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원저

The Effects of Jawoongo plus Flos Lonicerae on The Artificial Wound on Rats

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ABSTRACT

紫雲膏加 金銀花가 흰쥐의 創傷에 미치는 效果

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紫雲膏加 金銀花가 創傷治癒過程에 미치는 影響을 살펴 보고자 血淸中의 Leukocyte, CRP, Cortisol의 변화 및 상처크기의 縮小率을 實驗한 결과 백혈구의 변화에서는 SampleⅡ가 Control에 비해 減少의 유의성을 나타내었고 CRP含量의 변화에서는 뚜렷한 유의성을 나타내지 못하였고 Cortisol含量의 변화에서는 SampleⅡ가 Control에 비해 減少의 유의성을 나타내었지만 SampleⅢ와 비교시에는 SampleⅢ의 減少의 유의성이 높게 나타났다. 喪妻의 縮小率은 실험 10일과 15일째 Control 에 비해 유의성이 認定되었다.

以上을 살펴볼 때 紫雲膏加 金銀花가 創傷治療에 대해 效果的이며 藥材로서의 효능을 가지고 있음을 알 수 있으나 紫雲膏와 비교하였을 때는 金銀花의 첨가가 創傷治療에 크게 유의성있는 변화를 나타내지 못하였지만 紫雲膏의 單獨 投與시보다는 나은 효과를 나타내었으며 앞으로 韓方 軟膏의 개발을 위하여 더 많은 硏究가 필요할 것으로 思料된다.

Key Word : 자운고(Jawoongo), 금은화(Flos Lonicerae), wound healing, leukocyte, ointment

Ⅰ. Introduction

Most traditional oriental medicine have been used an oral administration for treating diseases, but some oriental medicine included Jawoongo have been used by spreading on the skin. Jawoongo, a traditional oriental medicine ointment, has been used for treating various dermatitis associated with skin diseases such as tinea manuum, eczema and chilblain, etc(1-4).

Jawoongo used in this study is derived from Yungigo supplemented with Adeps Suillus(豚脂). Yungigo was originally prescribed by Jin(5) for scabby scalp and has been widely applied in cutaneous

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diseases(1, 6).

Inflammation is a complex localized response to foreign substances such as bacteria or in some instance to internally produced substances. When the inflammation occurs in or just under the skin, it is characterized by redness, swelling, tenderness, and pain. When tissue is damaged, platelets adhere to exposed matrix via integrins that bind to collagen and laminin. Blood coagulation produces thrombin, which promotes platelet aggregation and granule release. The platelet granules generate an inflammatory response, leading to extravasation of white blood cells. Cytokines released by the white blood cells and platelets up-regulate integrins on macrophages, which migrate to the area of injury, and on fibroblasts and epithelial cells, which mediate wound healing and scar formation(7-9).

The experimental studies of Jawoongo have been reported previously by Eo[10] and Yi[11]. However, the effect of Jawoongo plus Flos Lonicerae(金銀花) has not been investigated to our knowledge.

Flos Lonicerae(金銀花) water extracts are used for antiviral, antibacterial, antifungal and anti-inflammatory effects. Recently, a review of the chemical constituents and pharmacological activity of Flos Lonicerae (金銀花) has been published in various journal(12-16).

The aim of this study is to investigate the effect of Jawoongo plus Flos Lonicerae (金銀花) on the healing of incisional skin wound in rats. After inducing an inflammation on the rats, we observed the amount of Leukocyte, the level of Cortisol and CRP(C-reactive protein), and have obtained the healing effect of wound by using Jawoongo plus Flos Lonicerae(金銀花).

So we reported this paper.

Ⅱ. Materials and Methods

1. Materials

1) Animals

Male sprague - dawley rats with a body weight of 250 - 300g were maintained in an airconditioned room with lighting from 7 a.m. to p.m. The room temperature(about 23℃) and humidity(about 60%) were controlled automatically. A laboratory pellet chew(Sam -Yang Co.) and water were given freely.

The rats were adapted themselves for 2 weeks to lab circumstances before being used.

2) Herbal prescription

Most of herbs for the prescription used in this study were purchased at Dong-Eui Oriental Medicine Hospital(Pusan. Korea), and Oleum Sesami(胡麻油) was purchased at market. The composition of Jawoongo plus Flos Lonicerae (金銀花) is described in Table 1.

Table 1.
Composition of Jawoongo plus Flos Lonicerae(金銀花)

Herbs	*Scientific Name*	Dose
胡麻油	*Oleum Sesami*	100g
金銀花	*Flos Lonicerae*	25g
當 歸	*Angelicae gigantis Radix*	25g
紫 草	*Lithospermi Radix*	25g
豚 脂	*Adeps Suillus*	25g
蜜 蠟	*Beeswax*	15g
Total		215g

2. Methods

1) Preparation of sample solution(1)

Oleum Sesami(胡麻油) was boiled for 1-2hr in the itself and Beeswax(蜜蠟) and Adeps Suillus(豚脂) were solved in this solution. Angelicae gigantis Radix(當歸) and

Lithospermi Radix(紫草) were added and heated until these color was red-violet. And then these herbs were filtered with cotton patch.

Flos Lonicerae(金銀花) was extracted with distilled water at 100℃ for 3hr by the extract machine. The extract was filtered through a filter paper, and concentrated through a evaporator resulting in a semifluid, and it was made into powder through the dry oven.

2) Wound creation and care

The back skin of rats was shaved under ether anesthesia. And we made an incision circular.

Rats used in experiment were divided into five groups.

Normal : Group of non-treated rats
Control : Group of skin wound and non-treated rats
Sample Ⅰ : Group of skin wound and Jawoongo applied rats
Sample Ⅱ : Group of skin wound and Jawoongo plus Flos Lonicerae (金銀花) applied rats
Sample Ⅲ : Group of skin wound and Madecassol® applied rats

* each sample was assigned with 6 rats

* Gel ointment used was the commercially available Madecassol® ointment from Dong Kook Pharm. Co. LTD.(Chung-Buk, Korea)

3) Observation of wound healing procedure

After inducing wound, we took the tissue on 1st, 5th, 10th and 15th day. Every day the rats were applied once to the incised site by the Jawoongo plus Flos Lonicerae (金銀花) and Madecassol®, respectively.

4) Blood - gathering

We obtained the blood sample(0.6ml) from the rats on 5th, 10th and 15day and the serum had been centrifuged for 15minute(4℃, 3000rpm).

5) Measurement of Leukocyte

The number of Leukocyte was measured by the Coulter counter(model s-plus, Coulter Co, U.S.A.).

6) Measurement of Cortisol

Cortisol in the serum was measured by RIA(radioimmunoassay) method and determined by kit (DPC, America) & Gamma counter (1470 Wizard, Finland).

7) Measurement of CRP(C-reactive protein)

CRP in the serum was measured by Latex method and determined by CRP latex kit(Japan) & spectrophotometer(Hitachi 7170, Japan).

8) Dying of tissues

In this histological examination, six rats in each group were sacrificed. To observe of wound healing procedure, skin taken from rats was fixed in 4% neutral formalin, dehydrated with alcohol and then dipped into paraffin. Tissue was cut 6μm in thickness, was dyed with hematoxylin-eosin (H-E) and was done periodis acid Schiff reaction. For the evaluation of the distribution of collagen fiber in the wound healing process, we used Masson's trichrome stain.

9) Statistical Evaluation

Results are expressed as mean±standard error of the mean. The results were analysed by Students's t-test. A P value of less than 0.05 was taken as significant.

Ⅲ. Results

1. Leukocyte measurement

The result of Leukocyte measurement is shown in Table 2.

Table 2.

The effect of Jawoongo plus Flos Lonicerae (金銀花) on the Leukocyte measurement in the skin wounded rats

(M±S.E., $\times 10^3/\mu\ell$)

Group \ Day	5	10	15
Normal	0.40±0.03		
Control	0.85±0.04	0.53±0.02	0.49±0.02
Sample I	0.84±0.06	0.49±0.03	0.52±0.01
Sample II	0.80±0.05	0.53±0.04	0.57±0.02**
Sample III	0.83±0.05	0.54±0.04	0.51±0.03

M±S.E. : Mean±Standard Error
Normal : Group of non-treated rats
Control : Group of skin wound and non-treated rats
Sample I : Group of skin wound and Jawoongo applied rats
Sample II : Group of skin wound and Jawoongo plus Flos Lonicerae (金銀花) applied rats
Sample III : Group of skin wound and Madecassol applied rats
* : Statistical significance as compared with Control
(* : P < 0.05, *** : P < 0.005)

2. CRP(C-reactive protein) measurement

The result of CRP measurement is shown in Table 3.

Table 3.

The effect of Jawoongo plus Flos Lonicerae (金銀花) on the CRP level in the skin wounded rats (M±S.E. ,㎎/dℓ)

Group \ Day	5	10	15
Normal	8.2±0.47		
Control	8.3±0.39	10.3±0.59	12.0±0.79
Sample I	8.7±0.26	10.2±0.30	8.5±0.26***
Sample II	8.0±0.49	10.8±0.52	8.1±0.48***
Sample III	8.9±0.53	9.1±0.20*	8.4±0.55***

Other legends are same as Table 2
* : Statistical significance as compared with Control
(** : P < 0.05)

3. Cortisol measurement

the result of Cortisol measurement is shown in Table 4.

Table 4.

Group \ Day	5	10	15
Normal	0.05±0.01		
Control	0.17±0.02	0.26±0.01	0.20±0.01
Sample I	0.14±0.01	0.21±0.02*	0.24±0.01**
Sample II	0.22±0.02	0.17±0.02***	0.16±0.01**
Sample III	0.48±0.03***	0.46±0.03***	0.06±0.04***

The effect of Jawoongo plus Flos Lonicerae (金銀花) on the Cortisol level in the skin wounded rats
(M±S.E. , ㎍/dℓ)
Other legends are same as Table 2
* : Statistical significance as compared with Control
(* : P < 0.05, ** : P< 0.01, *** : P < 0.005)

4. Wound area Measurement

The wound area was traced and the square size was calculated by an image analyzer. Data are expressed as % of the initial wound area which was measured on the day following wound.

The result of wound area measurement is shown in Table 5.

Table 5.

The effect of Jawoongo plus Flos Lonicerae (金銀花) on the size of incision and the rate of reduction (×mm)

group \ day	1	5	10	15
Control	10.55	5.57(47.2%)[a]	2.16(61.2%)[b]	0.84(61.5%)[c]
Sample I	11.18	6.92(38.1%)	2.11(69.5%)	0.27(87.2%)
Sample II	10.57	7.77(26.5%)	2.14(72.5%)	0.25(88.3%)
Sample III	11.43	7.23(36.8%)	4.68(35.3%)	1.08(76.9%)

Other legends are same as Table 2
The rate of reduction(%)
a) : (1day-5day) / 1day
b) : (5day-10day) / 5day
c) : (10day-15day) / 10day

5. Histologicl evaluation

Figure 1-6 show the results for the histologic evaluation of wound healing process. Angiogenesis, epithelial elongation and differentiation is showed higher value in the Jawoongo group, Jawoongo plus Flos Lonicerae(金銀花) group but lower or equal value in Madecassol® group than control group. The depths of necrotic layer in the wound revealed lower values in the experimental groups than control group, especially in Jawoongo plus Flos Lonicerae (金銀花) group.

In the depth of granulation layer, Madecassol® group showed lower values

than control group but the other groups showed higher values than control groups.

In the depth of subcutaneous collagenous tissue, Madecassol® group showed similar to higher values, but Jawoongo group and Jawoongo plus Flos Lonicerae(金銀花) group lower values.

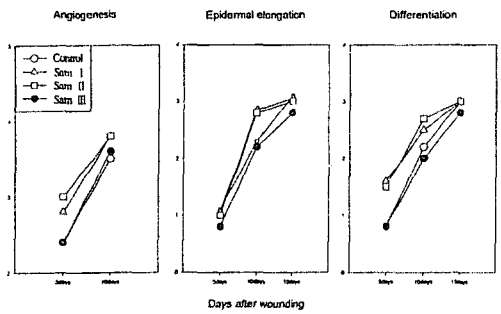


Fig. 1.

Fig. 1.
Histological evalution based on the scores of wound areas

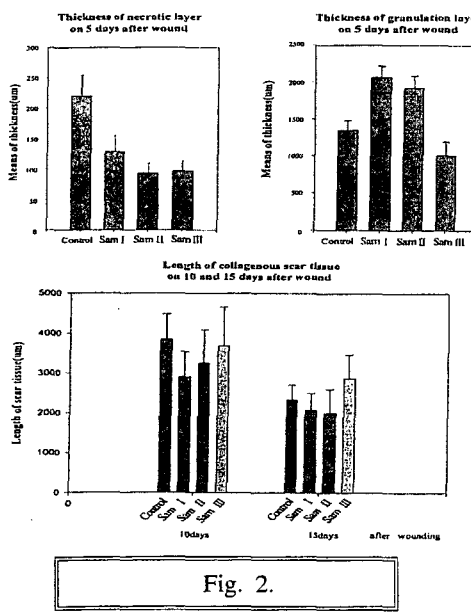


Fig. 2.

Fig. 2.
Histological measurment of wound areas

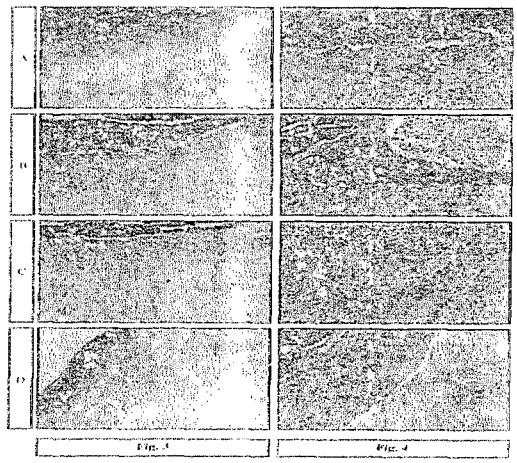


Fig. 3.

Back skin of rat showing excisional wound in the control (A), Sample I (B), Sample II (C) and Sample III (D) on 5 days after wound. H-E staining. × 100.

Fig. 4.

Back skin of rat showing excisional wound in the control (A), Sample I (B), Sample II (C) and Sample III (D) on 5 days after wound. PAS reaction. × 200.

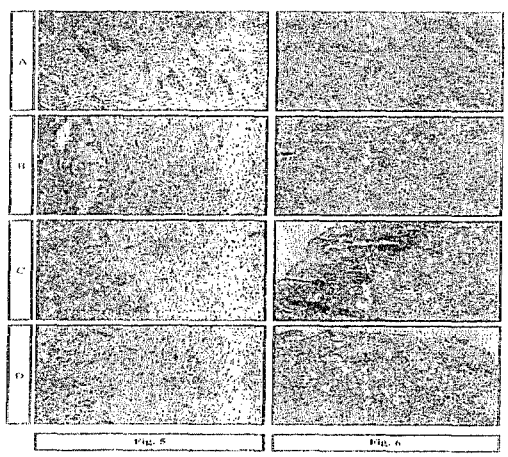
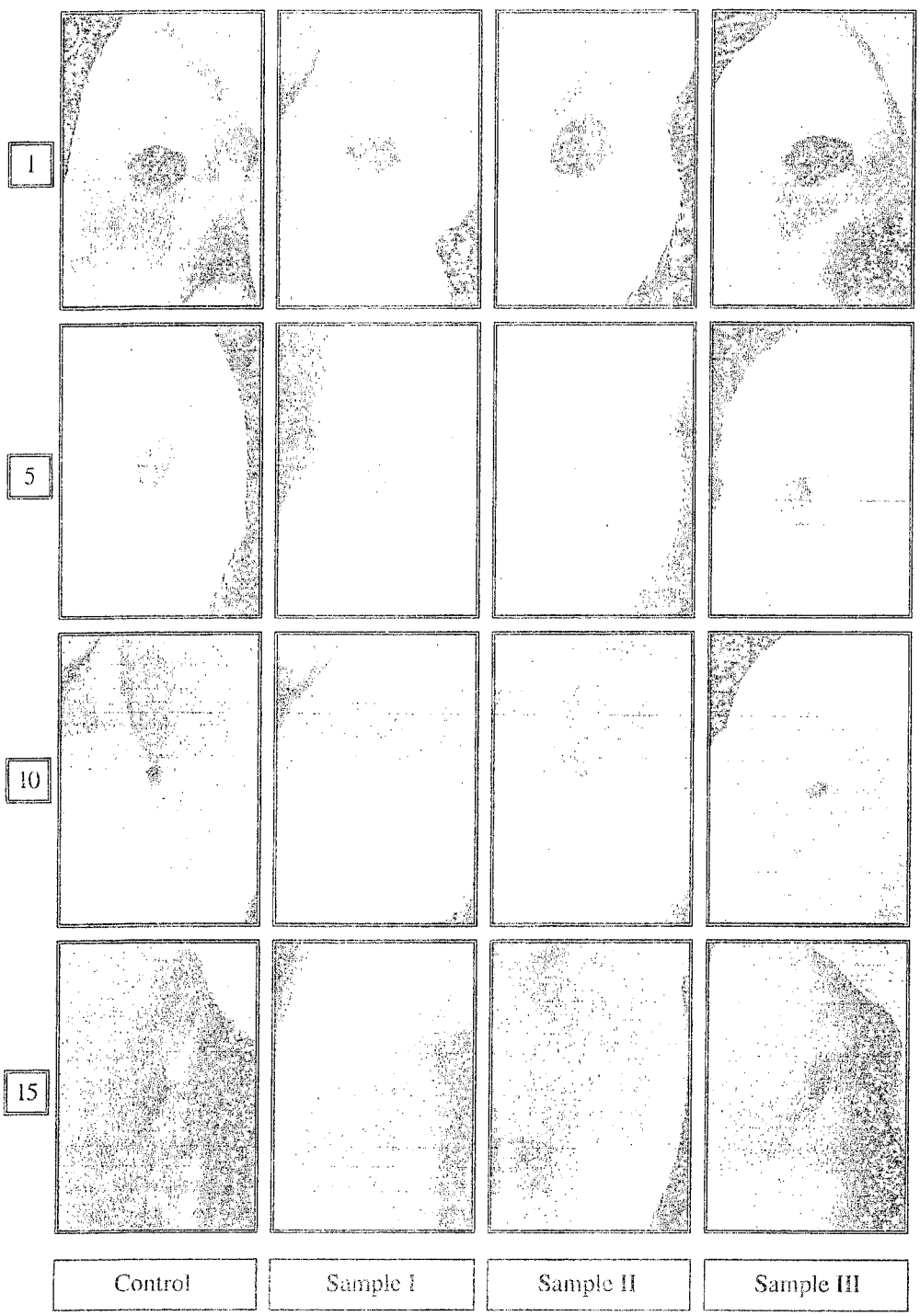


Fig. 5.

Back skin of rat showing excisional wound in the control (A), Sample I (B), Sample II (C) and Sample III (D) on 10 days after wound. Masson's trichrome staining. × 200.

Fig. 6.

Back skin of rat showing excisional wound in the control (A), Sample I (B), Sample II (C) and Sample III (D) on 5 days after wound. anti-iNOS antibody staining. × 200.


1
5
10
15
Control
Sample I
Sample II
Sample III

Ⅳ. Discussion

The application of medicinal herbs dates back to the beginning of civilization. Interestingly, medicinal herbs are still routinely used by most of world's population. Medicinal herbs have been used for the improvement of diseases in Asian countries for centuries. Over time, information has accumulated pertaining to the practical use of herbs, such as their efficacy and adverse reactions when used long term.

Oriental medicine views the body as an energy system and emphasizes abnormality in the balance or flow of energy as the sources of disease. Thus, the basic principle of the traditional Oriental medicine therapy is to regulate the homeostasis of the whole body and to normalize the physical disorders. One mainstay of Oriental medicine is the administration of medicinal herbs with a combination of a number of ingredients. But some oriental medicine included Jawoongo have been treated by spreading on the skin.

Jawoongo, a traditional oriental medicine ointment, has been used for patients with cutaneous diseases(17-19).

Jawoongo is a oriental herbal medicine formula consisting of four ingredients, is derived from Yungigo supplement with Adeps Suillus (豚脂). Yungigo was originally prescribed by Jin(5) for scabby scalp in A.D. 1555 and has been widely applied in seborrhea, fracture, abrasion, bruise, frostbite and scald, etc.(1, 3, 4, 6, 9, 20, 21).

Doctors have applied Jawoongo for treating eczema, neurodermatitis and impetigo, etc. by promoting blood flow(活血), dispersing wind(散風) and moistening (潤燥)(1-4, 22-24).

There have been many experimental studies on the wound. An(27) reported the effect of Sagunjatang extract and Sagunjatang added Radix Astragali(黃芪) extract on the granulation tissues. Eo(10) reported the effect of Jawoongo on the artificial wound on rat skin.

The skin is composed of two mutually dependent layers : the outer epidermis and inner dermis. The skin serves a variety of functions crucial to survival and health. In general, the functions may be correlated with properties of epidermal or dermal regions. The epidermis differentiates to form anucleate cornified cells that act as a relatively impermeable protective barrier to the outward loss of body fluids and the inward penetration of various substances and microorganisms. Two components of the dermis, the unique circulatory system and the specialized cutaneous appendages. Finally, the skin is important immunologically. Both the epidermis and dermis are sites at which a number of immunologic reactions occur that can give rise to unique inflammatory skin diseases(9, 25, 26).

Healing proceeds temporally in three phases : substrate, proliferative, and remodeling. The initial substrate phase, encompassing the first 3 to 4 days after wounding, is so named because the cellular and other interactions lead to preparation for subsequent events. During this phase vascular and inflammatory components prevail(vascular clotting in the severed vessels ; leukocyte and macrophage chemotaxis into the area to ingest bacteria, debride the wound, and degrade collagen). The proliferative phase (10 to 14 days after wounding) results in regeneration of epidermis, neoangiogenesis, and proliferation

of fibroblasts with increased collagen synthesis and closure of the skin defect. The final remodeling phase takes place over 6 to 12 months, during which time a more stable form of collagen is laid down to form a scar of progressively increasing tensile strength(8, 9, 28).

According to the present study, normal value of Leukocyte is 8.2±0.47(×103/㎕) and after 5day, 10day, 15day, Control is 8.3 ±0.39, 10.3±0.59, 12.0±0.79, Sample I is 8.7±0.26, 10.2±0.30, 8.5±0.26, SampleII is 8.0±0.49, 10.8±0.52, 8.1±0.48, SampleIII is 8.9±0.53, 9.1±0.20, 8.4±0.55, respectively. The value of SampleII was significantly decreased compared with that of Control.

Normal value of CRP is 0.40±0.03(㎎/dℓ) and after 5day, 10day, 15day, Control is 0.85±0.04, 0.53±0.02, 0.49±0.02, Sample I is 0.84±0.06, 0.49±0.03, 0.52±0.01, Sample II is 0.80±0.05, 0.53±0.04, 0.57±0.02, SampleIII is 0.83±0.05, 0.54±0.04, 0.51± 0.03, respectively. The value of SampleII was significantly increased compared with that of Control of 15day.

Normal value of Cortisol is 0.05±0.01(㎍/ dℓ) and after 5day, 10day, 15day, Control is 0.17±0.02, 0.26±0.01, 0.20±0.01, Sample I is 0.14±0.01, 0.21±0.02, 0.24±0.01, Sample II is 0.22±0.02, 0.17±0.02, 0.16±0.01, SampleIII is 0.48±0.03, 0.46±0.03, 0.06± 0.004, respectively. The value of SampleII were significantly decreased compared with those of Control of 10 day and 15day, while the value of SampleIII were significantly increased compared with those of Control of 5day and 10 day, and decreased compared with that of 15day.

We observed the size of incision every 1day, 5day, 10day, 15day. Control is 10.55, 5.57(47.2), 2.16(61.2), 0.84(61.5), Sample I is 11.18, 6.92(38.1), 2.11(69.5), 0.27(87.2), SampleII is 10.57, 7.77(26.5), 2.14(72.5), 0.25(88.3) and SampleIII is 11.43, 7.23(36.8), 4.68(35.3), 1.08(76.9), respectively. The rate of reduction of Sample II after 10day and 15day is higher than that of Control group with statistical significance. But the rate of reduction of Control is higher than that of other group with no statistical significance in 5day.

According to histologicl evaluation, angiogenesis, epithelial elongation and differentiation is showed higher value in the Jawoongo group, Jawoongo plus Flos Lonicerae(金銀花) group. The depths of necrotic layer in the wound revealed lower values in Jawoongo plus Flos Lonicerae(金銀花) group. In the depth of granulation layer, the experimental groups showed higher values than control group but not in Madecassol® group. In the depth of subcutaneous collagenous tissue, Jawoongo group and Jawoongo plus Flos Lonicerae(金銀花) group showed lower values. Skin wound healing is a complex process characterized by reepithelization and restoration of the underlying connective tissue. During this process, keratinocytes, endothelial cells, fibroblasts, and inflammatory cells proliferate and/or migrate to the site of injury, interacting with extracellular matrices. In the healing process, angiogenesis, granulation tissue formation and reepithelization are essential process histologically and wound spasm is used for the histologic marker and collagen fibers help connective tissue reconstruction(29-32).

Our purpose, which the new herbal ointment is developed in the herbal medicine through the this study, compared with the Madecasol ointment.

From this study, we have identified the effectiveness of Jawoongo plus Flos

Lonicerae(金銀花) as oriental medicine in wound healing. In comparison with Jawoongo alone, addition of Flos Lonicerae (金銀花) have showed some positive effects in wound healing but not show statistical significance. One problem if the error comes from preparation step or other step remains unsolved and further studies are required. The another problem which herbal ointment is absorped the skin to the some degree. But from this experiment, the effect of oriental ointment is proved in some degree. And detailed approach for more effective and stable ointment should be continued in the future.

V. Conclusion

To evaluate the effect of Jawoongo plus Flos Lonicerae(金銀花) in the process of wound healing, we performed the leukocyte measurement, CRP measurement, cortisol measurement and tissue stain with hematotoxylin- eosin(H-E). The results were as followed.

1. In leukocyte measurement, sample II was significantly decreased compared with control.
2. In CRP measurement, sample I, II, III were showed no stastical significance.
3. In cortisol measurement, the value of SampleII was significantly decreased compared with those of Control of 10 day and 15day, while the value of SampleIII was significantly increased compared with those of Control of 5day and 10 day, and decreased compared with that of 15day.
4. In the analysis of size of incision, the reduction rate of Sample II after 10day and 15day is higher than that of Control group with statistical significance.

These results imply that Jawoongo plus Flos Lonicerae(金銀花) has effect of wound healing, but has little statistical significance comparing with Jawoongo.

References

1. SiSuDoMyeong. HanBangChiRyoBaekHwa. Seoul : DongNamChoolPanSa, pp.322-325, 1991
2. Song byeong-ki. BangJungSinPyeon. Seoul : DongWonChoolPanSa, p.449, 450, 1983
3. Chae byeong-yun. HanBangOeKwa. Seoul : Komoonsa, p.397, 1991
4. Kim jae-kil. ImSangHanBangYakMulYoBeob. Seoul : Namsandang, p.46, 47, 550, 551, 1987
5. Jin Sil Kong. OeKwaJeongJong. Beijing : Inminwisaengchoolpansa, p. 268, 269, 1983
6. Pak seong-su. HanBangChiRyoEui SilJae. Seoul : Euihakyeongusa, p. 54, 508, 1979
7. Willam F. Ganong, M.D.. Review of Medical Physiology, U.S.A. : Prentice-Hall International Inc., p.576, 1993
8. DaeHanByeongRiHakHoi. Byeongrihak. Seoul : Komoonsa, pp.71-111, 1991
9. JAMES B. WYNGAARDEN, M.D.. CECIL TEXTBOOK of MEDICINE. U.S.A. : W.B. SAUNDERS COMPANY, pp.2280-2286, 1992
10. Eo KJ : The effects of Jawoongo on the artificial wound on the rat skin, Dong Eui University, 1997
11. Yi JY : The effect of Gami-Jawoongo on the granulation tissues, TaeJon university, 1994
12. Song Jin Lee, Eun Joo Shin, Kun Ho Son, Hyeun Wook Chang, Sam Sik Kang and Hyun Pyo Kim : Anti-inflammatory Activity of the Major Constituents of Lonicera japonica Arch. Pharm. Res. 18 : 133-135, 1995
13. KAwai, H., Kutoyanagi, M. and Ueno, A. : Iridoid glucosides from Lonicera japonica Thimb. Chem. Pharm. Bull. 36 : 3664-3666, 1988

14. Son, K. H., Kim, J. S., Kang, S. S., Kim, H. P. and Chang, H. W. : Isolation of flavonoids from Lonicera japonica. Kor. J. Pharmacogn. 25 : 24-27, 1994
15. Son, K. H. Jung, K. Y. Chang, H. W., Kim, H. P. and Kanf, S. S. : Triterpenoid saponins from the aerial parts of Lonicera japonica. Phytochem. 35 : 1005-1008, 1994
16. Lee, S. J., Son, K. H., Chang, H. W., Kang., S. S., Park, P. U., Kawk, W. J., Han, C. K. and Kim, H. P. : Development of plant anti-inflammatory agents : comparision of anti-inflammatory and analgesic activities of extracts from Lonicera japonica. Kor. J. Pharmacogn. 25 : 363-367, 1994
17. Seo yeong-dae. SeoYeongDaeSeonSaeng EuiSeoJeonJib. Seoul : Hanseongsa, p.91, 92, 1980
18. Kang soon-soo. BangJeHak. Seoul : Keuchukmoonhwoasa, p.29, 1984
19. Sin min-kyo. ImSangBonChoHak. Seoul : Namsandang, pp.221-223, 236, 237, 301, 1986 20. O kyeom. EuiJongKumKam, Beijing : Inminwisaengchoolpansa, p.71, 193, 1982
21. Han man-woo. HanSinHanBangYak. Daejeon : Hankuksinyakchoolpanbu, p.273, 1979
22. Ko bak kang. SilYongJungEuiOeKwahak. Shanghai : Shanghaikwoahakkisulchoolpansa, p.649, 1985
23. Ko bak kang. JungEuiOeKwaHak. Beijing : Inminwisaengchoolpansa, p.490, 1987
24. Weonanmijungeuihakweon. JungEuiImSang SuChaik. Seoul: Seongbosa, p.366, 1983
25. Daehanpibukwahakhoi. Pibukwahak. Seoul : Yeomoonkak, pp.1-25, 1994
26. Kim jin-jeong. WonSaekJoJikHakDoBo. Seoul : Koreaeuihak, pp.89- 96, 1992
27. Ahn SH : Effects of Sa Gun Ja Tang extract and Sa Gun Ja Tang added Radix Astragali(黃芪) on the Granulation tissues, Won Kwang University, 1988
28. DAVID C. SABISTON, Jr., M.D.. TEXTBOOK OF SURGERY, U.S.A., W.B. SAUNDERS COMPANY, pp.164-175, 1991
29. Niwano Y., Koga H., Kanai K., Hamaguchi H. and H Yamaguchi : Wound healing effect of the new imidazole antimycotic lanoconazole in rats. Drug Res. 46 : 218-223, 1996
30. Niwano Y., Koga H., A Sakai, Kanai K., Hamaguchi H., Uchida M. and T. Tachikawa : Wound healing effect of malotilate in rats. Drug Res. 46 : 450-455, 1996
31. Okada A., Tomasetto C., Lutz Y., Bellocq J-P., Rio M-C. and P Basset. : Expression of matrix metalloproteinases during rat skin wound healing: Evidence that membrane type-1 matrix metalloproteinase is a stromal activator of pro-gelatinase A. J. Cell Biol. 137 : 67-77, 1977
32. Sun L., Xu L., Henry FA., Spiegel S. and TB Nielsen : A new wound healing agent-sphingosylphosphorylcholine. J. Invest. Dermatol. 106 : 232-237, 1996