Efficacy of Early Initiation of a Gel Containing Extractum Cepae, Heparin, and Allantoin for Scar Treatment: An Observational, Noninterventional Study of Daily Practice

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ABSTRACT

Background: Contractubex® (Merz Pharmaceuticals GmbH, Frankfurt, Germany) is a gel containing extractum cepae, heparin, and allantoin with proven efficacy in the prevention of excessive scarring and promotion of physiological scar formation.
Aim: To investigate the efficacy of early initiation of Contractubex in the prevention of excessive scarring and promotion of physiological scar formation.
Methods: In total, 1,268 patients were included in this observational, noninterventional study. Patients were assessed at visit 1 (within 3 weeks of the injury), when treatment was initiated, with subsequent assessments after 2 to 3 months of treatment, and at the end of the study (after 4 to 5 months of treatment). Parameters measured included scar size, color, and pliability (consistency/hardness), as well as patients' and physicians' subjective assessments of treatment efficacy and tolerability.
Results: After 2 to 3 months of treatment, there were statistically significant improvements in color and pliability of the scar, sensation of pain, tension, and pruritus compared with visit 1 ($P<.0001$). By the end of the study, further statistically significant improvements compared with visit 1 were observed for all parameters. Only about 1% of scars were rated as markedly red or markedly hardened at the final visit. In addition, there was a reduction of 31.5% in mean scar width and of 47.8% in mean scar height at the end of the observation period. A high percentage of patients (85.8%) and physicians (86.6%) rated the treatment as good or very good with respect to prevention of excessive scarring and promotion of physiological scar development. Tolerability was described as good or very good by 92.0% of physicians and 91.5% of patients.
Conclusions: The results of this study suggest that the scar gel is effective in preventing excessive scarring and promoting physiological scar formation when treatment is initiated early. In addition, the treatment was well tolerated.

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INTRODUCTION

Scarring in the skin after surgery or accidental injury is a common medical problem. There are estimated to be approximately 44 million surgical procedures per year in the United States (unpublished data, Mattson Jack Group) and 42 million in the European Union (unpublished data, MedTech Insights and TforG) that could benefit from scar-reduction therapy.[1] A recent survey of 97 patients and 24 clinicians revealed that patients were dissatisfied with the appearance of their scars resulting from surgery, irrespective of gender, age, and ethnicity. Furthermore, 91% of patients surveyed reported that they would value even a small improvement in scarring.[2] These findings are supported by the large number of patients who seek scar revision surgery each year (a total of 171,000 patients in the United States in 2009).[3]

It is known that patients suffer both physically and psychologically as a result of scarring. Physical suffering often occurs when scars negatively affect functionality, especially when located over a joint. The lack of elasticity may severely impede mobility. This is particularly common after extensive injuries to the skin and softer tissue from burns or inflammation.

Severe scarring may also affect patients psychologically. Larger scar size has been significantly associated with self-consciousness and anxiety levels in patients with only minor facial injuries.[4] In 50 patients who had suffered facial trauma, there was a significant positive correlation between patients' self-perception of facial disfigurement scores and scores obtained in both the anxiety and depression subscales of the Hospital Anxiety and Depression Scale.[5] One-quarter of patients with a scar from congenital heart disease surgery (sternotomy, thoracotomy, or both) "did not like" or "hated" their scars.[6]

Despite the great need for effective therapies, scar treatment remains challenging. A wide variety of approaches have been employed, from the invasive (steroid injections, cryotherapy, and surgery) to the noninvasive (silicone gel sheeting, pressure garments, hydrating creams, and ointments).[1,7] To date, a combination including various approaches is frequently favored.[8] However, even today, established scars are particularly difficult to treat and effective prophylaxis remains of crucial importance. Options for prophylactic therapy are limited, but specific topical medications containing appropriate active substances are fre-

quently used for treatment of scars. While the efficacy of many topical scar treatments is yet to be established in robust, prospective clinical trials,[8] Contractubex® (Merz Pharmaceuticals GmbH, Frankfurt, Germany), a preparation containing extractum cepae, heparin, and allantoin, has demonstrated efficacy in scar improvement in a number of randomized controlled trials.[9,10]

The aim of this study was to investigate the efficacy of the scar gel containing extractum cepae, heparin, and allantoin in improving scar appearance, size, and skin sensation when treatment was initiated early in a large cohort of patients treated in routine clinical practice.

METHODS

This observational, noninterventional study included 1,268 patients treated by physicians from a range of disciplines: general practitioners, surgeons, gynecologists, and dermatologists. Patients 6 years and older with skin lesions were eligible for inclusion into the study. The study was performed during routine clinical treatment, with observations made and findings recorded at 3 examination appointments over a period of 4 to 5 months. Patients with a known allergy or sensitivity to skin-care products were excluded from the study, as were those with acute or chronic skin diseases (such as atopic dermatitis and atopic eczema), unless the scar area was unaffected by the disease.

Dosage and Period of Observation

Contractubex, a scar gel containing extractum cepae, heparin, and allantoin, was applied twice daily in accordance with the manufacturer's instructions. Patients were assessed when treatment was initiated (visit 1), with subsequent assessments after 2 to 3 months of treatment (visit 2), and at the end of the study after 4 to 5 months of treatment (visit 3). Treatment records were kept for all 3 visits.

Observational Parameters

At each visit, the treating physician evaluated the extent of scar formation with regard to pliability (consistency/hardness), color (redness), sensation, and size. Pliability was rated as one of the following: normal skin, slightly hardened, or markedly hardened. Color was rated as pale/skin-colored, slightly red, or markedly red. Skin sensation with respect to pain, tension, and pruritus could be rated as sensitive to pain, tight, or itchy. At visit 2, patients were asked to provide subjective ratings of the properties of the medication in terms of smell (pleasant, neutral, or unpleasant), spreadability (very good, moderate, or bad), absorption (rapidly absorbed, is absorbed, or is absorbed slowly), and skin sensation after application (improved, unchanged, or worse). Efficacy and tolerability of the treatment were rated at visits 2 and 3 by both the physician and the patient using a 4-point scale (4 = very good, 3 = good, 2 = moderate, 1 = poor). Any adverse drug reactions were also recorded.

Statistics

Results for color, pliability, sensation of pain, tension, and pruritus at both visits 2 and 3 were analyzed in comparison with those obtained at visit 1, using the McNemar 2-sided test.

RESULTS

Patient Demographics and Characteristics

In total, 1,268 patients were included in the study. Of these, 825 (65.1%) were female and 443 (34.9%) were male. The average age of the patients was 41 years.

Most patients had received injuries on the upper body (34.5%), followed by the extremities (32.2%) and other sites, including the head and neck (17.4%) and the face (10.8%). Surgical wounds (65.9%) were by far the most common cause of injury; other causes included cuts and abrasion wounds (18.8%), burns and scalds (7.4%), acne (4.6%), and cosmetic interventions (1.6%). The majority of injuries (56.2%) were less than 3 weeks old when treatment was initiated.

Twenty percent of patients had received wound/scar treatment before the study, consisting primarily of preparations containing iodine (12.1%), dexpanthenol (11.1%), antibiotics (10.7%), or cortisone (7.1%). Surgical revision had been carried out in at least 5% of cases. However, in 77.4% of patients, treatment with the scar gel containing extractum cepae, heparin, and allantoin was the first medication received for the lesion. In 2.6% of cases, no pretreatment information was available. In 28.5% of cases, delayed wound healing was recorded.

Scar Color and Pliability

Figure 1 shows the assessment of scar color (redness) and pliability (consistency/hardness) at each visit. At visit 2, there was a statistically significant improvement in both scar color and pliability compared with visit 1 ($P<.0001$ for both parameters); a further improvement was seen at visit 3, which was also significant compared with visit 1 ($P<.0001$ for both parameters). At treatment initiation (visit 1), 45.7% of lesions were rated as markedly red and 32.2% as markedly hardened, but at visit 2, the percentage of scars rated as markedly red had decreased to 3.6% and those rated as markedly hardened had decreased to 4.7%. By the end of the observation period (visit 3), there had been a further improvement, with only 1% of scars being classified as markedly red and 0.9% of scars being classified as markedly hard (Figure 1). In addition, 56.9% of scars had a normal consistency and 67.3% were similar in color to that of normal, healthy skin by the end of the observation period.

Scar Size

Reductions in both scar width and scar height, from visit 1 to visit 3, could be demonstrated in this study. Specifically, mean scar width decreased by 31.5% (from 8.9 mm to 6.1 mm), and mean scar height diminished by 47.8% (from 2.3 mm to 1.2 mm) (Figure 2).

FIGURE 1. Assessment of the color (redness) and pliability (consistency/hardness) of the scar over time. The percentage of lesions rated as markedly red or markedly hardened at each visit is shown. *P<.0001 compared with visit 1.

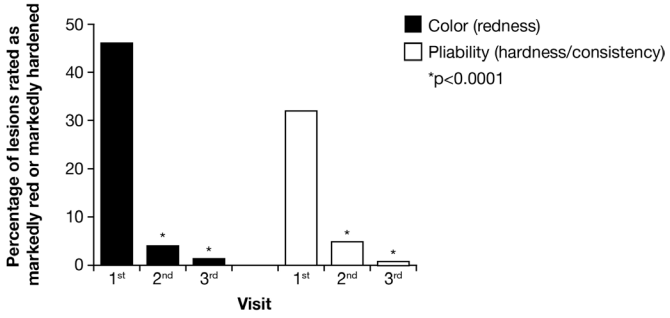


FIGURE 2. Assessment of scar width and height over time. The average width and height of scars at visit 1 and visit 3 are shown.

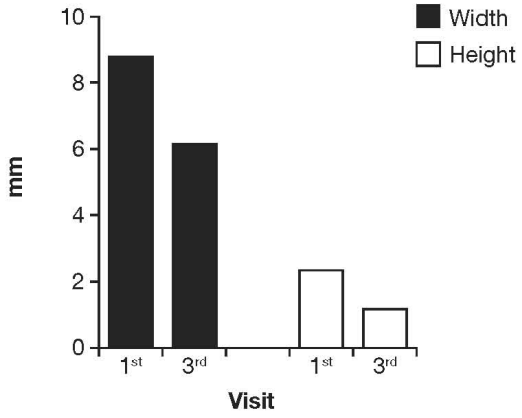
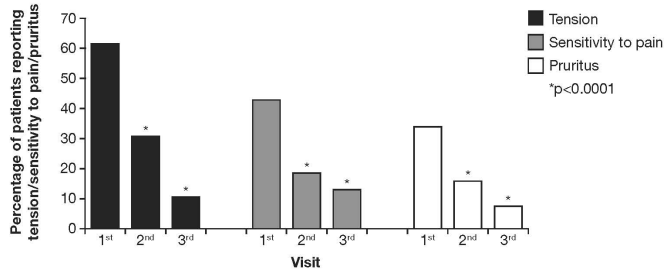


FIGURE 3. Assessment of tension, pain, and pruritus over time. The percentages of patients reporting tension, sensitivity to pain, and pruritus at each visit are shown. *P<.0001 compared with visit 1.



Patient-reported Subjective Impression of Skin Sensation

Reduction in scar size correlated with an improvement in skin sensation in the scar area. At visit 1, the majority of patients (62.6%) reported feelings of tension in the scar area. Nearly half of patients (42.4%) reported sensitivity to pain, while 33.4% reported pruritus (itchiness) (Figure 3). At visit 2, all 3 parameters had improved significantly compared with visit 1 (P<.0001 for each parameter). At visit 3, the percentage of patients reporting feelings of tension had decreased to 10%, with 12.8% reporting pain and 7.6% reporting pruritus (P<.0001 compared with visit 1 for each parameter).

Patient-reported Medication Properties

At visit 2, patients took part in a survey to assess the properties of the scar medication to investigate to what extent the medication met patient needs. Almost all patients (96.7%) rated the aroma as pleasant or neutral, and 84.4% of patients rated spreadability as very good. Only 3% of patients reported that the gel was absorbed into the skin slowly, while 54.6% of patients described the absorption rate as rapid. The subjective impression of 79.5% of patients was that skin sensation had improved. Suitability of the scar gel containing extractum cepae, heparin, and allantoin for the treatment of local wound healing with respect to prevention of excessive scarring and promotion of physiological scar formation was rated as good or very good by 86.5% of physicians (95% confidence interval [CI]: 85.5, 88.4) and 85.8% of patients (95% CI: 83.8, 87.7) (Figure 4).

Safety

Tolerability was described as good or very good by 92.0% of physicians (95% CI: 90.3, 93.4) and 91.5% of patients (95% CI: 89.8, 93.0) (Figure 5). Three patients (0.2%) experienced reversible adverse events in the form of local skin reactions.

DISCUSSION

Irrespective of the underlying cause of the injury—whether from an accident or surgical intervention—it is generally difficult to predict the course of scar formation. Genetic susceptibility, specific anatomic locations, prolonged inflammation, and delayed epithelialization may significantly contribute to an increased risk of developing abnormal or excessive scarring.[8] Besides the poor aesthetic appearance, excessive scarring can be associated with severe clinical symptoms such as pain, itching, and rigidity, thus significantly affecting the patient's quality of life both physically and psychologically. Currently, a variety of scar treatment options are available, with the respective treatment choice ultimately depending on the wound-healing stage and nature of the scar. Existing therapeutic strategies include intralesional triamcinolone acetonide, cryosurgery, radiation, laser therapy, 5-fluorouracil, and surgical excision. Nevertheless, therapy of established excessive scars remains challenging, and side effects with current therapeutic approaches are commonly observed. Since excessive scars may respond differently to the respective treatments, approaches frequently need to be combined or altered.

However, it is simpler—and a successful outcome is considerably more likely—to treat the scar at an early stage rather than attempting to remedy established hypertrophic scars or keloids at a later stage. Besides surgical approaches, such as achievement of rapid epithelialization and primary closure of wounds without tension, 3 main options for the prevention of excessive scarring are presently being discussed in the literature: pressure garments, silicone gel or silicone gel sheets, and the use of extractum cepae. Pressure therapy has been the preferred conservative method of prophylaxis and treatment of excessive scars since the 1970s. Recommendations for

FIGURE 4. Physician and patient ratings of treatment success. The percentages of patients and physicians who rated the success of the treatment as very good, good, moderate, or poor are shown.

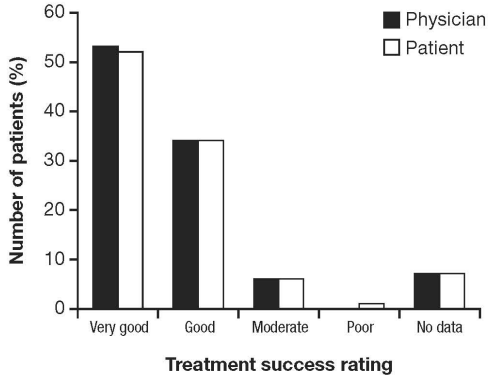
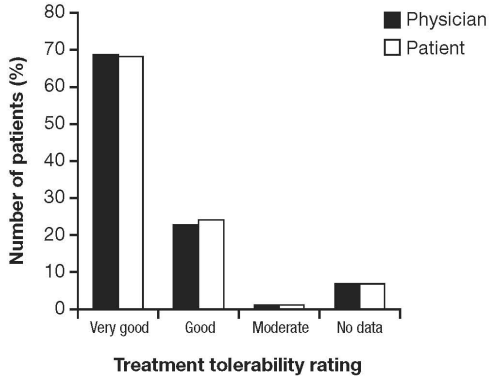


FIGURE 5. Physician and patient ratings of treatment tolerability. The percentages of patients and physicians who rated the tolerability of the treatment as very good, good, or moderate are shown.



the amount of pressure and the duration of the therapy are based merely on empirical observations,[11,12] and its efficacy may be limited by the ability to adequately fit the garment to the wounded area and by reduced compliance due to significant patient discomfort. Silicone-based gels and sheets have been advocated as promising means to reliably improve scar appearance and prevent excessive scar formation. A randomized, double-blind, placebo-controlled study of silicone gel for the prevention of hypertrophic scarring in the medial sternotomy wound showed promising efficacy, with no side effects and satisfactory compliance.[13] Although, a recent meta-analysis of 13 trials (including a total of 559 patients) concluded that there was only weak evidence for benefits of this treatment because of the poor study quality and their high susceptibility to bias.[14]

Thus, robust clinical trials with clear definitions of criteria for scar improvement have largely been lacking, and no treatment or regimen to manage postsurgery scarring has been universally adopted, although evidence-based medicine in this field is emerging.

The topical scar gel containing extractum cepae, heparin, and allantoin as active constituents has proven its value in both clinical studies and in routine practice for many years.[10,15-17] Each constituent has a complementary mechanism of action that may contribute to the therapeutic effect of the medication. By inhibiting excessive fibroblast proliferation and the release of extracellular matrix constituents (eg, proteoglycans) from fibroblasts, extractum cepae counteracts increased scar tissue formation (scar hypertrophy and keloid formation).[18-22] Heparin exerts an anti-inflammatory and antiedematous effect, as well as stimulating cell and tissue regeneration in the corium, where it also binds to the surface of scar collagen, inhibiting further collagen polymerization.[23,24] Allantoin has a hydrating action, promotes wound healing, and has a soothing effect on irritation.

The aim of the present study was to evaluate the effects of the scar gel containing extractum cepae, heparin, and allantoin on scar maturation after early initiation of treatment in a large, multicenter, observational clinical trial. Physicians from a number of different fields were included in this study to reduce the likelihood of bias, which could arise if the study was limited to physicians from a single specialty. To the authors' knowledge, no other studies of scar treatments have included such a large patient population.

The results of this study suggest that early initiation of the scar gel containing extractum cepae, heparin, and allantoin may positively promote the formation of physiological scars and prevent excessive scarring. At visits 2 and 3, there was a statistically significant improvement in both scar color and pliability compared with visit 1. At visit 3, which occurred 4 to 5 months after initiating treatment with the scar gel, only about 1% of scars were still rated as markedly red or markedly hardened compared with 45.7% and 32.2%, respectively, at visit 1. Conversely, 98.9% of scars were rated as normal or slightly hardened, while 99.0% were normal or slightly red. There were also improvements in scar size: mean scar height and mean scar width decreased by 47.8% and 31.5%, respectively. As expected, the treatment had little effect on scar length. Patient-reported assessments of tension, sensitivity to pain, and pruritus showed a statistically significant improvement at both visit 2 and visit 3 compared with visit 1.

Also, in subjective assessments of tolerability, 92% of physicians and patients described the scar gel containing extractum cepae, heparin, and allantoin as either very good or good. However, the specific odor of the scar gel, which is due to the onion extract, has been noted in daily practice in some patients. Nevertheless, the good tolerability and efficacy led to 87% of physicians and 86% of patients concluding that the suitability of the scar gel to early-stage scar treatment was either good or very good.

Many of the beneficial effects of the scar gel containing extractum cepae, heparin, and allantoin on scar maturation reported here have been already demonstrated in a prospective, randomized, controlled trial including 65 children who had undergone thoracic surgery. Here, early treatment with the scar gel containing extractum cepae, heparin, and allantoin starting 2 to 3 weeks after surgery led to a markedly smaller increase in scar size, a

tendency toward more rapid fading, and less frequent conversion from physiological scars to nonphysiological scars when compared with untreated scars. All scar-specific effects of the scar gel containing extractum cepae, heparin, and allantoin continued to persist after the end of treatment, as demonstrated at follow-up 12 months postsurgery.[10] An additional study demonstrated a considerable difference in scar size in favor of the patients treated with the scar gel containing extractum cepae, heparin, and allantoin compared with the untreated group after 6 to 12 months of treatment.[16] Another randomized, controlled, similarly designed study in children and adolescents aged between 1 and 18 years provides additional support for the efficacy of this treatment. In the group treated with the scar gel containing extractum cepae, heparin, and allantoin, scars were statistically significantly smaller compared with the control group at the 6-month and 12-month observation points, and more postoperative wounds healed into physiological scars.[17] Nevertheless, placebo-controlled studies evaluating the ultimate benefit of extractum cepae–containing scar creams are missing, and a recent double-blind study comparing the efficacy between a scar gel containing extractum cepae (Mederma; Merz Pharmaceuticals, Greensboro, NC) and a petrolatum-based emollient did not reveal any statistically significant differences between the 2 treatment groups in any of the outcome measures studied.[25] However, patient numbers were low in this study, and scars varied in location, origin, and age. Thus, reliable comparison between groups may be difficult in this study.[25]

CONCLUSIONS

The improvements in the parameters measured here support data from other clinical trials and suggest that the scar gel containing extractum cepae, heparin, and allantoin may be effective for the early treatment of scars arising from a variety of causes. Patients and physicians were very satisfied with the treatment, reporting that it was simple to use, reliable, and well tolerated. This treatment approach may help to prevent excessive scar formation and, based on data from a large patient cohort, may contribute to physiological scar development. However, more well-designed studies are needed in order to ultimately test the efficacy of the scar gel containing extractum cepae, heparin, and allantoin on prevention of excessive scars and scar maturation.

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REFERENCES

1. Bush J, So K, Mason T, Occleston NL, O'Kane S, Ferguson MW. Therapies with emerging evidence of efficacy: avotermin for the improvement of scarring. *Dermatol Res Pract.* 2010;2010. pii: 690613.
2. Young VL, Hutchison J. Insights into patient and clinician concerns about scar appearance: semiquantitative structured surveys. *Plast Reconstr Surg.* 2009;124(1):256-265.
3. American Society of Plastic Surgeons. 2009 Statistics. http://www.yourplasticsurgeryguide.com/trends/asps-2009.htm. Accessed March 2, 2012.
4. Tebble NJ, Thomas DW, Price P. Anxiety and self-consciousness in patients with minor facial lacerations. *J Adv Nurs.* 2004;47(4):417-426.
5. Islam S, Ahmed M, Walton GM, Dinan TG, Hoffman GR. The association between depression and anxiety disorders following facial trauma--a comparative study. *Injury.* 2010;41(1):92-96.
6. Crossland DS, Jackson SP, Lyall R, et al. Patient attitudes to sternotomy and thoracotomy scars. *Thorac Cardiovasc Surg.* 2005;53(2):93-95.
7. Gauglitz GG, Korting HC, Pavicic T, Ruzicka T, Jeschke MG. Hypertrophic scarring and keloids: pathomechanisms and current and emerging treatment strategies. *Mol Med.* 2011;17(1-2):113-125.
8. Gauglitz GG. Therapeutic strategies for the improvement of scars. *Prime.* 2012;2(1):16-27.
9. Ho WS, Ying SY, Chan PC, Chan HH. Use of onion extract, heparin, allantoin gel in prevention of scarring in chinese patients having laser removal of tattoos: a prospective randomized controlled trial. *Dermatol Surg.* 2006;32(7):891-896.
10. Maragakis M, Willital GH, Michel G, Görtelmeyer R. Possibilities of scar treatment after thoracic surgery. *Drugs Exp Clin Res.* 1995;21(5):199-206.
11. Macintyre L, Baird M. Pressure garments for use in the treatment of hypertrophic scars--a review of the problems associated with their use. *Burns.* 2006;32(1):10-15.
12. Van den Kerckhove E, Stappaerts K, Fieuws S, et al. The assessment of erythema and thickness on burn related scars during pressure garment therapy as a preventive measure for hypertrophic scarring. *Burns.* 2005;31(6):696-702.
13. Chan KY, Lau CL, Adeeb SM, Somasundaram S, Nasir-Zahari M. A randomized, placebo-controlled, double-blind, prospective clinical trial of silicone gel in prevention of hypertrophic scar development in median sternotomy wound. *Plast Reconstr Surg.* 2005;116(4):1013-1020.
14. O'Brien L, Pandit A. Silicon gel sheeting for preventing and treating hypertrophic and keloid scars. *Cochrane Database Syst Rev.* 2006;(1):CD003826.
15. Beuth J, Hunzelmann N, Van Leendert R, Basten R, Noehle M, Schneider B. Safety and efficacy of local administration of contractubex to hypertrophic scars in comparison to corticosteroid treatment. Results of a multicenter, comparative epidemiological cohort study in Germany. *In Vivo.* 2006;20(2):277-283.
16. Willital GH, Heine H. Efficacy of Contractubex gel in the treatment of fresh scars after thoracic surgery in children and adolescents. *Int J Clin Pharmacol Res.* 1994;14(5-6):193-202.
17. Chadzynska M, Jablonska S. Contractubex in the treatment of burn-induced hypertrophic,keloidal scars in children [in German]. *Dtsch Dermatol.* 1989;37:1288-1299.
18. Avuso MJ, Saenz MT. Antimitotic activity of a protein fraction isolated from viscum-cruciatum on the root meristems of Allium cepa. *Fitoterapia.* 1985;56:308-311.
19. Cho JW, Cho SY, Lee SR, Lee KS. Onion extract and quercetin induce matrix metalloproteinase-1 in vitro and in vivo. *Int J Mol Med.* 2010;25(3):347-352.
20. Phan TT, Lim IJ, Chan SY, Tan EK, Lee ST, Longaker MT. Suppression of transforming growth factor beta/smad signaling in keloid-derived fibroblasts by quercetin: implications for the treatment of excessive scars. *J Trauma.* 2004;57(5):1032-1037.
21. Phan TT, Lim IJ, Sun L, et al. Quercetin inhibits fibronectin production by keloid-derived fibroblasts. Implication for the treatment of excessive scars. *J Dermatol Sci.* 2003;33(3):192-194.
22. Sahin MT, Inan S, Ozturkcan S, et al. Comparison of the effects of Contractubex® gel in an experimental model of scar formation in rats: an immunohistochemical and ultrastructural study. *J Drugs Dermatol.* 2012;11(1):74-81.
23. Heine H. Transcutaneous heparin therapy. Experimental histological studies with the effective combination heparin–allantoin-D panthenol [in German]. *Med Welt.* 1983;34(20):602-604.
24. Heine H. Narbenbehandlung durch transepidermale heparinisierung - Wirkungsweise eines Narbenspezifikums [in German]. *Therapeutikon.* 1989;3:369-375.
25. Chung VQ, Kelley L, Marra D, Jiang SB. Onion extract gel versus petrolatum emollient on new surgical scars: prospective double-blinded study. *Dermatol Surg.* 2006;32(2):193-197.

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