in the punch wounds. The study showed the increase of hydroxyproline and collagen synthesis<sup>(1)</sup>. There were also study in gene expression revealed that triterpenoid compounds could increase angiogenesis and remodeling of extracellular matrix including several growth factor genes<sup>(3,4)</sup>.

There were several clinical studies showed the efficacy of wound healing by triterpenoid

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compounds<sup>(5-7)</sup>. However, all of the studies are the centella cream or ointments apply locally. There has not been any study of the oral form of *Centella asiatica* extract in human but only in diabetic pig<sup>(1)</sup> with no demonstrable of serious adverse effects in that particular study<sup>(8)</sup>. This protocol is the clinical study of the wound healing of diabetic foot ulcer patients who taking centlla extract orally.

### Material and Method

The protocol was approved by Thammasat University Ethic Committee on January 25<sup>th</sup> 2008, certificate of approval number MTU-E1-047/50. Two hundred of diabetic foot ulcer patients were enrolled into the study. The inclusion criteria were the entire diabetic patients who had got chronic wound in the department of surgery Faculty of Medicine Thammasat University who needed secondary healing starting from June 2008 to September 2009. The exclusion criteria were; low immune patient, oral steroid intake, age more than 80 year and less than 18 year, serum albumin less than 3.0 gm/dl, uncorrected peripheral arterial diseased patients, and uncontrolled infective wound. The termination criteria were patient refusal, wound infection, delayed primary sutured wound, secondary healing wound. The patients were divided to be two groups by random method, group A was *Centella asiatica* extract capsule group and group B was placebo group. After the inclusion criterion was met, wound size and depth was examined, wound characteristic was recorded. Asiatic capsules and placebos were prescribed in each group under the random sheet. The administration was 2 capsules after meal three times a day (50 mg of extracted asiaticoside/capsule in group A). The WHO recommendation dose of centella oral dose is 0.33-0.68 g three times daily or equal to freeze dry lyophilized extract capsule 100 mg three times daily<sup>(10)</sup>. Preparation of the *Centella asiatica* extract capsule in this study was 50 mg freeze dry lyophilized extract capsule. We prescribed 2 capsules per time, three times a day. The *Centella asiatica* extract capsule was prepared by the faculty of Pharmacy Khonkaen University. Stability test of the capsule was made by the faculty of Pharmacy Khonkaen University during April and June 2008. We allowed the diabetic and co morbid medical illness control under the standard treatment. The general symptoms, wound characteristic, wound size and depth were examined at day 7, day 14 and day 21 by the same investigator. Wound contraction was detected by the decrease of the volume of the wound; mild contraction means the volume

decreasing is not more than 10 percent of the original volume, moderate contraction means the volume decreasing more than 10 percent to 50 percent of the original volume and good contraction means volume decreasing more than 50 percent of the original volume. Wound granulation tissue forming was detected by the decrease of wound depth; mild granulation tissue means increase of granulation tissue not more than 10% of the wound area, moderate granulation tissue means increase of granulation tissue 10 to 50% of the wound area and marked granulation tissue means increase of granulation tissue more than 50% of the wound area. The demographic data of the sample were analyzed by student t-test and comparative wound characteristics were analyzed by Pearson Chi-square tests.

### Results

Two hundred diabetic wound patients were enrolled into the study. There were 20 cases dropped out from the study. There were 10 cases were terminated before the end of the protocol due to termination criteria were met. One hundred and seventy cases were analyzed. All of the patients were divided into group A (n = 84) and group B (n = 86) , the mean age is 58.59 years in both group. There were no difference in sample characteristics as shown in Table 1.

There were significance changes of wound contraction between placebo and study group. The study group trend to be good contraction earlier than placebo group as shown in Table 2 and there were more wound granulation tissue forming in the placebo group than the study group as shown in Table 3.

### Discussion

There was no significant difference of the demographic data between two group.

**Table 1.** Demographic data

	Group A (n = 84)	Group B (n = 86)	p-value#
Hematocrit (%)	34.51	34.58	0.92
Blood sugar (mg/dl)	109.5	111.6	0.72
Serum albumin	3.6	3.36	0.31
BUN/creatinine	15/1.0	14/1.0	0.94
Age	58.59	59.6	0.74

# t-test for equality of mean Sig. (2-tailed) p < 0.05 at 95% confidence interval

**Table 2.** Comparing of wound contraction

		Group A n = 84	Group B n = 86	Total	Pearson Chi-square	p-value
Day 7	No (%)	13 (15.47)	39 (45.35)	52 (30.59)	19.713	0.001
	Mild (%)	18 (21.42)	13 (36.05)	31 (18.24)		
	Moderate (%)	29 (34.52)	23 (26.74)	52 (30.59)		
	Good (%)	24 (28.57)	11 (12.79)	35 (20.58)		
Day 14	No (%)	5 (5.95)	23 (26.74)	28 (16.74)	25.765	< 0.001
	Mild (%)	14 (16.67)	28 (32.56)	42 (24.71)		
	Moderate (%)	33 (39.29)	19 (22.10)	52 (30.59)		
	Good (%)	32 (38.10)	16 (18.60)	48 (28.24)		
Day 21	No (%)	4 (4.76)	19 (22.09)	23 (13.53)	23.038	< 0.001
	Mild (%)	16 (19.05)	23 (26.74)	39 (22.94)		
	Moderate (%)	16 (19.05)	60 (6.98)	22 (12.94)		
	Good (%)	48 (57.14)	38 (44.19)	86 (50.59)		

**Table 3.** Comparing of wound granulation tissue Forming

		Group A n = 84	Group B n = 86	Total	Pearson Chi-square	p-value
Day 7	No (%)	36 (42.86)	14 (16.28)	50 (29.41)	36.886	< 0.001
	Mild (%)	32 (38.09)	18 (20.93)	50 (29.41)		
	Moderate (%)	11 (13.10)	35 (40.70)	46 (27.06)		
	Good (%)	5 (5.95)	19 (22.09)	24 (14.12)		
Day 14	No (%)	12 (14.29)	3 (3.49)	15 (8.82)	68.970	< 0.001
	Mild (%)	51 (60.71)	10 (11.63)	61 (35.880)		
	Moderate (%)	10 (11.90)	44 (51.16)	54 (31.76)		
	Good (%)	11 (12.79)	29 (33.72)	40 (23.53)		
Day 21	No (%)	8 (9.52)	3 (3.49)	11 (6.47)	34.631	< 0.001
	Mild (%)	26 (30.95)	7 (8.14)	33 (19.41)		
	Moderate (%)	7 (8.33)	28 (32.56)	35 (20.59)		
	Good (%)	42 (50.00)	38 (44.19)	80 (47.06)		

Group A is the *Centella asiatica* extract capsule group and Group B is placebo group. However, there were the differences of the wound size and depth between two group originally, so we observed the changing of volume (width by length by depth) and area of the wound. Wound contraction was detected by the decrease of the volume of the wound; mild contraction means the volume decreasing is not more than 10 percent of the original volume, moderate contraction means the volume decreasing more than 10 percent to 50 percent of the original volume and good contraction means volume decreasing more than 50 percent of the original volume. Wound granulation tissue forming was detected by the decrease of wound

depth; mild granulation tissue means increase of granulation tissue not more than 10% of the wound area, moderate granulation tissue means increase of granulation tissue 10 to 50% of the wound area and marked granulation tissue means increase of granulation tissue more than 50% of the wound area as in the results.

The study reveals that *Centella asiatica* extract capsule promotes wound healing process due to rapid wound contraction compare with the placebo group. The mechanism of actions are 1) stimulate human collagen I synthesis<sup>(11)</sup>. This collagen protein plays the major role in the wound healing process. There was the study in the monolayer culture of fibroblastic cell

showed centella extract (asiaticoside) stimulate collagen synthesis, promote cicatricial action of the wound. Centella asiatica extract capsule can also shorten wound healing time and increase tensile strength of the mice wound<sup>(9,10)</sup>. 2) increase remodeling of collagen matrix. There was the study in the wound chamber model in guinea pig revealed titrated centella extract increase DNA, total protein, collagen and peptidic hydroxyproline synthesis. 3) stimulate glycosaminoglycan synthesis<sup>(12)</sup>.

This study is also indicated that *Centella asiatica* extract capsule inhibits tissue overgrowth due to the significant change of granulation tissue forming between placebo group and study group. *Centella asiatica* extract capsule reduce scar forming and keloid formation as the result above. The possible mechanisms are increase collagen and acidic mucopolysaccharides and inhibit inflammatory process of hypertrophic scars and keloids<sup>(9)</sup>.

There were no systemic side effect or complications reported in this study and there was no significant difference of wound infection between two groups.

In conclusion the *Centella asiatica* extract capsule is the Thai herb preparation capsule that effective in the wound healing promotion and also suppress the scar in diabetic wound patients. The mechanism of action is by collagen protein stimulation collagen matrix remodeling and inhibits granulation tissue overgrowth of the wound. There was no demonstrable serious side effect of the *Centella asiatica* extract capsule. *Centella asiatica* extract capsule can shorten course of diabetic wound and can also be prescribed to the diabetic patients safely.

## References

1. Shukla A, Rasik AM, Jain GK, Shankar R, Kulshrestha DK, Dhawan BN. In vitro and in vivo wound healing activity of asiaticoside isolated from *Centella asiatica*. *J Ethnopharmacol* 1999; 65: 1-11.
2. Shukla A, Rasik AM, Dhawan BN. Asiaticoside-induced elevation of antioxidant levels in healing wounds. *Phytother Res* 1999; 13: 50-4.
3. Coldren CD, Hashim P, Ali JM, Oh SK, Sinskey AJ, Rha C. Gene expression changes in the human fibroblast induced by *Centella asiatica* triterpenoids. *Planta Med* 2003; 69: 725-32.
4. Lu L, Ying K, Wei S, Liu Y, Lin H, Mao Y. Dermal fibroblast-associated gene induction by asiaticoside shown in vitro by DNA microarray analysis. *Br J Dermatol* 2004; 151: 571-8.
5. Muangmun W, Rattanaoran K. Treatment of inflammatory wound by *Centella asiatica* ointment local application. In: Research collection of the clinical use of Thai herbs and Thai traditional medicine. Bangkok: Mahidol University; 2525: 36.
6. Kosalwatna S, Shaipanich C, Bhangnada K. The effect of one percent *Centella asiatica* on chronic ulcers. *Siriraj Hosp Gaz* 1988; 40: 455-61.
7. Belcaro GV, Grimaldi R, Guidi G. Improvement of capillary permeability in patients with venous hypertension after treatment with TTFCA. *Angiology* 1990; 41: 533-40.
8. Chewapat S, Chawalitthamrond P, Attawit A, et al. The study of toxicity of pennyworth. *Journal of Thai Traditional & Alternative Medicine* 2004; 2: 3-17.
9. World Health Organization. *Herba centellae*. In: WHO monographs on selected medicinal plants. Vol. 1. Geneva: WHO; 1999: 77-85.
10. Maquart FX, Chastang F, Simeon A, Birembaut P, Gillery P, Wegrowski Y. Triterpenes from *Centella asiatica* stimulate extracellular matrix accumulation in rat experimental wounds. *Eur J Dermatol* 1999; 9: 289-96.
11. Bonte F, Dumas M, Chaudagne C, Meybeck A. Influence of asiatic acid, madecassic acid, and asiaticoside on human collagen I synthesis. *Planta Med* 1994; 60: 133-5.
12. Suguna L, Sivakumar P, Chandrakasan G. Effects of *Centella asiatica* extract on dermal wound healing in rats. *Indian J Exp Biol* 1996; 34: 1208-11.

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## ผลทางคลินิกของสารสกัดจากบัวบกในผู้ป่วยเบาหวานที่มีแผลที่เท้า

### วิริยะ เกาเจริญ

**วัตถุประสงค์:** เพื่อศึกษาประสิทธิผลของสารสกัดจากบัวบกชนิดรับประทานที่มีต่อการหายของแผลที่เท้าในผู้ป่วยเบาหวาน และศึกษาผลข้างเคียงหรืออาการอันไม่พึงประสงค์ของสารสกัดที่รับประทาน

**วัสดุและวิธีการ:** เป็นการศึกษา แบบสุ่มไปข้างหน้าโดยผู้ป่วย 200 คน ที่ได้รับการรักษาในภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์มหาวิทยาลัยธรรมศาสตร์ ขอบ่งชี้ในการคัดเลือกออกจากการศึกษาได้แก่ ผู้ป่วยที่มีภาวะภูมิคุ้มกันต่ำ ได้รับยาสตีรอยด์ชนิดรับประทาน อายุมากกว่า 80 ปี หรือน้อยกว่า 18 ปี ระดับโปรตีนในเลือดน้อยกว่า 3.0 กรัมต่อเดซิลิตร มีภาวะหลอดเลือดแดงส่วนปลายตีบตันโดยยังไม่ได้รับการแก้ไข มีการติดเชื้อที่เท้าที่ยังควบคุมไม่ได้ข้อบ่งชี้ในการยุติการศึกษาได้แก่ ผู้ป่วยปฏิเสธการเข้าร่วมโครงการต่อไปแผลติดเชื้อแผลหายด้วยวิธีการเย็บหรือวิธีการหัตถ์ตัวเอง ผู้ป่วยจะถูกสุ่มเพื่อแบ่งเป็น 2 กลุ่ม กลุ่ม เอ คือกลุ่มที่ได้รับสารสกัดจากบัวบก และกลุ่มบีคือกลุ่มที่ได้ยาหลอก ผู้ป่วยจะได้รับยาเป็นแคปซูล รับประทานครั้งละ 2 แคปซูลหลังอาหาร 3 เวลา โดยมีสารออกฤทธิ์ของบัวบก 50 มิลลิกรัม ในแคปซูลของกลุ่ม เอ ส่วนกลุ่มบีจะเป็นยาหลอกทั้งสองกลุ่มจะได้รับการรักษาเรื่องเบาหวาน และเรื่องวิธีการทำแผลเหมือนกัน ทั้งสองกลุ่มจะได้รับการประเมินการหายของแผล โดยดูจากการหดตัวของแผล และปริมาณแผลที่เปลี่ยนแปลงไปร่วมกับดูการเจริญเติบโตของเนื้อเยื่อบริเวณแผล นอกจากนี้ยังได้รับการประเมินอาการอันไม่พึงประสงค์ของยาที่ได้รับ

**ผลการศึกษา:** มีการหายของแผลที่เร็วขึ้นในกลุ่มที่ได้รับสารสกัดจากบัวบก และมีการเจริญเติบโตของเนื้อเยื่อที่แผล ผิดปกติน้อยลงในกลุ่มที่ได้รับสารสกัดจากบัวบก ไม่มีกลุ่มใดที่เกิดภาวะแทรกซ้อนหรืออาการอันไม่พึงประสงค์

**สรุป:** สารสกัดจากบัวบกชนิดรับประทานสามารถช่วยทำให้แผลในผู้ป่วยเบาหวานหายเร็วขึ้นในขณะที่จะก่อให้เกิดแผลเป็นชนิดนูนน้อยลง โดยที่ไม่พบผลข้างเคียงหรืออาการอันไม่พึงประสงค์

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