Comparative Study of the Biological Activity of Allantoin and Aqueous Extract of the Comfrey Root

Vesna Lj. Savić,Vesna D. Nikolić,Ivana A. Arsić,Ljiljana P. Stanojević,Stevo J. Najman,Sanja Stojanović,Ivana I. Mladenović-Ranisavljević

First published: 16 April 2015

https://doi.org/10.1002/ptr.5356

Abstract

This study investigates the biological activity of pure allantoin (PA) and aqueous extract of the comfrey (*Symphytum officinale L*.) root (AECR) standardized to the allantoin content. Cell viability and proliferation of epithelial (MDCK) and fibroblastic (L929) cell line were studied by using MTT test. Anti-irritant potential was determined by measuring electrical capacitance, erythema index (EI) and transepidermal water loss of artificially irritated skin of young healthy volunteers, 3 and 7 days after application of creams and gels with PA or AECR. Pure allantoin showed mild inhibitory effect on proliferation of both cell lines at concentrations 40 and 100 μg/ml, but more pronounced on MDCK cells. Aqueous extract of the comfrey root effect on cell proliferation in concentrations higher than 40 μg/ml was significantly stimulatory for L929 but inhibitory for MDCK cells. Pharmaceutical preparations that contained AECR showed better anti-irritant potential compared with PA. Creams showed better effect on hydration and EI compared with the gels that contained the same components. Our results indicate that the biological activity of the comfrey root extract cannot be attributed only to allantoin but is also likely the result of the interaction of different compounds present in AECR. Topical preparations that contain comfrey extract may have a great application in the treatment of skin irritation.

Profile of wound healing process induced by allantoin[1]

Perfil do processo de cicatrização induzido pela alantoína

Lorena Ulhôa Araújo[I], Andrea Grabe-Guimarães[II], Vanessa Carla Furtado Mosqueira[II], Claudia Martins Carneiro[III], Neila Márcia Silva-Barcellos[II]

[I] Master in Pharmaceutical Sciences, Post-graduate Program, Pharmacy School, UFOP, Ouro Preto-MG, Brazil.
[II] Associate Professor, Department of Pharmacy, Pharmacy School, UFOP, Ouro Preto-MG, Brazil.
[III] Associate Professor, Department of Clinical Analysis, Pharmacy School, UFOP, Ouro Preto-MG, Brazil.

ABSTRACT

Purpose: To evaluate and characterize the wound healing process profile induced by allantoin incorporated in soft lotion oil/water emulsion using the planimetric and histological methods. **Methods**: Female Wistar rats (n=60) were randomly assigned to 3 experimental groups: (C) control group-without treatment; (E) group treated with soft lotion O/W emulsion excipients; (EA) group treated with soft lotion O/W emulsion containing allantoin 5%. The emulsions either containing or not allantoin were topically administered for 14 days and the wound area was evaluated by planimetry and by qualitative and quantitative histological analysis of open wound model. **Results**: The data which were obtained and analyzed innovate by demonstrating, qualitatively and quantitatively, by histological analysis, the profile of healing process induced by allantoin. The results suggest that the wound healing mechanism induced by allantoin occurs via the regulation of inflammatory response and stimulus to fibroblastic proliferation and extracellular matrix synthesis. **Conclusion**: This work show, for the first time, the histological wound healing profile induced by allantoin in rats and demonstrated that it is able to ameliorate and fasten the reestablishment of the normal skin.
Key words: Wound Healing. Allantoin. Histology. Animal Experimentation. Rats.

RESUMO

Objetivo: Avaliar e caracterizar o perfil cicatricial induzido pela alantoína incorporada em uma emulsão óleo/água, sob os aspectos planimétrico e histológico. **Métodos**: Ratos Wistar fêmeas (n=60) foram agrupados aleatoriamente em três grupos experimentais grupo controle – sem tratamento (C); grupo tratado com emulsão pura (E); grupo tratado com emulsão contendo 5% de alantoína (EA). As emulsões contendo ou não alantoína foram administradas topicamente durante 14 dias e a área da ferida foi avaliada por planimetria e por análise histológica qualitativa e quantitativa em modelo de ferida aberta. **Resultados**: Na análise planimétrica não foi observado diferenças significativas entre os grupos experimentais. Os resultados da análise histológica sugerem que o mecanismo de cicatrização induzido pela alantoína ocorre via controle da resposta inflamatória e estímulos à proliferação fibroblástica e síntese de matrix extracelular de maneira mais intensa e rapidamente em relação aos grupos controles. **Conclusão**: Este trabalho mostra pela primeira vez o perfil histológico de cicatrização induzido pela alantoína em ratos, demonstrando ser capaz de melhorar e acelerar o processo de reconstituição da pele.
Descritores: Cicatrização de Feridas. Alantoína. Histologia. Experimentação Animal. Ratos.

[1]Research performed at the Post-graduate Program in Pharmaceutical Sciences, Pharmacy School, Ouro Preto Federal University (UFOP), Minas Gerais, Brazil.

Introduction

Wound healing is a physiological process which restores the skin integrity, aiming to repair the damaged tissues[1,2]. This process starts with the hemostasis and proceeds in three interrelated dynamic and overlapping phases: inflammation, proliferation and remodeling[1,3-5]. The evolution of these phases involves events of cellular migration and transmigration, vasoconstriction, vasodilatation, angiogenesis, formation of granulation tissue and deposition of extracellular matrix.

The allantoin (Figure 1), 5-ureide-hydantoin, has been widely cited in literature as holder of numerous pharmacological activities, among them: wound healing[6,7], anti-irritating, hydrating and remover of necrotic tissue[6], stimulating the cell mitosis[8]; as well as promoter of epithelial stimulation, analgesic action[9] and keratolytic activity[10]. For all these reports, the allantoin has been used in cosmetic and pharmaceutical preparations for over 70 years with different therapeutic purposes and especially as a

wound healing booster. However, despite this broad description and therapeutic application, surprisingly enough, there are no data that support these pharmacodynamic actions, and the allantoin action mechanism is still unknown[11].

In this context, the aim of this study was to evaluate and describe the wound healing process profile induced by allantoin incorporated in soft lotion oil/water emulsion using planimetric and histological analysis. For this purpose an *in vivo* wound rat model was used and the macro and microscopic contractions of treated lesions were evaluated.

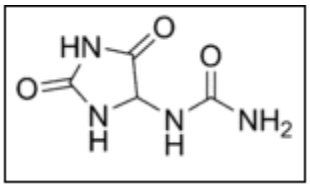

FIGURE 1 - Allantoin structure: 5-ureidohydantoin

Methods

Solvents and reagents

Allantoin was purchased from Sigma-Aldrich® (Italy); methylparben and propylparaben were provided by Synth® (Brazil); cetostearyl alcohol and sodium cetilstearilsulfate were purchased from Natural Pharma® (Brazil); ethylic alcohol, mineral oil and sorbitol solution 70% were purchased by Tedia® (USA). Water was purified by Milli-Q system from Millipore (USA).

Pharmaceutical formulating

The Table 1 shows the composition of soft lotion oil/water (O/W) emulsion pharmaceutical formulation used as vehicle for allantoin.

TABLE 1 - Composition (w/w) of soft lotion O/W emulsion

Components	Soft lotion O/W emulsion
Methylparaben	0,10g
Propylparaben	0,15g
Ethilic alcohol	2,0 mL
Cetostearyl alcohol	3,6g
Sodium Cetilestearilsulfato	0,4g
Mineral oil	4,0 mL
Sorbitol solution 70% w/v	5,0 mL
Allantoin	5,0g
Water	79,75mL

Animals

Sixty healthy female Wistar rats (180-200g) obtained from Ouro Preto Federal University (UFOP) were used in all studies. The experimental protocol was approved by the Ethical Committee of UFOP (number 2007/98) and was in agreement with the Guide for the Care and Use of Laboratory Animals, published by the US National Institute of Health (NIH Publication, revised in 1985). All the experimental procedures were in conformity with the rules of the Brazilian College for Animal Experimentation (COBEA). The animals were housed in standard individual polypropylene cages in a room and were maintained in an alternating 12 hours light-dark cycle with a standard pellet diet (Labcil Petilizado-Socil, Brazil) and purified drinking water *ad libitum* during the period of acclimatization (7 days) and throughout the experimental period.

Experimental groups

The animals were randomly distributed into three groups: (C) control group-without treatment; (E) group treated with soft lotion O/W emulsion excipients; (EA) group treated with soft lotion O/W emulsion containing allantoin 5%.

Experimental open wound model

The animals were anesthetized by intraperitoneal injection of sodium pentobarbital (50 mg/Kg) and after the anesthesia had reached the necessary depth, trichotomy of the dorsal back of each animal was carried out and an excision of about 1 cm^2 was made by removing a full thickness piece of the skin (epidermis and dermis), as described by Sekine *et al.*[12], exposing the dorsal fascia muscle (Figure 2). The treatment, which started soon after the wound was produced, consisted of applying 0.25g of each topical formulation. In C group no topical application was performed, and it was considered a negative control.

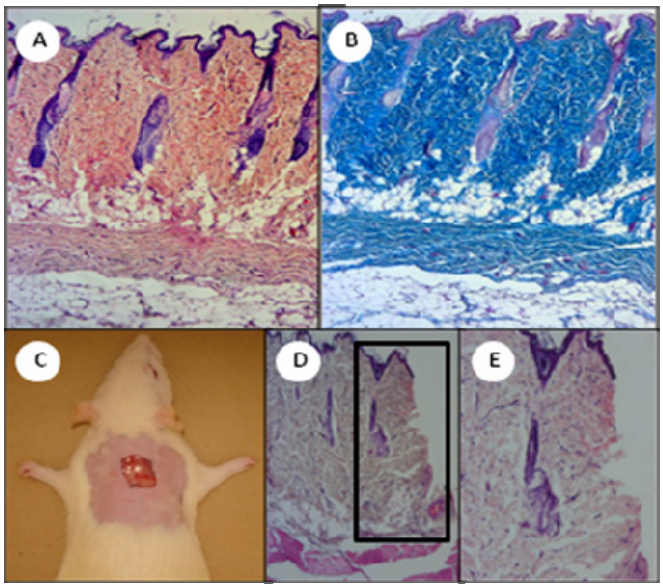

FIGURE 2 - A and **B**: Histological appearance of the normal rat skin (**A**: Hematoxylin-Eosin and **B**: Masson's trichrome); **C**: Open wound; **D** and **E**: Histological appearance of the skin after the wound and removed from the skin and dermis (**D**) and depth of the wound area (**E**)

Planimetric analysis

The size of lesions was determined using the planimetric method, projecting the lesion onto a transparent pattern foil on 0, 3rd, 7th and 14th days. The images were transposed to a computer and analyzed using the software AutoCad® 2006. The wound contraction rate was measured as percentage reduction in wound size. Wound contraction (WC) was calculated from the area determinations as follows[13]:

$$WC = \frac{(\text{Area } D_0 - \text{Area } D_t) \times 100}{\text{Area } D_0} \qquad \text{where } t = 3, 7 \text{ and } 14 \text{ days.}$$

Histological analysis

Collection and preparation of the biological material

After sacrifice, using overdose of sodium pentobarbital (100 mg/kg), the wounds of animals were excised on the 3rd, 7th, 14th, 21st and 28th days after the surgery, containing a margin of normal skin around the edges of the wound. Then, the tissues were preserved in 10% buffered formalin until the proceedings. 4 µm thickness sections were stained with Hematoxylin-Eosin and with Masson Trichrome. The cuts were analyzed microscopically by the same pathologist without prior knowledge of the identification of the groups.

Qualitative analysis

In order to characterize qualitatively the wound healing process induced by allantoin, the tissue parameters, epithelialization, congestion, inflammatory process, presence or absence of necrosis and tissue neoformation, were analyzed by optical microscopy (Olympus CH30, Japan) on the 3rd, 7th, 14th, 21st and 28th days after the surgery. The histological parameters were classified according to the intensity of occurrence in five levels (- absence; + discrete; ++ moderate; +++ intense; ++++ very intense).

Quantitative analysis (Morphometry)

The quantitative analysis was performed using scans of the tissues to quantify the inflammatory process and neoformation of collagen induced by allantoin. All cellular nucleus and collagen fibers in the skin fragments were quantified in 20 randomly fields (total covered area equal to 1.5×10^6 µm^2). The images were amplified, acquired by a Microcamera Leica and the software DM5000B Leica Application Suite (Version 2.4.0 R1 Leica Microsystems, Switzerland Ltd) and analyzed by Leica Software QWin V3 (Leica Microsystems, Switzerland Ltd).

Analysis statistics

The data of planimetric and histological analysis were presented as mean ± S.E.M. and statistical evaluation was performed by ANOVA and Tukey post-test. Values lower than $P<0.05$ were considered significant. All analyzes were performed using the GraphPad Prism 4.0 Software (Prism software, Irvine, CA, USA).

Results

Planimetric analysis

The planimetry evaluation (Figure 3) of the wound contraction showed gradual reduction of wound area in all experimental groups as time passed, except for some animals, which presented an increase of the wound size on the 3rd day of analysis. It was observed that only at this time (3rd day) there was a significant difference in the wound contraction from untreated group (C) and the group treated with allantoin (EA).

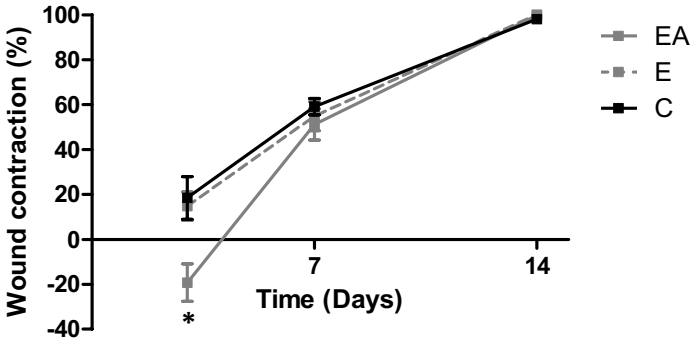

FIGURE 3 - Kinetic of the percentage of wound contraction in the untreated (**C**) and treated animals with soft lotion O/W emulsion containing (**EA**) or not allantoin (**E**) in the times on 3rd, 7th and 14th days. Results were expressed as mean ± S.E.M. (*$p \leq 0.05$)

Histological analysis

Qualitative analysis

In general, similar wound healing histological pattern was observed with the treatment with soft lotion O/W emulsion containing (EA) or not (E) allantoin or in the animals untreated (C) (Figure 4). On the 3rd post-operative day (Figure 4: A, B, G, H, M and N) an inflammatory process was observed, presenting congestion, hyperemia, necrosis, inflammatory cells, some collagen deposition and absence of epithelium. On the 7th day, there was still the presence of the congestion characteristic of the 3rd day, although with less intensity. The inflammatory process was more intense and diffused, with great presence of inflammatory cells, and intense necrosis. It was also observed the presence of new blood vessels (angiogenesis) and a greater amount of fibroblasts, that induced a greater collagen neoformation (fibers were more numerous and more mature-looking) compared to 3rd day. Additionally, fibrin-leukocyte crusts were present in the wounds in all groups evaluated. On the 14th day (Figure 4: C, D, I, J, O and P) the wound healing process was advanced, presenting reduction of the inflammatory process characterized by a smaller amount of inflammatory cells, discrete inflammatory infiltrated and absence of necrosis, reepithelization of the tissues and collagen deposition presenting more differentiate fibers. On the 21st day, the wound

healing process was more advanced, with small amount of inflammatory cells and completely reconstructed epithelium. The granulation tissue was formed, characterized by intense collagen deposition (numerous and many mature aspect fibers). Additionally, on the 28th day (Figure 4: E, F, K, L, Q and R) intense collagen deposition was observed, characterizing a fully formed scar tissue and the tissue morphology was more similar to a normal state.

When comparing the wound healing process induced by the three groups studied (C, E and EA), it was observed that, despite having similar profiles as described above, they differ on the intensity and speed of occurrence of the three phases of wound healing (inflammatory, fibroplasia and maturation), as seen in Table 2, which presents the intensity of histological parameters and Figure 4 which shows photomicrographs of induced wound healing.

The results obtained indicated that the treatment with soft lotion O/W emulsion containing or not allantoin had a positive effect on the wound healing process, due to the epithelial stimulation (14th day), congestion (3rd, 7th and 14th day), inflammation reduction (3rd, 14th and 21st) and also collagen deposition stimulation (14th, 21st and 28th day), as can be observed in Table 2 and in Figure 4. However, the group treated with allantoin (EA) induced a reduction of inflammatory cells and stimulated the collagen deposition early, already on 3rd post-operative day (Figure 4: M and N). On the 14th day, the treated groups (E and EA) presented greater collagen deposition, with more organized tissue observed in the EA group (Figure 4: O and P). And, finally on the 28th day, it was observed that the treatment with allantoin induced to a more organized tissue, close to a healthy skin (Figure 4: Q and R).

TABLE 2 - Intensity of histological parameters assessed in untreated animals (C) and treated with soft lotion O/W emulsion containing (EA) or not (E) allantoin

		Histological Parameters				
Groups	**Days**	**Epithelialization**	**Congestion**	**Inflammation**	**Necrosis**	**Collagen**
C	3	-	+ + + +	+ + +	+ +	-
	7	-	+ + +	+ + +	+ + +	+
	14	+	+	+ +	-	+ +
	21	+ +	-	+ +	-	+ +
	28	+ +	-	-	-	+ +
E	3	-	+ +	+ +	+ +	+
	7	-	+ +	+ + +	+ + +	++
	14	+ +	-	+	-	+ ++
	21	+ +	-	-	-	+ ++
	28	+ +	-	-	-	+ + +
EA	3	-	+ +	+ +	+ +	+
	7	-	+ +	+ +	+ + +	++
	14	+ +	-	+	-	+ ++
	21	+ +	-	-	-	+ ++
	28	+ +	-	-	-	+ + ++

Classification of histological parameters according to the intensity of occurrence: - absence; + discrete; ++ moderate; +++ intense; ++++ very intense.

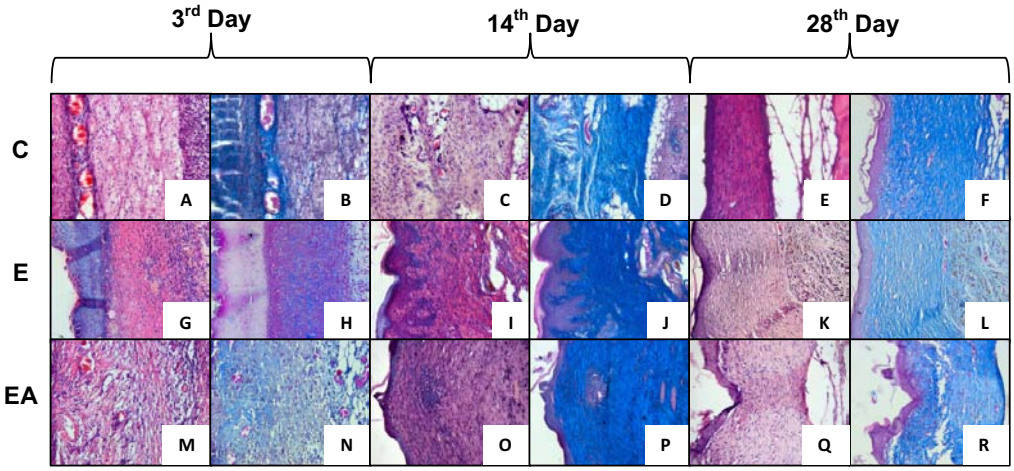

FIGURE 4 - Photomicrographs of the skin of rats not treated and treated with soft lotion O/W emulsion containing or not allantoin in the times of 3rd (A, B, G, H, M, N), 14th (C, D, I, J, O, P) and 28th (E, F, K, L, Q, R) day. Hematoxilina - Eosine (A, C, E, G, I, K, M, O, Q) and Masson's Tricromic (B, D, F, H, J, L, N, P, R).

Quantitative analysis

The inflammatory process (Figure 5A) analyzed by counting the cell number in the injured tissue were similar between the C and EA groups, although the C group presented the more intense inflammatory process. On the other hand, the E group demonstrated an inflammatory peak on the 7th day, which differentiated this group among the others. The processes of synthesis, degradation and remodeling of collagen (Figure 5B) analyzed by the determination of the collagen occupied area were similar in all groups studied (C, E and EA), although, as previously described, with variable intensities. In the untreated group (C) the inflammatory profile was characterized by a high amount of inflammatory cells on 3rd, 7th, 14th and 21st, falling on the 28th day (Figure 5A). The EA group demonstrated the best wound healing activity, because the allantoin incorporated into emulsion induced a reduction of inflammatory cells on the 7th day, in contrast with the inflammatory peak of the control groups and mainly due to the significant reduction of inflammatory cell number on the 21st day (Figure 5A).

Moreover, the results about collagen content demonstrated that it increased after the 3rd post-operative day and remained in a constant level after 14th day. The collagen deposition, mainly after the 14th day, was higher in the EA group on the qualitative analysis, although significant differences were not observed (Figure 5B).

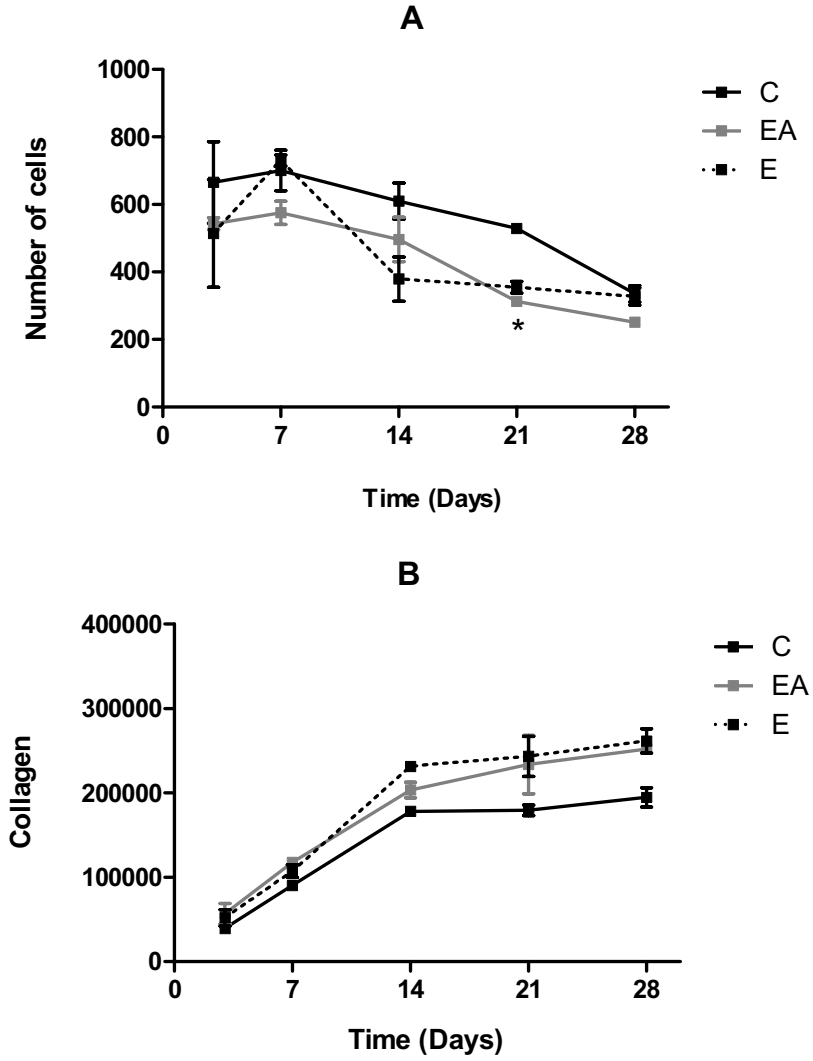

FIGURE 5 - Kinetics of inflammatory process (**A**) and collagen neoformation (**B**) in the rat's skin not treated (**C**) and treated with soft lotion O/W emulsion containing (**EA**) or not (**E**) allantoin. Results were expressed as mean ± S.E.M. (*p ≤ 0.05).

Discussion

Planimetric analysis

In 1910 Alexis Carrel introduced the use of measurement of changes on surface area, as an index of the frequency of wound contraction[14] and since that time, countless works have used this method in studies of wound healing[15,16]. However, in this work, only the planimetric analysis did not allow the identification of significant differences of the wound contraction profiles, regardless of pharmacological treatment used (Figure 2). As previously described, there was a significant increase only in the wound size on the 3rd post-operative day for the EA group. According to Cross *et al.*[14] and Teo and Naylor[17] the increase of the initial wound area occurs because of the centrifugal retraction of the wound edges and due to the tension of the surrounding elastic skin, loss of adherence to deep fascia and mobility of mouse skin. So, qualitative and quantitative microscopic analyses were carried out to identify the effective pharmacological response of allantoin and elucidate its wound healing action mechanism.

Histological analysis

For the histological analysis of tissue, several types of stain are employed. In this work, Hematoxylin-Eosin (HE), for general morphological analysis of tissues and Masson's Trichrome (TM), for observation of the connective tissue, were used in qualitative and quantitative analysis.

The Figure 2 shows the histological healing profile induced by allantoin, when compared to control groups. The histological profile observed on the 3rd post-operative day in the three groups studied (C, E and EA) was similar to the one observed by Simoes *et al.*[18] and Grillo *et al.*[19] in a wound healing study in pigs where a small, but measurable collagen amount was present in the wound on the 3rd and 4th days of analysis. This histological profile is characteristic of the initial phase of the wound healing process, when micro-circulatory and cell changes occur, presenting vasodilatation, increase of vascular permeability, edema and neutrophils and monocytes migration[1,18,20,21]. During this stage of wound healing some characteristics of the proliferation phase can also be observed, such as presence of fibroblasts and endothelial cells that produce the granulation tissue[1,22]. Additionally, the fibrin-leukocyte crusts were present in greater length in the wounds on the 7th day in all groups studied. This histological profile is characteristic of the two initial phases of the wound healing process, when vasodilatation, inflammatory exudates, many inflammatory cells, angiogenesis, fibroblasts and increased collagen deposition are usually observed. On the other hand, it was also already possible to identify on this 7th day, elements of the last phase of this process, characterized by synthesis, degradation and reorganization of collagen by fibroblasts. On the 14th day the healing process was advanced presenting reduction of the inflammatory process, reepithelization of the tissues and collagen deposition presenting more differentiate fibers. Sanchez Neto *et al.*[23] observed a high concentration of polymorphonuclear cells (PMN) by the initial phase of the process, after which it decreased gradually, fact that was also observed in the present work. These events were characteristic of the maturation phase of the wound healing process, where the synthesis, degradation and reorganization of collagen by fibroblasts promote scar formation as the final result. Finally, on the 21st and 28th days, typical characteristics of a remodeling phase of the wound healing process were observed.

The inflammatory response is an important step of the wound healing process as it prepares the environment of the wound for the process of repairing. However, this stage should not be very intense, because an excessive inflammatory response can cause delay in wound healing, in addition of favoring the disturbance of balance between synthesis and degradation of collagen and promoting degradation of the matrix[24].

Our results suggest that the allantoin modulates the inflammatory response (Figures 4 and 5A), possibly by inhibiting the chemotaxis of inflammatory cells in the site of the wound, thus preventing the release of reactive species responsible for the oxidative stress and tissue damage as proposed by Bradbury *et al.*[25] in a study of pathogenesis of vascular diseases. On the other hand, the well formed collagen fibers observed in EA group by qualitative analysis could support the allantoin effectiveness in fibroblastic proliferation and synthesis of extracellular matrix during wound healing. The processes of synthesis, degradation and remodeling of collagen remained at a constant level after the 14th day post-operative in all groups, which may indicate that during this period there was a quantitative and qualitative protein balance due to the dual function of fibroblast, synthesis and reabsorption of collagen (Figure 5B).

Normally, the pharmaceutical formulations containing allantoin (Septalan®, Alphosyl lotion®) use the concentration around 2%. In this work, the concentration of 5%, was used aiming to ensure its effectiveness as wound healing, since allantoin is normally linked to other active substances in the commercial formulations and here it was used alone. The results showed that allantoin at 5% in soft lotion O/W emulsion has a wound healing effect when compared with the controls groups, however it is not as intense as described in literature. It must be remembered that, despite of extensive use in pharmaceutical and cosmetic preparations and the multiple bibliographic citations that refer to allantoin wound healing properties[6,7], none of these studies showed, so far, the allantoin histological profile of the wound healing or its action mechanism. This work innovates by demonstrating, qualitatively and quantitatively (by morphometric analysis), the histological profile of wound healing process induced by allantoin.

Conclusion

This work show, for the first time, the histological wound healing profile induced by allantoin in rats, and demonstrated that it is able to ameliorate and fasten the reestablishment of the normal skin.

References

1.Mondolin M, Bevilacqua RG. Cicatrização das feridas. Síntese das aquisições recentes. Rev Bras Clin Terap. 1985;14:208-13.

2.Gillitzer R, Goebeler M. Chemokines in cutaneous wound healing. J Leukoc Biol. 2001;69:513-21.

3. Martin P. Wound healing – aiming for perfect skin regeneration. Science. 1997;276:75-81.

4. Singer AJ, Clark RAF. Cutaneous wound healing. N Engl J Med. 1999;341(10):738-46.

5. Rahban SR, Garner WL. Fibroproliferative scars. Clin Plast Surg. 2003;30(1):77-89.

6. Saito ML, Oliveira F. Confrei: virtudes e problemas. Rev Bras Farmacogn. 1986;1:74-85.

7. Oliveira SM, Silva JBP, Hernandes MZ, Lima MCA, Galdino SL, Pitta IR. Structure, reactivity, and biological properties of hidantoines. Quim Nova. 2008;31(3):614-22.

8. Loots JM, Loots GP, Joubert WS. The effect of allantoin on cellular multiplication in degenerating and regeneration nerves. S Afr Med J. 1979;55(2):53-6.

9. Shestopalov AV, Shkurat TP, Mikashinovich ZI, Kryzhanovskaya IO, Bogacheva MA, Lomteva SV, Prokofev VN, Guskov EP. Biological functions of allantoin. Biol Bull. 2006;33:437-40.

10. Veraldi S, Menter A, Innocenti M. Treatment of mild to moderate seborrhoeic dermatitis with MAS064D (Sebclair), a novel topical medical device: results of a pilot, randomized, double-blind, controlled trial. J Eur Acad Dermatol Venereol. 2008;22(3):290-6.

11. European Medicines Agency. The European Agency for the Evaluation of Medical Products. Committee for Veterinary Medicinal Products. Allantoin. October, 2001.

12. Sekine T, Kojima K, Ota T, Matsumoto T, Yamamoto T, Maitani Y, Nagai T. Preparation and evaluation of shikonin ointment for wound healing. Effectiveness in an experimental wound healing model in rats. Pharma Sci. 1998;8:249-53.

13. Agren MS, Mertz PM, Franzén L. A comparative study of three occlusive dressing in the treatment of full-thickness wounds in pigs. J Am Acad Dermatol. 1997;36:53-8.

14. Cross SE, Naylor IL, Coleman RA, Teo TC. An experimental model to investigate the dynamics of wound contraction. Br J Plast Surg. 1995;48(4):189-97.

15. Branco-Neto MLC, Ribas-Filho JM, Malafaia O, Oliveira-Filho MA, Czeczko NG, Aoki S, Cunha R, Fonseca VR, Teixeira HM, Aguiar LRF. Avaliação do extrato hidroalcoólico de Aroeira (*Schinus terebinthifolius Raddi*) no processo de cicatrização de feridas em pele de ratos. Acta Cir Bras. 2006;21(2):17-22.

16. Garros IC, Campos ACL, Tâmbara EM, Tenório SB, Torres OJM, Agulham MA, Araújo ACF, Santis-Isolan PMB, Oliveira RM, Arruda ECM. Extract from *Passiflora edulis* on the healing of open wounds in rats: morphometric and histological study. Acta Cir Bras. 2006;21(3):55-65.

17. Teo TC, Naylor IL. Modifications to the rate of wound contraction by allopurinol. Br J Plast Surg. 1995;48(4):198-202.

18. Simões MJ, Cabral ACV, Boyaciyan K, Kulay JR, Sasso WS. Aspectos ultra-estruturais dos fibroblastos e dos macrófagos durante o processo de reparação da pele de ratos. Rev Paul Med. 1986;104:132-5.

19. Grillo HC, Watts GT, Gross J. Studies in wound healing: contraction and the wound contents. Ann Surg. 1958;148(2):143-52.

20. Kiritsy CP, Lynch AB, Lynch SE. Role of growth factors in cutaneous wound healing: a review. Crit Rev Oral Biol Med. 1993;4(5):729-60.

21. Rappolee DA, Patel Y, Jacobson K. Expression of fibroblast growth factor receptors in peri-implantation mouse embryos. Mol Reprod Dev. 1998;51(3):254–64.

22. Witte MB, Barbul A. General principles of wound healing. Surg Clin North Am. 1997;77(3):509-28.

23. Sanchez Neto R, Barone B, Tevês DC, Simões MJ, Novo NF, Juliano Y. Aspectos morfológicos e morfométricos da reparação tecidual de feridas cutâneas em ratos com e sem tratamento com solução de papaína a 2%. Acta Cir Bras. 1993;8(1):18-23.

24. Ashcroft GS, Mills SJ, Ashworth JJ. Ageing and wound healing. Biogerontology. 2002;3:337-45.

25. Bradbury AW, Murie JA, Rucley CV. Role of the leucocyte in the pathogenesis of vascular disease. Br J Surg. 1993;80(12):1503-12.

Acknowledgment

We are grateful to the scholarship afforded by Ouro Preto Federal University (UFOP) to the first author.

Conflict of interest: none
Financial source: FAPEMIG

Correspondence:
Neila Márcia Silva Barcellos
Rua Costa Sena, 171
35400-000 Ouro Preto - MG Brasil
Phone: (55 31)3559-1040
neila@ef.ufop.br

Received: February 10, 2010
Review: April 14, 2010
Accepted: May 11, 2010

How to cite this article
Araújo LU, Grabe-Guimarães A, Mosqueira VCF, Carneiro CM, Silva-Barcellos NM. Profile of wound healing process induced by allantoin. Acta Cir Bras. [serial on the Internet] 2010 Sept-Oct;25(5). Available from URL: http://www.scielo.br/acb

***Color figures available from www.scielo.br/acb**

NATURAL MEDICINE JOURNAL
January 16, 2014

Aloe Vera Gel Research Review

An overview of its clinical uses and proposed mechanisms of action

Oliver Grundmann

BPharm,ms,PHD

Abstract

Aloe vera, commonly known as Barbados or Curaçao Aloe, is an herbal medicine with a long tradition of use by a variety of cultures. The succulent plant grows in arid and subtropical climates and is best known for 2 distinct preparations: the clear mucilaginous gel that is widely used for the treatment of minor burns, especially sunburns, and the thick sap of the leaves that turns yellow-brown and has strong laxative effects that caution its use. The traditional uses of the clear mucilaginous gel are manifold, ranging from topical applications to reduce perspiration to oral dosing for diabetes and a range of gastrointestinal ailments. The efficacy of aloe vera gel to treat burn wounds, genital herpes, and seborrheic dermatitis have been shown in clinical trials, but other indications such as psoriasis or internal application for the treatment of type 2 diabetes remain inconclusive. The main limitation of the current clinical knowledge about aloe vera gel is small clinical studies that often lack rigorous methodology. Several clinical trials are being conducted to further evaluate the use of aloe vera gel for a variety of disorders, as well as to further confirm traditional uses of the plant extract.

Introduction

Aloe vera (syn. *Aloe barbadensis* Mill., Fam. Liliaceae), also known as Barbados or Curaçao Aloe, has been used in traditional and folk medicines for thousands of years to treat and cure a variety of diseases. Although the plant is native to

northern parts of Africa, it has rapidly spread across the world because its cultivation is easy. An important distinction has to be made between the strongly laxative and purgative latex derived from the bundle-sheath cells and the clear mucilaginous gel. The plant has been used by Egyptians, Assyrians, and Mediterranean civilizations, as well as in Biblical times. A variety of aloe species are still used in folk medicines of Africa and Asia. Hunters in the Congo reportedly rub their bodies in the clear mucilaginous gel to reduce perspiration; some African tribes apply the gel for chronic conjunctivitis; the gel is used in India for the treatment of asthma.[1]

Aloe vera gel is used as an ethnomedicine in Trinidad and Tobago for hypertension.[2] The most common folk use of aloe has been for the treatment of burn wounds and specifically to aid in the healing process, reduce inflammation, and tissue scaring. The gel was described by Dioscorides and used to treat wounds and mouth infections, soothe itching, and cure sores.[3] The use of aloe vera gel as a household remedy in the United States was triggered by reports of its beneficial effect on radiation dermatitis[4] followed by a boom in cultivation in the 1930s; it remains a common plant and for burns and abrasions.[1,5] Important contemporary uses of the gel exist in traditional medicines of India, China, and Mexico, as well as Middle America and the West Indies. Mexico is producing roughly 47% of aloe worldwide with a total sales volume of $123.5 million US dollars as of 2008.[6]

Despite its widespread popularity, scientific evidence on the aloe vera gel remains sparse. Aloe vera gel is regarded as safe if applied topical with only a few allergic reactions being reported.[7] The efficacy of aloe vera gel to treat burn wounds, genital herpes, and seborrheic dermatitis have been shown in clinical trials, but other indications such as psoriasis or internal application for the treatment of type 2 diabetes remain inconclusive. The major application of aloe vera gel remains as a skin moisturizer in cosmetics and as an après treatment for sunburns, for which it has proven its effectiveness.[8,9]

Description

Aloe vera is a succulent plant with thick, fleshy, serrated, lanceolate-shaped leaves of green-greyish color. Aloe vera inner gel is obtained from the lower leaves of the plant by slicing the leaf open. The gel is clear, odorless, and tasteless and should be free of leaf skin or yellow parts. No consistent standardization has been established, but the International Aloe Science

Council (IASC), a trade association of internationally based aloe producers and marketers, requires adherence to certain specifications for the product to be certified.[10] Other preparations include a hydrophilic cream containing 0.5% aloe vera gel and an emulsion consisting of 30% aloe vera gel.

Primary Uses

(determined by clinical trials)

External

- Mild to moderate burns[11–13] as well as erythema[14]
- Genital herpes[15,16]
- Seborrheic dermatitis[17]

Internal

- Adjunct therapy of spontaneous fibrosarcomas in dogs and cats[18,19]

Other Potential Uses

(determined by clinical trials and/or official monographs and/or empirical use)

- Psoriasis vulgaris[20]
- Skin moisturizer[8]
- Type 2 diabetes[21–23]
- Malignancies and immunodeficiency viruses in cats[24,25]
- Oral lichen planus infections[26,27]
- Angina pectoris[23]
- Ulcerative colitis[28–31]
- UV-induced erythema14 Kidney stones[32,33]
- Alveolar osteitis[34]

Dosage

External

- For burns: Clear mucilaginous gel (pure aloe vera inner gel or preparations containing 10%–70% aloe inner gel). Gel must be

stabilized by pasteurization at 75–80°C for less than 3 minutes[3] and applied on affected area 3 times daily.
- For seborrheic dermatitis: 30% aloe vera in a hydrophilic emulsion twice daily to affected area[17]
- For psoriasis and genital herpes: Hydrophilic cream containing 0.5% aloe gel 3 times daily to affected area[16,20]

Internal

- Treatment of diabetes and angina pectoris: recommended in humans, 100 mg of fresh inner gel each day or 1 tablespoon twice daily.[23,35]
- For ulcerative colitis and irritable bowel syndrome: a dose of 25–50 ml of 95% aloe inner gel is recommended 3 times daily.[28]
- Adjuvant therapy in feline and canine malignancies: Acemannan Immunostimulant®, a special preparation of the clear mucilaginous gel specifically for injection, for intraperitoneal injection in cats and dogs following chemotherapy. Weekly injections over at least 6 weeks; recommended dose is 1 mg/kg body weight of animal.[18,19]

Duration of Administration

External administration 3–4 times daily to affected area until improvement is seen.[15,17,20] No information for duration after oral application in humans is available, but generally the gel is taken as long as the symptoms persist.[23]

Chemistry

The fresh gel mainly consists of water (99.1%) and mesophyll cells (0.9% dry matter), which can be divided into 3 distinct fractions: cell wall, microparticles, and liquid gel [accounting for 16.2%, 0.7%, and 83.1% of dry pulp (w/w), respectively]. The predominant sugar component is mannose as mannose-6-phosphate[36] in all 3 fractions [20.4% in cell wall, 32.2% in microparticles, and 62.9% in the liquid gel (% of total sugars)], followed by other sugars in varying concentrations depending on the fraction. Overall, the 5 neutral sugars (ie, arabinose, xylose, mannose, galactose, glucose) account for 69.2% of the total sugars in the gel.[37] Mucopolysaccharides are mainly present as acemannan [a highly acetylated, β-1-4-linked polysaccharide (> 1kDa) made mainly of mannose] with various side chain glycosylation patterns.[38] The anthraquinone content should be below 50 ppm and is

considered an impurity from the leaf extract of aloe vera.[7] Other ingredients include various amino acids, enzymes, and vitamins, which have not been quantified. The IASC maintains a certification program, in which "whole aloe vera leaf gel" has to adhere to the following specifications: solids (0.46%–1.31%); pH (3.5–4.7); calcium (98.2–448 mg/L); magnesium (23.4–118 mg/L; malic acid (817.8–3,427.8 mg/L); acemannan in raw materials (≥5% by dry weight); isocitrate (≤5% for inner leaf by dry weight); raw materials ash content (≤40%); aloin (≤10 ppm in 0.5% aloe vera solids solution for oral consumption). Quality products should contain high amounts (95%) of pure aloe vera gel.[39] One way of quantifying aloe polysaccharides is a colorimetric assay, which has been suggested for use in quality control of commercial products.[40] Quality control and identification of commercial aloe vera products has also been accomplished by nuclear magnetic resonance spectrometry.[41]

Pharmacological Actions

Note: Information on the precise chemical composition of the aloe vera inner gel used for most of the below listed observed pharmacological activities is lacking. Therefore, results should be interpreted with caution in regard to reproducibility of the stated effect.

Human

Mild (first degree) to moderate (second degree) burn wounds;[11–13,42] genital herpes at first onset;[16,20] seborrheic dermatitis;[17] oral lichen planus infections;[26] postdermabrasion wound healing;[43] normalization of gastric pH;[44] treatment of diabetes and angina pectoris.[23]

Animal

Acceleration of wound healing in mice and rats;[36,45–47] reduction of radiation-induced skin reactions in irradiated mice and rats;[48–50] prevention of progressive dermal ischaemia caused by burns and frostbite in rats and guinea pigs; [51–53] antidiabetic in type-2 diabetic and insulin-resistant mice;[21,54–57] chemopreventive in skin papillomagenesis in mice;[58,59] anti-inflammatory in mice;[36,60–64] enhancement of immune responsiveness in chicks and mice;[65,66] amelioration of UV-induced immune suppression in mice;[67] promotion of gastric ulcer healing in rats;[68,69] protection of alcohol dehydrogenase and reduction of blood ethanol concentrations in

rats;[70] reduction of salmonella-mediated inflammation in mice;[71] antioxidant and cholesterol-lowering effects in aged rats.[72]

In vitro

Inhibits collagenase and metalloproteinase activity in *Clostridium histolyticum*;[73] exerts cytotoxic effects in normal and malignant tissues;[74] suppresses bactericidal inflammation in human leukocytes;[75,76] causes antioxidant activities and enhanced phagocytosis in human neutrophils;[77-79] cell wall material stabilizes growth factors;[80] inhibits pro-inflammatory cytokines;[81-83] acemannan enhances T cell response through monocyte activation;[84,85] induces hematopoietic and hematologic activity of carbohydrate fraction;[86] acts as antifungal;[87,88] stimulates cell proliferation in keratinocytes by glycoprotein fraction;[47] accelerates wound healing in diabetic human skin fibroblasts;[89] di(2-ethylhexyl)phthalate isolated from aloe vera leaves exerts antitumor activity;[90] Aloe vera gel fraction on calf pulmonary artery endothelial cells has angiogenic activity.[91]

Proposed Mechanisms of Action

- Stimulation of macrophage and fibroblast activity, increased collagen and proteoglycan synthesis[36,62,85]
- Mannose-6-phosphate binds to growth factor receptor on fibroblasts and enhances their activity[36,92]
- Macrophage activation through increased nitric oxide synthase activity by acemannan, leading to release of fibrogenic cytokines[49,93,94]
- Upregulation of phagocytosis and fungicidal activity of macrophages by acemannan[95]
- Acemannan and other cell wall biomaterial may promote stability of growth factors and prolong stimulation of granulation tissue[48,80]
- Inhibition of Thromboxan A_2[36,53]
- May promote hypoglycemic effect by normalizing membrane-bound enzyme activities of phosphatases and hydrolases and increased glucose metabolism;[55,56] potential active compounds include the phytosterols lophenol, cycloartenol and their alkylated derivatives[21]
- Anti-inflammatory effect of plant sterols like lupeol, campesterol, and β-sitosterol[92] through bradikinase activation,[61] prostaglandin F2 and E2, as well as thromboxane A2 inhibition[45,81,96] and inhibition of IL-10 secretion[83]

- Inhibitory effect on release of reactive oxygen species from human neutrophils by reducing intracellular free calcium levels[77]
- Increase in mRNA expression of metalloproteinases and plasminogen activator may lead to angiogenic activity in endothelial cells[91]

Contradictions

Known allergy against aloe vera; discontinue use if skin irritation develops or worsens[97]

Pregnancy and Lactation

It is not recommended to use aloe vera gel during pregnancy or while breastfeeding.[7] There is, however, no evidence that suggests a reproductive or genotoxic effect of topical aloe vera inner gel preparations. Internal use in combination with digoxin is contraindicated due to possible acceleration of potassium depletion.[98]

Adverse Effects

In general, topical application of aloe vera preparations has been regarded as safe as assessed by the Cosmetic Ingredient Review Expert Panel.[7] However, several case reports of the development of hypersensitivity reactions and contact dermatitis in response to topically applied aloe gel preparations have been published.[99–103] This allergic reaction has been attributed in most cases to anthraquinone contaminations in the gel.[97] Macrophage infiltration and emesis has been observed in dogs treated intravenously with acemannan.[104] Oral application of aloe vera gel may lower blood glucose levels and enhance the activity of antidiabetic treatments.[23] No genotoxic effects have been observed following oral administration of an aloe vera inner leaf gel (Qmatrix® by Aloecorp, Inc., which is a standardized inner gel extract that has not been heated after extraction from the leaf) to rats after 90 days.[105] An important factor for adverse effects is the purity of the aloe vera gel used, since anthraquinones like aloin might be related to the development of hypersensitivity reactions.[99,106]

Drug Interactions

When aloe vera gel is administered topical, it is generally regarded as safe.[7] Aloe gel might enhance the ability of hydrocortisone to reduce swelling if applied topically.[107] If ingested, it might lead to increased hypoglycemia in conjunction with oral antidiabetics or insulin.[97] The American Pharmaceutical Association rates aloe vera gel for external use in category 2, meaning that "according to a number of well-designed studies and common use, this substance appears to be relatively effective and safe when used in recommended amounts."[39] Aloe vera inner gel may significantly increase the absorption of vitamins C and E after oral application.[108] Aloe vera gel for systemic application is not recommended in combination with antidiabetic, diuretic, or laxative drugs; sevoflurane; or digoxin.[107] In general, a 2-hour time period is recommended between oral drug application and aloe vera ingestion due to increased intestinal motility and reduced drug absorption.[98] If aloe vera gel is used with any other prescription drug, the patient should inform the physician and/or pharmacist.

Clinical Review

Clinical data on aloe vera gel is sparse, which might be in part due to the many possible indications for the gel. The table outlines 18 clinical trials on a total of 7,297 subjects conducted for various types of aloe gel-derived preparations on numerous indications. The design of the clinical studies evaluated ranges from placebo-controlled, double-blind, multicenter studies to equivalence investigations. One of the most important factors is the composition of the aloe vera preparation used, which in most cases is a certain purity aloe vera gel without further elucidation of compound quantity. This discrepancy complicates a direct comparison of the studies.

Three randomized studies on the efficacy of aloe vera gel for radiation-induced dermatitis[109–111] reported either a delayed onset of skin changes if aloe vera gel was applied in addition to mild soap against mild soap alone[111] or no efficacy of the gel against a placebo gel or aqueous cream.[109,110] A review of aloe vera for radiation-induced skin damage concluded that there is no evidence for a protective effect of the gel and that more research with well-designed studies is needed to evaluate potential benefits.[112] Similar results were obtained from a clinical study evaluating the use of aloe vera gel for the treatment of radiation-induced oral mucositis with no significant differences from the placebo group.[113]

The historical application of aloe vera gel for the treatment of wounds has been evaluated in surgical wounds and the randomized study concluded that there was a significant delay in complete wound healing for the aloe vera gel compared to standard treatment.[114]

The use of aloe vera gel for the treatment of lichen planus lesions was examined in 2 clinical trials with small sample sizes. One study examined the use of aloe vera gel (containing 70% mucilage) in oral lichen planus lesions compared to placebo over 8 weeks and found a significant improvement in 88% of patients versus 4% in the placebo group.[26] Another study used a similar design but with unspecified composition of the aloe vera gel and reported significant improvement in 82% of patients versus 5% in the placebo group over a period of 8 weeks.[115]

Three clinical trials on the effect of aloe vera gel for the treatment of psoriasis vulgaris were inconclusive. One study reported a significant beneficial effect of aloe vera extract 0.5% in hydrophilic cream compared to hydrophilic cream alone in reducing psoriatic plaques and inflammation,[20] while the other study did not find a significant benefit of 98% pure aloe vera gel versus placebo after 12 weeks.[116] A third study compared aloe vera cream containing 70% mucilage to 0.1% triamcinolone acetonide cream over the course of 8 weeks and found it to be equally effective.[117]

One study evaluated the effect of aloe vera 0.5% in hydrophilic cream and aloe vera gel versus placebo for the treatment of genital herpes[15] and concluded that aloe vera in hydrophilic cream is more effective than aloe vera gel, but that both resulted in faster healing times compared to placebo.

An aloe vera emulsion showed significant benefits for the treatment of seborrheic dermatitis in a double-blind, randomized study compared to placebo,[17] but the placebo formulation was different from the base used for the emulsion.

A randomized, double-blind clinical trial evaluated the effectiveness of a prepared 70% aloe vera gel for the treatment of oral lichen planus infections compared to the base gel alone and reported a significant improvement of symptoms in the aloe vera group.[26]

The use of aloe vera gel in the traditional medicine of India has triggered an observational, inter-patient control study using fresh aloe vera inner gel in

addition to adding psyllium (*Plantago ason*, Plantaginaceae) seeds to the daily diet of 5,000 patients diagnosed with angina pectoris. Over the course of 5 years, patients were observed and blood cholesterol, glucose, and triglyceride levels evaluated. A cofounding variable was the influence of aloe vera gel on diabetes mellitus. Aloe vera gel had a significant influence on normalizing blood parameters and relief of angina pectoris symptoms, as well as diabetic symptoms.[23] In many patients, the continued use of aloe vera gel daily led to the discontinuation of prescription medications. An important drawback of the study is the absence of a control group and no chemical definition of the aloe vera gel used in the study.

The widespread use of aloe vera gel as moisturizer and for the treatment of xerosis was evaluated in two studies.[8,118] The moisturizing effects of aloe vera resulted in increased water content in the stratum corneum after short-term and long-term application of a hydrophilic cream containing various concentrations of freeze-dried aloe vera concentrate compared to the base cream alone.[8] A partially blinded, non-placebo study suggests a benefit of freeze-dried aloe vera gel on the inner side of a glove to dry skin, although this study lacks both control and complete blinding.[118]

In addition, aloe vera gel lotions are popular for the treatment of sunburn (UV-induced erythema). One randomized, double-blind, placebo-controlled trial compared the anti-inflammatory effect of 97.5% pure aloe vera gel to 1% hydrocortisone and a placebo gel. Aloe vera gel, if applied under an occlusive bandage for 2 days following UV exposure, significantly reduced inflammation compared to placebo gel or 1% hydrocortisone in placebo gel, but was less effective than 1% hydrocortisone cream. The authors suggest that aloe vera gel might be useful for the treatment of inflammatory skin conditions.[14]

Two studies evaluated beneficial effects of aloe vera gel on irritable bowel syndrome[30] and ulcerative colitis,[28] which resulted in no significant effect for either indication, although a patient-evaluated improvement was seen for the treatment of ulcerative colitis after 1 month.

Based on its immunomodulatory effect, acemannan was evaluated for the adjunct treatment of HIV infections in addition to standard treatment (either zidovudine or didanosine).[119] The one-year, double-blind, placebo-controlled, randomized trial concluded that there were no differences in CD4 count or survival after 48 weeks between acemannan capsules and placebo.

A non-controlled trial reported a positive influence of nutritional dietary supplements partially containing aloe vera on fibromyalgia and chronic fatigue syndrome, but failed to differentiate between the various supplements.

Since acemannan has been shown to stimulate macrophage activation and enhances wound healing, 1 study evaluated the use of acemannan hydrogel in a patch for the treatment of alveolar osteitis after oral surgery.[34] Acemannan significantly reduced the incidence and severity of the inflammatory process compared to clindamycin Gelfoam patches. Although the study lacks a complete clinical design, the comparison between the treatment groups showed an impressive advantage of acemannan in the prevention of alveolar osteitis in a large patient collective (n=1,194).

One randomized, double-blind, placebo-controlled study investigated the use of aloe vera inner leaf gel for its anti-hyperglycemic and anti-hypercholesteremic effects in a small study population and found a slight decrease in fasting blood glucose, HbA_{1C}, total cholesterol, and LDL levels, although this may be attributed to a restricted diet that patients in both groups were prescribed.[120]

Two promising clinical trials with fresh aloe vera gel in healthy adult[33] and pediatric[32] volunteers showed increased calcium and oxalate urinary secretions, which might confirm the traditional use of aloe vera gel in the treatment of kidney stones.[1] However, confirmation through clinical studies for this indication in patients suffering from kidney stones is lacking to date.

A non-controlled trial reported a positive influence of nutritional dietary supplements partially containing aloe vera on fibromyalgia and chronic fatigue syndrome, but failed to differentiate between the various supplements.[121]

Conclusions

In conclusion, the use of aloe vera gel or its components for the treatment of a variety of conditions and diseases needs further clinical evidence through well-designed studies with defined aloe extracts and matching placebo controls. Currently (June 2012), 5 national and international clinical studies are listed by the United States National Institutes of Health clinical trial database with a major emphasis on the use of aloe vera in the treatment of wounds.[122] This indicates the scientific significance of aloe vera gel and the

need to establish it as a valid treatment option for wounds. However, the use of aloe vera gel in topical applications has widely been confirmed in the clinical studies as safe.

Clinical Studies on Aloe vera (*Aloe barbadensis* Mill.) Inner Gel

External Applications* of Aloe Vera Formulations					
Author/Year	Subject	Design	Duration	Dosage	Pre
Syed et al, 1996	Genital herpes	R, DB, PC, PG, N=120	2 weeks	3x/day to herpetic lesions, max. 30 applications	Alo hyd gel
Choonhakarn et al, 2009	Lichen planus	R, DB, PC, SC, N=54	8 weeks	2x/day to erosive and ulcerative lesions	Alo (co alo
Rajar et al, 2008	Lichen planus	R, DB, PC, SC, N=34	8 weeks	2x/day to erosive and ulcerative lesions	Alo fur
Syed et al, 1996	Psoriasis vulgaris	R, PC, PG, N=60	4 weeks	3x/day to lesions, max. 15 applications per week	Alo hyd

Paulsen et al, 2005	Psoriasis vulgaris	DB, R, PC, SC, IC, N=40	4 weeks	2x/day to left or right arm, treatment with emollients and Vaseline allowed	AC ver Søl wit
Choonhakarn et al, 2010	Psoriasis vulgaris	DB, R, SC, N=80	8 weeks	2x/day to affected area, no other treatment allowed	Alc (co alo cor tria ace
Reuter et al, 2008	UV-induced erythema	R, DB, PC, SC, N=40	2 days	Occlusive bandage for 2 days	97. cor pre hyc pla hyc &
Vardy et al, 1999	Seborrheic dermatitis	DB, R, PC, N=44	4-6 weeks	2x/day to affected areas	Alc cru def bas
Heggie et al, 1998	Radiation-induced dermatitis	R, DB, PC, MC, N=208	Duration of radiation treatment & 2 weeks post-treatment	3x/day to affected area	98% aqu pla
Olsen et al, 2001	Radiation-induced dermatitis	R, SB, SC, N=70	Duration of radiation treatment	6-8x/day to irradiated area	100 (Fr add or pat pre pro

Williams et al, 1996	Radiation-induced dermatitis	R, DB, PC, N=191	Duration of radiation treatment	2x/day to irradiated area	98 gel gel hyd
Schmidt et al, 1991	Surgical wounds	R, SC, N=21	Time to complete healing	Initially change of wound dressing every 8 hours until granulation tissue established, thereafter every 12 hours	Ca wo tre
Poor et al, 2002	Alveolar osteitis	R, N=1,194	7 days post-surgery	SaliCept Patch® applied to surgery site	Sal cor hyd cli cor ant wa
West et al, 2003	Xerosis	PB, SC, N=29	30 days, 30 days rest, 10 days	Wearing glove with aloe gel for 8h/day	Alo wit fre wh gel ski pla
Dal'Belo et al, 2006	Moisturizer	R, SB, PC, N=20	Short-term (0-3h) & long-term (2 weeks)	Single application & 2x/day for 2 weeks	0.1 of cor AC GE hyd
Internal Applications+ of Aloe Vera Formulations					

Author/Year	Subject	Design	Duration	Dosage	Pre
Davis et al, 2006	Irritable Bowel Syndrome	R, DB, PC, N=41	1 month	4x/day 50 ml	Alo Liv for
Langmead et al, 2004	Ulcerative colitis	R, DB, PC, N=44	1 month	2x/day 100 ml	Alo Liv for
Montaner et al, 1996	HIV infection	R, DB, PC, MC, N=63	48 weeks	4x/day capsules	100 cap pla
Choonhakarn et al, 2008	Oral lichen planus infections	R, DB, PC, N=54	8 weeks	2x/day to affected area	70% hyd gel cor
Su et al, 2004	Radiation-induced mucositis	R, DB, SC, PC, N=58	Duration of radiation treatment & 6 weeks post-treatment	4x/day 20 ml p.o.	Lil 94.
Huseini et al, 2012	Hypercholesteremia and diabetes	R, SC, DB, PC, IC, N=60	8 weeks	2x/day 300 mg aloe powder, restricted diet	Fre inn aft and and ace by
Agarwal, 1985	Angina pectoris and diabetes	IC, R, N=5,000	5 years	100mg fresh inner gel in combination with bread containing seeds from *Plantago ovata*	Fre fro che

** Please note: in most external studies, the exact amount for topical application was not defined. It is assumed that the amount is equal to what would be applied as a standard topical cream about 1/8 inch thick to the affected area.*

+ Please note: for oral application of the inner gel the exact dose equivalent of mucopolysaccharides was not provided. In many studies it is assumed that the dose corresponds to fresh Aloe inner leaf gel, the composition of which is described in the section "chemistry" above. There is significant variation among products and therefore the instructions of the manufacturer should be followed.

Abbreviation Key: IC – interpatient control, PB – partially blinded, SC – single-center, MC – multi-center, R – randomized, DB – double-blinded, PC – placebo-controlled, SB – single-blinded, PG – parallel group

Categorized Under

- PEER-REVIEWED ARTICLES

Oliver Grundmann

BPharm,ms,PHD

Oliver Grundmann, BPharm, MS, PhD, is a clinical assistant professor at the University of Florida in the Department of Medicinal Chemistry, College of Pharmacy, and assistant professor in the Department of Adult and Elderly Nursing, College of Nursing, as well as adjunct assistant professor at

Midwestern University College of Pharmacy. He is involved in several collaborative research projects on natural products both in preclinical and clinical stages, especially the treatment of irritable bowel syndrome and other intestinal disorders using complementary and alternative medicine, as well as herbal medicines for the treatment of neurological disorders. He has been a fellow of the Japan Society for the Advancement of Science and the German Academic Exchange Program while studying at Tokushima University in 2006. His teaching involvement covers areas related to medicinal chemistry, natural products, forensic toxicology, and clinical toxicology, as well as general pharmaceutical sciences.

References

1. Morton JF. Folk uses and commercial exploitation of Aloe leaf pulp. *Economic botany.* 1961;15(4):311-19.
2. Lans CA. Ethnomedicines used in Trinidad and Tobago for urinary problems and diabetes mellitus. *J Ethnobiol Ethnomed.* 2006;2:45.
3. Grindlay D, Reynolds T. The Aloe vera phenomenon: a review of the properties and modern uses of the leaf parenchyma gel. *J Ethnopharmacol.* 1986;16(2-3):117-51.
4. Collins CE, Collins C. Roentgen dermatitis treated with fresh whole leaf of Aloe vera. *American Journal of Roentgenology.* 1935;33(3):396-97.
5. Halles JS. A drug for all seasons. Medical and pharmacological history of aloe. *Bull N Y Acad Med.* 1990;66(6):647-59.
6. Rodriguez S. How Large is the Aloe Market. [PowerPoint presentation]. 2008. Accessed 07/03/2008, 2008.
7. CIREP CIREP. Final Report on the Safety Assessment of Aloe Andongensis Extract, Aloe Andongensis Leaf Juice, Aloe Arborescens Leaf Extract, Aloe Arborescens Leaf Juice, Aloe Arborescens Leaf Protoplasts, Aloe Barbadensis Flower Extract, Aloe Barbadensis Leaf. *Int J Toxicol.* 2007;26:1-50.
8. Dal'Belo SE, Gaspar LR, Maia Campos PM. Moisturizing effect of cosmetic formulations containing Aloe vera extract in different concentrations assessed by skin bioengineering techniques. *Skin Res Technol.* 2006;12(4):241-46.
9. Thornfeldt C. Cosmeceuticals containing herbs: fact, fiction, and future. *Dermatol Surg.* 2005;31:873-80.
10. Diehl B, Teichmueller EE. Aloe vera, Quality inspection and identification. *Agro Food Ind Hi Tech.* 1998;9:14-6.
11. Thamlikitkul V, Bunyapraphatsara N, Riewpaiboon W, Theerapong S, Chantrakul C, Thanaveerasuwan T. Clinical trial of aloe vera Linn. for treatment of minor burns. *Siriraj Hosp*

Gaz. 1991;43(5):313-316.
12. Visuthikosol V, Chowchuen B, Sukwanarat Y, Sriurairatana S, Boonpucknavig V. Effect of aloe vera gel to healing of burn wound a clinical and histologic study. *J Med Assoc Thai.* Aug 1995;78(8):403-09.
13. Akhtar MA, Hatwar SK. Efficacy of aloe vera extract cream in management of burn wound. *J Clin Epidemiol.* 1996;49:24.
14. Reuter J, Jocher A, Stump J, Grossjohann B, Franke G, Schempp CM. Investigation of the anti-inflammatory potential of Aloe vera gel (97.5%) in the ultraviolet erythema test. *Skin Pharmacol Physiol.* 2008;21(2):106-10.
15. Syed TA, Afzal M, Ashfaq AS. Management of genital herpes in men with 0.5% Aloe vera extract in a hydrophilic cream. A placebo-controlled double-blind study. *J Derm Treatment.* 1997;8(2):99-102.
16. Syed TA, Cheeman KM, Ahmad SA, Holt AH. Aloe vera extract 0.5% in hydrophilic cream versus Aloe vera gel for the management of genital herpes in males. A placebo-controlled, doubleblind, comparative study. *J Eur Acad Dermatol Venereol.* 1996;7:294-95.
17. Vardy AD, Cohen AD, Tchetov T. A double-blind, placebo-controlled trial of Aloe vera (A. barbadensis) emulsion in the treatment of seborrheic dermatitis. *J Derm Treatment.* 1999;10(1):7-11.
18. King GK, Yates KM, Greenlee PG, et al. The effect of Acemannan Immunostimulant in combination with surgery and radiation therapy on spontaneous canine and feline fibrosarcomas. *J Am Anim Hosp Assoc.* 1995;31(5):439-47.
19. Harris C, Pierce K, King G, Yates KM, Hall J, Tizard I. Efficacy of acemannan in treatment of canine and feline spontaneous neoplasms. *Mol Biother.* 1991;3(4):207-13.
20. Syed TA, Ahmad SA, Holt AH, Ahmad SA, Ahmad SH, Afzal M. Management of psoriasis with Aloe vera extract in a hydrophilic cream: a placebo-controlled, double-blind study. *Trop Med Int Health.* 1996;1(4):505-09.
21. Tanaka M, Misawa E, Ito Y, et al. Identification of five phytosterols from Aloe vera gel as anti-diabetic compounds. *Biol Pharm Bull.* 2006;29(7):1418-22.
22. Yeh GY, Eisenberg DM, Kaptchuk TJ, Phillips RS. Systematic review of herbs and dietary supplements for glycemic control in diabetes. *Diabetes Care.* 2003;26(4):1277-94.
23. Agarwal OP. Prevention of atheromatous heart disease. *Angiology.* 1985;36(8):485-92.
24. Sheets MA, Unger BA, Giggleman GF, Jr., Tizard IR. Studies of the effect of acemannan on retrovirus infections: clinical stabilization of feline leukemia virus-infected cats. *Mol Biother.* 1991;3(1):41-5.
25. Yates KM, Rosenberg LJ, Harris CK, et al. Pilot study of the effect of acemannan in cats infected with feline immunodeficiency virus. *Vet Immunol Immunopathol.* 1992;35(1-2):177-89.
26. Choonhakarn C, Busaracome P, Sripanidkulchai B, Sarakarn P. The efficacy of aloe vera gel in the treatment of oral lichen planus: a randomized controlled trial. *Br J*

Dermatol. 2008;158(3):573-77.
27. Hayes SM. Lichen planus--report of successful treatment with aloe vera. *Gen Dent.* May-1999;47(3):268-72.
28. Langmead L, Feakins RM, Goldthorpe S, et al. Randomized, double-blind, placebo-controlled trial of oral aloe vera gel for active ulcerative colitis. *Aliment Pharmacol Ther.* 2004;19(7):739-47.
29. Blitz JJ, Smith JW, Gerard JR. Aloe vera gel in peptic ulcer therapy: preliminary report. *J Am Osteopath Assoc.* 1963;62:731-35.
30. Davis K, Philpott S, Kumar D, Mendall M. Randomised double-blind placebo-controlled trial of aloe vera for irritable bowel syndrome. *Int J Clin Pract.* 2006;60(9):1080-86.
31. Avijgan M. Phytotherapy: an alternative treatment for non-healing ulcers. *J Wound Care.* 2004;13(4):157-58.
32. Kirdpon S, Kirdpon W, Airarat W, Thepsuthammarat K, Nanakorn S. Changes in urinary compositions among children after consuming prepared oral doses of aloe (Aloe vera Linn). *J Med Assoc Thai.* 2006;89(8):1199-205.
33. Kirdpon S, Kirdpon W, Airarat W, Trevanich A, Nanakorn S. Effect of aloe (Aloe vera Linn.) on healthy adult volunteers: changes in urinary composition. *J Med Assoc Thai.* 2006;89 Suppl 2:S9-14.
34. Poor MR, Hall JE, Poor AS. Reduction in the incidence of alveolar osteitis in patients treated with the SaliCept patch, containing Acemannan hydrogel. *J Oral Maxillofac Surg.* 2002;60(4):374-79.
35. Elton B Stephens Company (EBSCO) Commodity Research Bureau (CRB). Aloe. 2008. Accessed 08/03/2008, 2008.
36. Davis RH, Donato JJ, Hartman GM, Haas RC. Anti-inflammatory and wound healing activity of a growth substance in Aloe vera. *J Am Podiatr Med Assoc.* 1994;84(2):77-81.
37. Ni Y, Turner D, Yates KM, Tizard I. Isolation and characterization of structural components of Aloe vera L. leaf pulp. *Int Immunopharmacol.* 2004;4(14):1745-55.
38. Tai-Nin Chow J, Williamson DA, Yates KM, Goux WJ. Chemical characterization of the immunomodulating polysaccharide of Aloe vera L. *Carbohydr Res.* 2005;340(6):1131-42.
39. Peirce A. *The American Pharmaceutical Association Practical Guide to Natural Medicines.* Vol 1. First ed: William Morrow; 1999.
40. Eberendu AR, Luta G, Edwards JA, et al. Quantitative colorimetric analysis of aloe polysaccharides as a measure of Aloe vera quality in commercial products. *J AOAC Int.* 2005;88(3):684-91.
41. Bozzi A, Perrin C, Austin S, Arce Vera F. Quality and authenticity of commercial aloe vera gel powders. *Food Chem.* 2006;103(1):22-30.
42. Mantle D, Gok MA, Lennard TW. Adverse and beneficial effects of plant extracts on skin and skin disorders. *Adverse Drug React Toxicol Rev.* 2001;20(2):89-103.

43. Fulton JE, Jr. The stimulation of postdermabrasion wound healing with stabilized aloe vera gel-polyethylene oxide dressing. *J Dermatol Surg Oncol.* 1990;16(5):460-67.
44. Bland J. Effect Of Orally Consumed Aloe Vera Juice On Gastrointestinal Function In Normal Humans. *Preventive Medicine.* 1985;14(2).
45. Shelton RM. Aloe vera. Its chemical and therapeutic properties. *Int J Dermatol.* 1991;30(10):679-83.
46. Heggers JP, Kucukcelebi A, Listengarten D, et al. Beneficial effect of Aloe on wound healing in an excisional wound model. *J Altern Complement Med.* 1996;2(2):271-77.
47. Choi SW, Son BW, Son YS, Park YI, Lee SK, Chung MH. The wound-healing effect of a glycoprotein fraction isolated from aloe vera. *Br J Dermatol.* 2001;145(4):535-45.
48. Tizard IR, Busbee D, Maxwell B, Kemp MC. Effects of acemannan, a complex carbohydrate, on wound healing in young and aged rats. *Wounds.* 1995;6:201-09.
49. Roberts DB, Travis EL. Acemannan-containing wound dressing gels reduce radiation-induced skin reactions in C3H mice. *Int J Radiat Oncol Biol Phys.* 1995;15:1047-52.
50. Wang ZW, Zhou JM, Huang ZS, et al. Aloe polysaccharides mediated radioprotective effect through the inhibition of apoptosis. *J Radiat Res.* 2004;45(3):447-54.
51. Somboonwong J, Thanamittramanee S, Jariyapongskul A, Patumraj S. Therapeutic effects of Aloe vera on cutaneous microcirculation and wound healing in second degree burn model in rats. *J Med Assoc Thai.* 2000;83(4):417-25.
52. Rodriguez-Bigas M, Cruz NI, Suarez A. Comparative evaluation of aloe vera in the management of burn wounds in guinea pigs. *Plast Reconstr Surg.* 1988;81(3):386-89.
53. McCauly R. Frostbite-methods to minimize tissue loss. *Postgrad Med.* 1990;88:67-70.
54. Perez YY, Jimenez-Ferrer E, Zamilpa A, et al. Effect of a polyphenol-rich extract from Aloe vera gel on experimentally induced insulin resistance in mice. *Am J Chin Med.* 2007;35(6):1037-46.
55. Rajasekaran S, Sivagnanam K, Ravi K, Subramanian S. Hypoglycemic effect of Aloe vera gel on streptozotocin-induced diabetes in experimental rats. *J Med Food.* 2004;7(1):61-6.
56. Rajasekaran S, Sriram N, Arulselvan P, Subramanian S. Effect of aloe vera leaf gel extract on membrane bound phosphatases and lysosomal hydrolases in rats with streptozotocin diabetes. *Pharmazie.* 2007;62(3):221-25.
57. Beppu H, Shimpo K, Chihara T, et al. Antidiabetic effects of dietary administration of Aloe arborescens Miller components on multiple low-dose streptozotocin-induced diabetes in mice: investigation on hypoglycemic action and systemic absorption dynamics of aloe components. *J Ethnopharmacol.* 2006;103(3):468-77.
58. Chaudhary G, Saini MR, Goyal PK. Chemopreventive potential of Aloe vera against 7,12-dimethylbenz(a)anthracene induced skin papillomagenesis in mice. *Integr Cancer Ther.* 2007;6(4):405-12.
59. Akev N, Turkay G, Can A, et al. Tumour preventive effect of Aloe vera leaf pulp lectin

(Aloctin I) on Ehrlich ascites tumours in mice. *Phytother Res.* 2007;21(11):1070-75.
60. Udupa SI, Udupa AL, Kulkarni DR. Anti-inflammatory and wound healing properties of Aloe vera. *Fitoterapia.* 1994;65:141-45.
61. Fujita K, Teradaira R, Nagatsu T. Bradykinase activity of aloe extract. *Biochem Pharmacol.* 1976;25(2):205.
62. Davis RH, Stewart GJ, Bregman PJ. Aloe vera and the inflamed synovial pouch model. *J Am Podiatr Med Assoc.* 1992;82(3):140-48.
63. Davis RH, Maro NP. Aloe vera and gibberellin. Anti-inflammatory activity in diabetes. *J Am Podiatr Med Assoc.* 1989;79(1):24-6.
64. Davis RH, Rosenthal KY, Cesario LR, Rouw GA. Processed Aloe vera administered topically inhibits inflammation. *J Am Podiatr Med Assoc.* 1989;79(8):395-97.
65. Chinnah AD, Baig MA, Tizard IR, Kemp MC. Antigen dependent adjuvant activity of a polydispersed beta-(1,4)-linked acetylated mannan (acemannan). *Vaccine.* 1992;10(8):551-57.
66. t'Hart LA, van den Berg AJ, Kuis L, van Dijk H, Labadie RP. An anti-complementary polysaccharide with immunological adjuvant activity from the leaf parenchyma gel of Aloe vera. *Planta Med.* 1989;55(6):509-12.
67. Strickland FM, Pelley RP, Kripke ML. Prevention of ultraviolet radiation-induced suppression of contact and delayed hypersensitivity by Aloe barbadensis gel extract. *J Invest Dermatol.* 1994;102(2):197-204.
68. Eamlamnam K, Patumraj S, Visedopas N, Thong-Ngam D. Effects of Aloe vera and sucralfate on gastric microcirculatory changes, cytokine levels and gastric ulcer healing in rats. *World J Gastroenterol.* 2006;12(13):2034-39.
69. Korkina L, Suprun M, Petrova A, Mikhal'chik E, Luci A, De Luca C. The protective and healing effects of a natural antioxidant formulation based on ubiquinol and Aloe vera against dextran sulfate-induced ulcerative colitis in rats. *Biofactors.* 2003;18(1-4):255-64.
70. Sakai K, Saitoh Y, Ikawa C, Nishihata T. Effect of water extracts of aloe and some herbs in decreasing blood ethanol concentration in rats. II. *Chem Pharm Bull (Tokyo).* 1989;37(1):155-59.
71. Rishi P, Rampuria A, Tewari R, Koul A. Phytomodulatory potentials of Aloe vera against Salmonella OmpR-mediated inflammation. *Phytother Res.* 2008;22(8):1075-82.
72. Lim BO, Seong NS, Choue RW, et al. Efficacy of dietary aloe vera supplementation on hepatic cholesterol and oxidative status in aged rats. *J Nutr Sci Vitaminol (Tokyo).* 2003;49(4):292-96.
73. Barrantes E, Guinea M. Inhibition of collagenase and metalloproteinases by aloins and aloe gel. *Life Sci.* 2003;72(7):843-50.
74. Winters WD, Benavides R, Clouse WJ. Effects of aloe extracts on human normal and tumor cells in vitro. *Economic Botany.* 1981;35:89-95.
75. Habeeb F, Stables G, Bradbury F, et al. The inner gel component of Aloe vera suppresses bacterial-induced pro-inflammatory cytokines from human immune

cells. *Methods.* 2007;42(4):388-93.
76. Habeeb F, Shakir E, Bradbury F, et al. Screening methods used to determine the anti-microbial properties of Aloe vera inner gel. *Methods.* 2007;42(4):315-20.
77. t Hart LA, Nibbering PH, van den Barselaar MT, van Dijk H, van den Berg AJ, Labadie RP. Effects of low molecular constituents from Aloe vera gel on oxidative metabolism and cytotoxic and bactericidal activities of human neutrophils. *Int J Immunopharmacol.* 1990;12(4):427-34.
78. Shida T, Yagi A, Nishimura H, Nishioka I. Effect of aloe extract on peripheral phagocytosis in adult bronchial asthma. *Planta Med.* 1985;51(3):273-75.
79. Yagi A, Shida T, Nishimura H. Effect of amino acids in Aloe extract on phagocytosis by peripheral neutrophil in adult bronchial asthma. *Arerugi.* 1987;36(12):1094-101.
80. Ni Y, Turner D, Yates K, Tizard I. Stabilization of growth factors relevant to wound healing by a plant cell wall biomaterial. *Planta Med.* 2007;73(12):1260-66.
81. Vazquez B, Avila G, Segura D, Escalante B. Antiinflammatory activity of extracts from Aloe vera gel. *J Ethnopharmacol.* 1996;55(1):69-75.
82. Strickland FM, Darvill A, Albersheim P, Eberhard S, Pauly M, Pelley RP. Inhibition of UV-induced immune suppression and interleukin-10 production by plant oligosaccharides and polysaccharides. *Photochem Photobiol.* 1999;69(2):141-47.
83. Byeon SW, Pelley RP, Ullrich SE, Waller TA, Bucana CD, Strickland FM. Aloe barbadensis extracts reduce the production of interleukin-10 after exposure to ultraviolet radiation. *J Invest Dermatol.* 1998;110(5):811-17.
84. Womble D, Helderman JH. Enhancement of allo-responsiveness of human lymphocytes by acemannan (Carrisyn). *Int J Immunopharmacol.* 1988;10(8):967-74.
85. Zhang L, Tizard IR. Activation of a mouse macrophage cell line by acemannan: the major carbohydrate fraction from Aloe vera gel. *Immunopharmacol.* 1996;35(2):119-28.
86. Talmadge J, Chavez J, Jacobs L, et al. Fractionation of Aloe vera L. inner gel, purification and molecular profiling of activity. *Int Immunopharmacol.* 2004;4(14):1757-73.
87. Ali MI, Shalaby NM, Elgamal MH, Mousa AS. Antifungal effects of different plant extracts and their major components of selected aloe species. *Phytother Res.* 1999;13(5):401-07.
88. Rosca-Casian O, Parvu M, Vlase L, Tamas M. Antifungal activity of Aloe vera leaves. *Fitoterapia.* 2007;78(3):219-22.
89. Abdullah KM, Abdullah A, Johnson ML, et al. Effects of Aloe vera on gap junctional intercellular communication and proliferation of human diabetic and nondiabetic skin fibroblasts. *J Altern Complement Med.* 2003;9(5):711-18.
90. Lee KH, Kim JH, Lim DS, Kim CH. Anti-leukaemic and anti-mutagenic effects of di(2-ethylhexyl)phthalate isolated from Aloe vera Linne. *J Pharm Pharmacol.* 2000;52(5):593-98.
91. Lee MJ, Lee OH, Yoon SH, et al. In vitro angiogenic activity of Aloe vera gel on calf pulmonary artery endothelial (CPAE) cells. *Arch Pharm Res.* 1998;21(3):260-65.
92. Davis RH, DiDonato JJ, Johnson RW, Stewart CB. Aloe vera, hydrocortisone, and sterol

influence on wound tensile strength and anti-inflammation. *J Am Podiatr Med Assoc.* 1994;84(12):614-21.
93. Karaca K, Sharma JM, Nordgren R. Nitric oxide production by chicken macrophages activated by Acemannan, a complex carbohydrate extracted from Aloe vera. *Int J Immunopharmacol.* 1995;17(3):183-88.
94. Ramamoorthy L, Kemp MC, Tizard IR. Acemannan, a beta-(1,4)-acetylated mannan, induces nitric oxide production in macrophage cell line RAW 264.7. *Mol Pharmacol.* 1996;50(4):878-84.
95. Stuart RW, Lefkowitz DL, Lincoln JA, Howard K, Gelderman MP, Lefkowitz SS. Upregulation of phagocytosis and candidicidal activity of macrophages exposed to the immunostimulant acemannan. *Int J Immunopharmacol.* 1997;19(2):75-82.
96. Robson MC, Heggers J, Hagstrom WJ. Myth, magic, witchcraft or fact? Aloe vera revisited. *J Burn Care Rehabil.* 1982;3:157-62.
97. World Health Organization (WHO), ed *WHO Monographs on Selected Medical Plants, Vol 1.* 1 ed. Geneva, Switzerland: World Health Organization; 1999. Organization WH, ed. WHO Monographs on Selected Medical Plants; No. 1.
98. Jellin JM. Aloe. In: Database NMC, ed. Natural Medicines Comprehensive Database: Therapeutic Research Faculty; 2008.
99. Morrow DM, Rapaport MJ, Strick RA. Hypersensitivity to aloe. *Arch Dermatol.* 1980;116(9):1064-65.
100. Shoji A. Contact dermatitis to Aloe arborescens. *Contact Dermatitis.* 1982;8(3):164-67.
101. Nakamura T, Kotajima S. Contact dermatitis from aloe arborescens. *Contact Dermatitis.* 1984;11(1):51.
102. Hunter D, Frumkin A. Adverse reactions to vitamin E and aloe vera preparations after dermabrasion and chemical peel. *Cutis.* 1991;47(3):193-96.
103. Ferreira M, Teixeira M, Silva E, Selores M. Allergic contact dermatitis to Aloe vera. *Contact Dermatitis.* 2007;57(4):278-79.
104. Fogleman RW, Chapdelaine JM, Carpenter RH, McAnalley BH. Toxicologic evaluation of injectable acemannan in the mouse, rat and dog. *Vet Hum Toxicol.* 1992;34(3):201-05.
105. Williams LD, Burdock GA, Shin E, et al. Safety studies conducted on a proprietary high-purity aloe vera inner leaf fillet preparation, Qmatrix. *Regul Toxicol Pharmacol.* 2010;57(1):90-8.
106. Fujii S. Evaluation of hypersensitivity to anthraquinone-related substances. *Toxicol.* 2003;193(3):261-67.
107. Brinker F. *Herb Contraindications and Drug Interactions.* 2nd ed: Eclectic Medical Publications; 1998.
108. Vinson JA, Al Kharrat H, Andreoli L. Effect of Aloe vera preparations on the human bioavailability of vitamins C and E. *Phytomedicine.* 2005;12(10):760-65.

109. Heggie S, Bryant GP, Tripcony L, et al. A Phase III study on the efficacy of topical aloe vera gel on irradiated breast tissue. *Cancer Nurs.* 2002;25(6):442-51.
110. Williams MS, Burk M, Loprinzi CL, et al. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. *Int J Radiat Oncol Biol Phys.* 1996;36(2):345-49.
111. Olsen DL, Raub W, Jr., Bradley C, et al. The effect of aloe vera gel/mild soap versus mild soap alone in preventing skin reactions in patients undergoing radiation therapy. *Oncol Nurs Forum.* 2001;28(3):543-47.
112. Richardson J, Smith JE, McIntyre M, Thomas R, Pilkington K. Aloe vera for preventing radiation-induced skin reactions: a systematic literature review. *Clin Oncol (R Coll Radiol).* 2005;17(6):478-84.
113. Su CK, Mehta V, Ravikumar L, et al. Phase II double-blind randomized study comparing oral aloe vera versus placebo to prevent radiation-related mucositis in patients with head-and-neck neoplasms. *Int J Radiat Oncol Biol Phys.* 2004;60(1):171-77.
114. Schmidt JM, Greenspoon JS. Aloe vera dermal wound gel is associated with a delay in wound healing. *Obstet Gynecol.* 1991;78(1):115-17.
115. Rajar UD, Majeed R, Parveen N, Sheikh I, Sushel C. Efficacy of aloe vera gel in the treatment of vulval lichen planus. *J Coll Physicians Surg Pak.* 2008;18(10):612-14.
116. Paulsen E, Korsholm L, Brandrup F. A double-blind, placebo-controlled study of a commercial Aloe vera gel in the treatment of slight to moderate psoriasis vulgaris. *J Eur Acad Dermatol Venereol.* 2005;19(3):326-31.
117. Choonhakarn C, Busaracome P, Sripanidkulchai B, Sarakarn P. A prospective, randomized clinical trial comparing topical aloe vera with 0.1% triamcinolone acetonide in mild to moderate plaque psoriasis. *J Eur Acad Dermatol Venereol.* 2010;24(2):168-72.
118. West DP, Zhu YF. Evaluation of aloe vera gel gloves in the treatment of dry skin associated with occupational exposure. *Am J Infect Control.* 2003;31(1):40-2.
119. Montaner JS, Gill J, Singer J, et al. Double-blind placebo-controlled pilot trial of acemannan in advanced human immunodeficiency virus disease. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996;12(2):153-7.
120. Huseini HF, Kianbakht S, Hajiaghaee R, Dabaghian FH. Anti-hyperglycemic and anti-hypercholesterolemic effects of Aloe vera leaf gel in hyperlipidemic type 2 diabetic patients: a randomized double-blind placebo-controlled clinical trial. *Planta Med.* 2012;78(4):311-16.
121. Dykman KD, Tone C, Ford C, Dykman RA. The effects of nutritional supplements on the symptoms of fibromyalgia and chronic fatigue syndrome. *Integr Physiol Behav Sci.* 1998;33(1):61-71.
122. ClinicalTrials.gov. National Institues of Health (NIH), National Library of Medicine (NLM), Department of Health and Human Service (HHS); 2008. Accessed 08/03/2008.

Aloe vera in dermatology: a brief review

https://pubmed.ncbi.nlm.nih.gov/19218914/

G Ital Dermatol Venereol

. 2009 Feb;144(1):85-91.

A Feily[1], M R Namazi

Affiliation

- [1]Department of Dermatology, Jondishapur University of Medical Sciences, Ahvaz, Iran. dr.feily@yahoo.com

- PMID: 19218914

Abstract

Aloe vera Linne or aloe barbadensis Miller is a succulent from the Aloe family (400 different species), a tropical plant which is easily grown in hot and dry climates and widely distributed in Asia, Africa and other tropical areas. The use of aloe vera is being promoted for a large variety of conditions. The aim of this systematic review was to summarize all dermatology-oriented in vitro and in vivo experiments and clinical trials on aloe vera preparations. Extensive literature search were carried out to identify all in vitro and in vivo studies as well as clinical trials on the subject. Data were extracted from these in a predefined standardized manner. Forty studies were located. The results suggest that oral administration of aloe vera in mice is effective on wound healing, can decrease the number and size of papillomas and reduce the incidence of tumors and leishmania parasitemia by >90% in the liver, spleen, and bone marrow. Topical application of aloe vera is not an effective prevention for radiation-induced injuries and has no sunburn or suntan protection. It can be effective for genital herpes, psoriasis, human papilloma virus, seborrheic dermatitis, aphthous stomatitis, xerosis, lichen planus, frostbite, burn, wound healing and inflammation. It can also be used as a biological vehicle and an anti-microbial and antifungal agent and also as a candidate for photodynamic therapy of some kinds of cancer. Even though there are some promising results with the use of aloe vera for diverse dermatologic conditions, clinical effectiveness of oral and topical aloe vera is not sufficiently and meticulously explored as yet.

IJMS
Vol 44, No 1, January 2019

Review Article

The Effect of Aloe Vera Clinical Trials on Prevention and Healing of Skin Wound: A Systematic Review

CME Article

Davood Hekmatpou[1], PhD;
Fatemeh Mehrabi[2],
Kobra Rahzani[1], PhD;
Atefeh Aminiyan[3], PhD

[1]Department of Nursing, Nursing and Midwifery Faculty, Arak University of Medical Sciences, Arak, Iran;
[2]Student of Nursing, Nursing and Midwifery Faculty, Arak University of Medical Sciences, Arak, Iran;
[3]Department of Clinical Pharmacology; Arak University of Medical Sciences, Arak, Iran

Correspondence:
Davood Hekmatpou, PhD;
Payambar-e-Azam Educational Complex, Basij Sq., Arak, Iran
Tel: +98 918 1616539
Fax: +98 86 34173528
Email: dr_hekmat@arakmu.ac.ir
Received: 30 April 2017
Revised: 28 May 2017
Accepted: 2 September 2017

Abstract

Background: Aloe vera is an herbaceous and perennial plant that belongs to the Liliaceae family and used for many medicinal purposes. The present study aimed to systematically review clinical trials regarding the effect of Aloe vera on the prevention and healing of skin wounds.

Methods: To identify all related published studies, we searched SID, IRANDOC, Google Scholar, PubMed, MEDLINE, Scopus, Cochrane Library, and ScienceDirect databases in both the English and Persian languages from 1990 to 2016. The keywords used were Aloe vera, wound healing, and prevention. All clinical trials using Aloe vera gel, cream, or derivatives that included a control group with placebo or comparison with other treatments were included in the study. The PRISMA checklist (2009) was used to conduct the review.

Results: In total, 23 trials that met the inclusion criteria were studied. The results of the studies showed that Aloe vera has been used to prevent skin ulcers and to treat burn wounds, postoperative wounds, cracked nipples, genital herpes, psoriasis, and chronic wounds including pressure ulcers.

Conclusion: Considering the properties of Aloe vera and its compounds, it can be used to retain skin moisture and integrity and to prevent ulcers. It seems that the application of Aloe vera, as a complementary treatment along with current methods, can improve wound healing and promote the health of society.

Please cite this article as: Hekmatpou D, Mehrabi F, Rahzani K, Aminiyan A. The Effect of Aloe Vera Clinical Trials on Prevention and Healing of Skin Wound: A Systematic Review. Iran J Med Sci. 2019;44(1):1-9.

Keywords ● Aloe ● Clinical trial ● Wound healing ● Prevention ● Wounds and injuries ● Systematic review

What's Known

- Aloe vera is a medicinal plant, traditionally used to improve skin integrity.
- Aloe vera is known for its anti-inflammatory, skin protection, anti-bacterial, anti-viral, antiseptic, and wound healing properties.

What's New

- Aloe vera can be used to retain skin moisture and integrity, and to prevent ulcers. However, there are limited studies on this topic.
- The use of Aloe vera to improve wound healing is recommended as the main or complementary treatment alongside other methods.

Introduction

The process of wound healing is a complex biological process and promotion of tissue recovery is the main objective of medical interventions. Skin lesions are caused due to different reasons such as burns, arterial diseases, surgery, and trauma.[1] Wound healing is a dynamic process that takes place in three phases. The first phase is inflammation, congestion, and leukocyte infiltration. The second phase involves the removal of dead tissue and the third phase of proliferation includes epithelial regeneration and fibrous tissue formation.[2] Several studies on Aloe vera have been conducted and shown to be effective in the prevention and healing of skin wounds.

Aloe vera is a medicinal plant traditionally used since 1500 BC in many countries such as Greece, China, and Mexico. It also has

been used for centuries as a traditional medicine for various diseases and skin lesions.[3] Aloe vera is an indigenous plant from tropical Madagascar, Saudi Arabia, and Iran. It belongs to the Liliaceae family; it is similar to Cactus and is an herbaceous and perennial plant with thick, fleshy and long leaves. The Egyptian queens Nefertiti and Cleopatra used Aloe vera as part of their regular beauty regime.[4] So far, 75 known compounds have been identified in Aloe vera, including 20 minerals, 20 amino acids, vitamins, and water.[5, 6] In vitro studies and studies conducted on living organisms have shown that Aloe vera can inhibit thromboxane (an inhibitor of wound healing), improve the wound healing process, and reduce inflammation.[3, 7] Magnesium lactate available in the gel can prevent the production of histamine that causes itching and irritation of the skin.[8, 9] It also enhances the immune system and the synthesis of cytokines. Aloe vera is effective in inhibiting inflammatory reactions by the inhibition of IL-6 and IL-8, the reduction of leukocyte adhesion, an increase of IL-10 levels, and decrease of TNF alpha levels.[10] Its regenerative properties are due to the compound glucomannan, which is rich with polysaccharides like mannose. Glucomannan affects fibroblast growth factor receptors and stimulates their activity and proliferation, which in turn increases the production of collagen. Aloe vera gel can not only increase the amount of collagen in wounds but also change the composition of collagen, increase collagen cross-linking and thereby promote wound healing.[11] Scientific studies have shown that the gel can increase the flexibility and reduce the fragility of the skin since 99% of the gel is water.[4] Additionally, mucopolysaccharides along with amino acids and zinc present in Aloe vera can lead to skin integrity, moisture retention, erythema reduction, and helps to prevent skin ulcers.[12] Several studies have shown the positive effects of Aloe vera to treat wounds such as psoriasis, mouth sores, ulcers, diabetes, herpes, bedsores, and burn wounds.[1, 4, 6, 13-15] Aloe vera is known for its anti-tumor, anti-inflammatory, skin protection, anti-diabetic, anti-bacterial, anti-viral, antiseptic, and wound healing properties.[6]

Considering the availability of several clinical trials on the effect of Aloe vera on the prevention and healing of skin wounds, as well as its popularity among people and widespread use in the cosmetic industry, the present study aimed to review research studies on this topic.

Materials and Methods

Search Strategy

The present study is a review of clinical trials on the effect of Aloe vera in preventing and healing of skin wounds. Articles published in both national and international journals were considered. Articles published online (1990-2016) were selected from the national databases (SID, IRANDOC) and international databases (Google Scholar, PubMed, MEDLINE, Scopus, Cochrane Library, and ScienceDirect). Moreover, the references of the identified articles were searched for additional sources of information. The used keywords were Aloe vera, wound healing, and prevention. All keywords were searched electronically, the titles and abstracts of all identified articles were screened, and duplicated articles were omitted. Each article was independently screened by four reviewers and possible disagreements were resolved in a joint review meeting. The language of the articles was either Persian or English.

Inclusion Criteria

All clinical trials using Aloe vera gel, cream, or derivatives that included a control group with placebo or comparison with other treatments were included in the study. The sample size of at least 30 cases was considered sufficient.

Exclusion Criteria

All studies using animal models, lack of access to full text, lack of transparency of statistical results, and sample size less than 30 cases were excluded.

Methodological Appraisal

The PRISMA checklist (2009) was used to conduct the review. Articles that were performed on animals, duplicated articles, non-transparent statistical results (without mean, standard deviation, confidence interval, test, P value, etc.), incomplete articles (duration of intervention, dosage, frequency, lost to follow-up, type of control groups, number of treatment sessions, and with no results based on its goals), and all articles with less than 30 sample size were removed. Eventually, 23 trials that met the inclusion criteria were studied (figure 1).

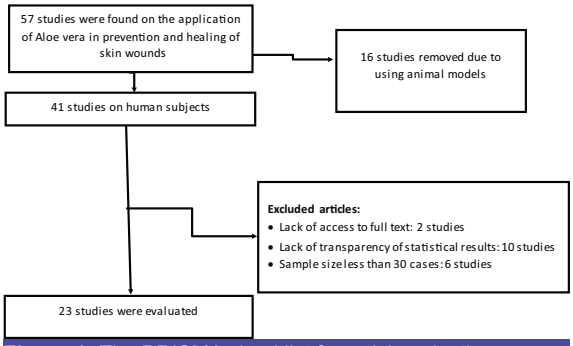

Figure 1: The PRISMA checklist for article selection.

Data Extraction

Data such as the author's name, year of publication, study region, study design, sample size, age of participants, sex, type of wound, type of intervention, duration of treatment, intervention and control groups, and main results were extracted.

Results

In total, 57 articles were identified out of which 16 were conducted on animals, 2 lacked access to the full text, 10 lacked transparency of statistical results, and 6 had a sample size less than 30 cases. These articles were removed and eventually, 23 articles were evaluated.

Wound healing and preventive effects of Aloe vera have been reported in several studies.[16] Topical application of Aloe vera to prevent ulcers and enhance the healing process of dermal injuries (e.g., burns, frostbite, skin infections, surgical wounds, inflammation, herpes ulcers, diabetic foot ulcers, pressure sores, and chronic wounds) has been reported.[17] Aloe vera is highly suitable for wound dressings.[18] Most of the studies were conducted on burn wounds. Aloe vera is considered as the traditional therapy for burns. Five studies investigated burn wound healing. In these studies, Aloe vera was more effective than petroleum jelly gauze dressing, silver sulfadiazine 1% ointment, and framycetin cream. Moreover, it reduced the recovery time, prevented infection in the wound area, and prevented redness and itching.[4, 14, 19-21] In these studies, Aloe vera was more effective in first- and second-degree burn wounds than in the other degrees. As described in table 1, it is concluded that Aloe vera can reduce the healing time of first- and second-degree burns to 9 days (P=0.006).[15]

As described in table 2, Aloe vera was used on postoperative wounds such as episiotomy, cesarean section, skin biopsy, hemorrhoidectomy, gynecologic laparotomy surgery, and graft.[22-28] In these studies, the use of Aloe vera gel and cream reduced the pain and recovery time compared to other conventional treatments. Only one study group, Aloe vera dressing for skin shave biopsy, did not show any difference in terms of improvement compared to the combined dressing group.[27]

Table 1: Analysis of studies using Aloe vera for first- and second-degree burns

Authors	Year	Sample size	Methods	Results
Malek Hosseini et al.[4]	2013	64 patients with second-degree burns	32 patients were dressed with Aloe vera gel and 32 other patients were dressed with silver sulfadiazine 1% cream, daily. Parameters of the wound on the 1st, 7th, and 15th days were studied using Bates-Jensen wound assessment tool.	By comparing the average improvement in both groups at baseline and on the 15th day, a significant difference was found between the two groups (P<0.0001). Finally, it was reported that wounds healed faster using Aloe vera gel dressing than silver sulfadiazine
Khorasani et al.[19]	2009	30 patients with burns on two areas of the body	In each patient, one part of the body was randomly used to apply Aloe vera cream 0.5% and the other part with sulfadiazine 1%. In both groups, Aloe vera and sulfadiazine were applied twice a day. The healing time was 19 days.	80% of the SSD group and 100% of the AV group were cured after 19 days. The mean days of recovery in the AV and SSD groups were 15.9±2 and 18.73±2.56 days, respectively. In addition, no infection was observed in both groups (P<0.0001).
Moghbel et al.[14]	2007	30 patients with second-degree burn wounds	The patients applied Aloe vera dressing and silver sulfadiazine 1% ointment on each hand as the experimental and control groups, symmetrically.	They reported improvements within 10 days in 90.6% of the experimental group and 28.7% of the control group (P<0.001).
Akhtar et al.[20]	1996	100 patients with burns	100 patients were divided into two groups. The AV group applied Aloe vera dressing three times a day and the control group applied framycetin ointment.	The average improvement for the AV group was 18 days versus 30.9 days.
Tamlikikal et al.[21]	1991	38 patients with first- to third-degree burns in which less than 30% of their body surface area was burned.	The samples were assigned into two groups by random allocation; in SSD group silver sulfadiazine was applied twice a day and in the AV group Aloe vera was applied twice a day.	55% (11/20) with mucilage AV and 39% (7/18) with SSD were recovered.

Table 2: Analysis of studies using Aloe vera on postoperative wounds

Authors	Year	Sample size	Methods	Results
Malazem et al.[22]	2015	90 women undergoing cesarean section	Aloe vera gel dressing was used in the intervention group and a simple dressing on the wound immediately after cesarean section was applied in the other group. The pain and improvement in the first 24 hours and the 8th day were compared.	In the Aloe vera group, wound healing was faster than the control group in the first 24 hours (P=0.003). However, no difference was observed on the 8th day (P=0.283). Finally, the positive effect of Aloe vera treatment was confirmed.
SabzAli Gol et al.[23]	2014	84 women undergoing nulliparous episiotomy	In the intervention group, Aloe vera gel was used twice a day for 10 days and betadine bath was used for the control group twice a day for 10 days.	In the Aloe vera group, 57.1% on the 7th day and 30% on the 10th day had complete remission. The pain intensity average was 2.3 on the 7th day and 1.21 on the 10th day.
Eghdam Poor et al.[24]	2013	74 women undergoing nulliparous episiotomy	Aloe vera ointment every 8 hours for 5 days was applied in the intervention group and the control group used betadine bath every 4 hours for 5 days.	The average improvement in the Aloe vera group was 1.62, which was significantly high (P<0.0001).
Jahdi et al.[25]	2011	74 women undergoing nulliparous episiotomy	In the intervention group, Aloe vera ointment (3 cc) was applied every 8 hours for 5 days and betadine bath used in the control group every 4 hours for 5 days.	Regarding pain intensity, the average pain score was 1.86 in the Aloe vera group, which was significantly low (P<0.001).
Khorasani et al.[26]	2011	45 skin graft donor sites	A group using Aloe vera cream (three times daily), a placebo group (three times daily), and the other group without any topical agent were studied. Dressing was applied daily in all three groups.	It was concluded that the effect of Aloe vera gel on the donor sites resulted in a significant improvement in recovery time between the control group (without any topical agent: 17±8.6), the placebo group (without Aloe vera cream: 8.8±2.8), and the experimental group (cream without Aloe vera: 9.7±2.9). However, there was no difference in the placebo and experimental group, which can be due to the moisturizing effect of both creams.
Eshghi et al.[27]	2010	49 patients after hemorrhoidectomy	Aloe vera gel 0.05% was used in the intervention group and placebo was used in the control group 12 hours after hemorrhoidectomy three times a day for 28 days.	The complete time of remission was considered as 14 days. 100% of the intervention group and only 4% of the control group cured after 14 days.
Philips et al.[28]	1995	49 patients undergoing skin shave biopsy	The intervention group used Aloe vera gel dressing and the control group used the combined dressing (hydrogel parkside, antibiotic ointment, and absorbent dressing) twice a day.	After 14 days, no difference was observed between the two groups in terms of the healing and 24/24 in the AV group and 23/23 in the control group recovered.

As described in table 3, Aloe vera was used for healing of cracked nipples in 2 studies and it reduced the pain and discharge in the area.[29, 30]

Aloe vera has been effective in chronic wounds such as pressure ulcers, diabetic ulcers, chronic anal fissure wounds, chronic wounds caused by accidents, psoriasis, and genital herpes. In this regard, 7 articles were studied and Aloe vera was more effective compared to saline gauze dressing, phenytoin, and current treatments.[31-37] Only in one study, no differences were found between the two groups which can be due to the small sample size compared to the other studies.[36] Aloe vera reduced the pain, bleeding, and recovery time in chronic wounds (table 4).

Aloe vera has also been effective in the prevention of ulcers. Mucopolysaccharides along with amino acids and zinc available in Aloe vera can lead to skin integrity, moisture retention, erythema reduction, and helps to prevent skin ulcers. As described in table 5, two studies were reviewed.[12, 38]

Table 3: Analysis of studies using Aloe vera for healing of cracked nipples

Authors	Year	Sample size	Methods	Results
Alamolhoda et al.[29]	2013	110 nulliparous lactating women	In one group, after each breastfeeding, lactating women applied 0.5 ml of Aloe vera gel on their nipples and around the areola. The control group applied 4 drops of their breast milk. Both groups were evaluated at days 10 and 14 postpartum.	The pain and damage of the nipple and discharge in the Aloe vera group were much less than the control group and Aloe vera improved the fissure (P<0.001).
Tafazoli et al.[30]	2009	100 lactating women with breast fissure	Two groups were divided into lanolin ointment or Aloe gel groups (three times a day for 1 week).	There was a statistically significant difference between the two groups on the 3rd day (P=0.048) and 7th day (P=0.003). Aloe vera gel was more effective than lanolin ointment in healing cracked nipples.

Table 4: Analysis of studies using Aloe vera on chronic wounds

Authors	Year	Sample size	Methods	Results
Avijegan et al.[31]	2016	60 patients with chronic wounds	In the intervention group, 30 patients used Aloe vera gel twice a day in combination with current treatments and the control group only used conventional treatments. Patients were evaluated 1 week and 3 months after treatment.	After 3 months follow-up, wound healing occurred in 28 (93.3%) of patients in the Aloe vera group and 14 (46.7%) patients in the control group (P<0.05). The overall mean time of wound healing was 31.25±11.2 and 63.2±20.4 in the Aloe vera and control groups, respectively (P<0.05). The mean hospitalization time was 35.2±6.4 and 67.4±8.9 in the Aloe vera and control groups, respectively (P<0.05).
Panahi et al.[32]	2015	60 patients with chronic wounds (41 patients with pressure ulcers, 13 patients with diabetic ulcers, and 6 patients with ulcer caused by venous disorders)	Aloe vera cream in combination with olive oil was used in the intervention group and the control group used phenytoin cream for 30 days. The pain, depth, size, edema around the wound area, the amount of exudate, and necrotic tissue were examined using Bence Jones and VAG tools.	The pain, depth, size, edema around the wound area, the amount of exudate, and necrotic tissue in the intervention group showed a statistically significant difference compared with the control group (P<0.001). Aloe vera gel in combination with olive oil was much more effective in reducing pain and wound healing compared with phenytoin.
Rahmani et al.[33]	2014	60 patients with a confirmed diagnosis of chronic anal fissures	Aloe vera cream 0.5% (3 grams) was used in the intervention group three times a day for 3 weeks and the control group used the placebo.	A statistically significant difference was observed in the pain, bleeding, and wound healing of chronic anal fissure before and at the end of the 1st week of the study compared with the control group (P<0.001) and topical application of Aloe vera was considered effective in treating wounds.
Choonhakarn et al.[34]	2010	80 patients with a diagnosis of psoriasis vulgaris	Mucilage from Aloe vera (70%) twice a day without any treatment was used in the intervention group and triamcinolone cream 0.1% was used in the control group for 8 weeks.	Aloe vera cream was at least as effective in reducing psoriatic plaque in patients as triamcinolone acetonide cream with significantly more reduction in psoriasis area severity index and equal reduction in dermatology life quality index.

(Contd...)

Table 4: (*Continued*)

Authors	Year	Sample size	Methods	Results
Thomas et al.[35]	1998	30 patients with two-, three- and four-degree ulcer with a wound size≥1 cm^2	16 people used carrasyn dressing derived from Aloe vera gel (along with the acemannan Aloe vera) and 14 of the patients used saline gauze dressing, daily. They were followed up for 10 weeks.	63% of the Aloe vera group and 64% of the saline gauze dressing group recovered after 10 weeks. The mean time of improvement was 5.3±2.3 for AV group and 5.2±2.4 for saline gauze dressing group and there was no difference.
Syed et al.[36]	1996	120 patients with a diagnosis of genital herpes	0.05% cream or Aloe vera gel was used in the intervention group three times a day and the placebo was used for 2 weeks in the control group.	Both Aloe cream and gel were effective in reducing healing time compared to placebo (4.8 vs. 7.0 vs. 14.0 days, respectively), Aloe cream was more efficacious in the number of cured patients compared to gel (70% vs. 45% vs. 7%, respectively.
Syed et al.[37]	1996	60 patients with a diagnosis of psoriasis vulgaris	The intervention group used 0.05% cream or Aloe vera gel maximum three times a day (or 15 times a week) and in the control group, the placebo was used for 4 weeks.	Aloe hydrophilic cream cured 83.3% of patients treated versus 6.6% in the control group. Psoriatic plaques were significantly ($P<0.001$) reduced and biopsies presented with reduced inflammation and parakeratosis.

Discussion

Based on a detailed review of articles, the application of Aloe vera as a medicinal plant for skin wound healing is confirmed.[1-40] Aloe Vera is widely used for its antibacterial, anti-viral, anti-inflammatory effects and has been considered in medical sciences.[2, 3, 6] Dat and colleagues (2012) showed that Aloe vera is more effective in chronic than acute wounds.[1] Aloe vera is mainly used to treat first- and second-degree burn wounds resulting in reduced recovery time to 9 days. Aloe vera dressing for once or twice a day has been more effective than the current treatments, including petroleum jelly gauze dressing, silver sulfadiazine 1% ointment, and framycetin cream. It has resulted in reduced recovery time, the absence of wound infection, and the lack of redness and itching.[4, 14, 21] Aloe vera has long been used to treat burns and is commonly known as the burn tree and first aid plant.[39] Due to anti-inflammatory, increased immune activity, anti-bacterial and anti-viral effects, and decreased histamine activity properties of Aloe vera, it accelerates the healing process of burn wounds. The outcome of the present review study shows that Aloe vera is unanimously considered as the ideal dressing. Most studies have been performed on grade 1 and 2 ulcers and there are limited studies on grade 3 ulcers. The latter could be due to full thickness skin loss in grade 3 wounds and possible onset of wound infection.

Aloe vera gel or cream on postoperative wounds (three times a day for 5-10 days) could reduce pain and recovery time.[22-28] Only one study indicated that there was no difference between the experimental and placebo groups.[28] This could be due to inappropriate placebo or the optimal time point for improvement. Cracked nipples could also be treated using Aloe vera if applied 3 times a day or after each breastfeeding. It would reduce the pain due to cracked nipples.[29, 30] This finding was also confirmed in a study by Eshgizade and colleagues (2016).[40]

It is indicated that Aloe vera (as a gel or cream) can be effective to treat chronic wounds such as psoriasis lesions (twice a day for 4-8 weeks),[34, 37] pressure ulcers (1-3 months), venous, diabetic,[31, 32] and herpes ulcers and chronic anal fissure (2-3 weeks).[33-36] In these articles, in addition to the recovery time, the following factors were also checked: Lesion scores;[34] depth, size, edema around the wound area, the amount of exudate and necrotic tissue,[32] inflammation,[34, 37] pain and bleeding,[33] and infection.[19] It was shown that Aloe vera could have a positive effect on the above-mentioned factors and their reduction. Only Thomas and colleagues found no healing difference between saline and Aloe vera in the

Table 5: Analysis of studies using Aloe vera to prevent ulcers

Authors	Year	Sample size	Methods	Results
West et al.[12]	2003	30 adult females with bilateral occupational dry skin with or without irritant contact dermatitis (with or without erythema, fissures, and excoriations)	The intervention group wore a glove containing Aloe vera gel 8 hours a day for 30 days on one hand and the control group (the other hand) did not use any material. The patients rested for 30 days and the intervention was repeated for an additional 10 days.	Average recovery of the dry skin time was 3.5 days for the intervention group and no event occurred in the control group. Aloe vera could help in preventing the onset of erythema, dryness and eczema, and scarring (P<0.0001).
Williams et al.[38]	1996	194 women receiving radiation therapy for breast cancer	Aloe vera gel was used in the intervention group (98%) in combination with common treatments. The control group only used common treatments.	No difference was observed between the two groups.

treatment of pressure ulcers. Perhaps the small sample size (30 cases) was the reason behind their findings.[35] As the secondary objective, many studies measured the length of hospitalization, cost of scar treatment, and redness and itching of the wound area. They indicated that Aloe vera is superior to other treatments.[14, 21, 31]

Several studies noted the traditional belief that a wound should not be covered, allowing it to become dry and detach itself from the wound area since it inhibits the migration of cells and growth factors leading to wound healing. Aloe vera as a wound cover would keep the wound area moist and allows optimal migration of fibroblasts and epidermal. Aloe vera (1 to 100 mg/kg) can improve wound healing.[41]

The main limitations of the present systematic review were the quality of available literature, lack of access to all articles, and unpublished reports. Moreover, only the literature in English and Persian were reviewed. These have considerably reduced our sample size regarding various data parameters and consequently hindered our ability to determine statistically significant results. Furthermore, not all articles were blind experiments, which is a challenge to determine the true effect of Aloe vera on wound healing. In total, 57 articles had to be excluded since they involved multiple procedures or multiple indications without providing specific outcomes data for the Aloe vera effect on wound healing. Since the present study was not a meta-analysis and had no major summary, data analysis to determine publication bias with the STATA software was not performed. However, qualitative analysis of both the survey responses and the focus group discussion identified possible ways of reducing publication bias. This was done through increased transparency, improvements in trial registries, search engines and databases, enhancing the role of the institutional review boards, and positive support from the scientists. The above-mentioned approaches minimized publication bias.

Conclusion

Due to the properties of Aloe vera and its compounds, it can be used to retain skin moisture and integrity. It also prevents skin ulcers as it contains mucopolysaccharides, amino acids, zinc, and water. In terms of quality and speed of wound healing, Aloe vera is much more effective and less costly compared to the currently available alternative treatments. Considering the tendency to promote traditional medicine as well as rare side effects of Aloe vera, the use of this medicinal plant to improve wound healing is recommended as the complementary treatment alongside other methods.

Conflict of Interest: None declared.

References

1. Dat AD, Poon F, Pham KB, Doust J. Aloe vera for treating acute and chronic wounds. Cochrane Database Syst Rev. 2012:CD008762. doi: 10.1002/14651858.CD008762.pub2. PubMed PMID: 22336851.
2. Reddy CU, Reddy KS, Reddy JJ. Aloe vera-A wound healer. Asian Journal of Oral Health & Allied Sciences-Volume. 2011;1:91-2.
3. Shelton RM. Aloe vera. Its chemical and therapeutic properties. Int J Dermatol. 1991;30:679-83. doi: 10.1111/j.1365-4362.1991.tb02607.x. PubMed PMID: 1823544.
4. Malek Hosseini A, Ghaffarzadegan R, Alizadeh SA, Ghaffarzadegan R, Haji Agaei R, Ahmadlou M. Effect of aloe vera gel, compared to 1% silver sulfadiazine cream on second-degree burn wound healing. Complementary Medicine Journal of faculty of Nursing and Midwifery. 2013;3:418-28.
5. Subramanian S, Kumar DS, Arulselvan P. Wound healing potential of Aloe vera leaf gel studied in experimental rabbits. Asian J

Biochem. 2006;1:178-85.
6. Sahu PK, Giri DD, Singh R, Pandey P, Gupta S, Shrivastava AK, et al. Therapeutic and medicinal uses of Aloe vera: a review. Pharmacol Pharm. 2013;4:599-610. doi: 10.4236/pp.2013.48086.
7. Heck E, Head M, Nowak D, Helm P, Baxter C. Aloe vera (gel) cream as a topical treatment for outpatient burns. Burns. 1981;7:291-4. doi: 10.1016/0305-4179(81)90112-1.
8. Bunyapraphatsara N, Jirakulchaiwong S, Thirawarapan S, Manonukul J. The efficacy of Aloe vera cream in the treatment of first, second and third degree burns in mice. Phytomedicine. 1996;2:247-51. doi: 10.1016/S0944-7113(96)80050-X. PubMed PMID: 23194624.
9. Somboonwong J, Thanamittramanee S, Jariyapongskul A, Patumraj S. Therapeutic effects of Aloe vera on cutaneous microcirculation and wound healing in second degree burn model in rats. J Med Assoc Thai. 2000;83:417-25. PubMed PMID: 10808702.
10. Mosayebi G, Ghazavi A, Aghili B, Mirshafiei A. Immunomodulating activity of Aloe Vera in animal model of multiple sclerosis. Arak Medical University Journal. 2009;12:109-15. Persian.
11. Boudreau MD, Beland FA. An evaluation of the biological and toxicological properties of Aloe barbadensis (miller), Aloe vera. J Environ Sci Health C Environ Carcinog Ecotoxicol Rev. 2006;24:103-54. doi: 10.1080/10590500600614303. PubMed PMID: 16690538.
12. West DP, Zhu YF. Evaluation of aloe vera gel gloves in the treatment of dry skin associated with occupational exposure. Am J Infect Control. 2003;31:40-2. doi: 10.1067/mic.2003.12. PubMed PMID: 12548256.
13. Shaugh Nessy B. Physicians Desk Reference (PDR) for Herbal Medicine. 2nd ed. New Jersey: Medical Economics Company; 2000.
14. Moghbel A, Ghalambor A, Allipanah S. Wound healing and toxicity evaluation of Aloe vera cream on outpatients with second degree burns. Iranian Journal of Pharmaceutical Sciences. 2007;3:157-60.
15. Maenthaisong R, Chaiyakunapruk N, Niruntraporn S, Kongkaew C. The efficacy of aloe vera used for burn wound healing: a systematic review. Burns. 2007;33:713-8. doi: 10.1016/j.burns.2006.10.384. PubMed PMID: 17499928.
16. Radha MH, Laxmipriya NP. Evaluation of biological properties and clinical effectiveness of Aloe vera: A systematic review. J Tradit Complement Med. 2015;5:21-6. doi: 10.1016/j.jtcme.2014.10.006. PubMed PMID: 26151005; PubMed Central PMCID: PMCPMC4488101.
17. Joseph B, Raj SJ. Pharmacognostic and phytochemical properties of Aloe vera linn an overview. Int J Pharm Sci Rev Res. 2010;4:106-10. doi: 10.3923/ijp.2011.40.45.
18. Schmidt JM, Greenspoon JS. Aloe vera dermal wound gel is associated with a delay in wound healing. Obstet Gynecol. 1991;78:115-7. PubMed PMID: 2047051.
19. Khorasani G, Hosseinimehr SJ, Azadbakht M, Zamani A, Mahdavi MR. Aloe versus silver sulfadiazine creams for second-degree burns: a randomized controlled study. Surg Today. 2009;39:587-91. doi: 10.1007/s00595-008-3944-y. PubMed PMID: 19562446.
20. Akhtar MA, Hatwar S. Efficacy of aloe vera extract cream in management of burn wound. J Clin Epidemiol. 1996;49:S24.
21. Thamlikitkul V, Bunyapraphatsara N, Riewpaiboon W, Theerapong S, Chantrakul C, Thanaveerasuwan T, et al. Clinical trial of aloe vera linn. for treatment of minor burns. Siriraj Med J. 1991;43:313–6.
22. Molazem Z, Mohseni F, Younesi M, Keshavarzi S. Aloe vera gel and cesarean wound healing; a randomized controlled clinical trial. Glob J Health Sci. 2014;7:203-9. doi: 10.5539/gjhs.v7n1p203. PubMed PMID: 25560349; PubMed Central PMCID: PMCPMC4796446.
23. Sabzaligol M, Safari N, Baghcjeghi N, Latifi M, Bekhradi R, Taghizadeh M, et al. The effect of Aloevera gel on prineal pain & wound healing after episiotomy. Complementary Medicine Journal of faculty of Nursing and Midwifery. 2014;4:766-75.
24. Eghdampour F, Jahdie F, Kheyrkhah M, Taghizadeh M, Naghizadeh S, Haghani H. The effect of aloe vera ointment in wound healing of episiotomy among primiparous women. The Iranian Journal of Obstetrics, Gynecology and Infertility. 2013;15:25-31. Persian.
25. Jahdi F, Kheyrkhah M, Haghani H, Taghizadeh M, Mehrabi E, Eghdampour F. The effect of Aloe Vera ointment on the intensity of perineal pain following episiotomy: A randomized blind clinical trial. Asrar. Journal of Sabzevar School of Medical Sciences. 2011;18:243-9. Persian.
26. Khorasani G, Ahmadi A, Jalal Hosseinimehr S, Ahmadi A, Taheri A, Fathi H. The Effects of Aloe Vera Cream on Split-thickness Skin Graft Donor Site

Management: A Randomized, Blinded, Placebo-controlled Study. Wounds. 2011;23:44-8. PubMed PMID: 25881055.
27. Eshghi F, Hosseinimehr SJ, Rahmani N, Khademloo M, Norozi MS, Hojati O. Effects of Aloe vera cream on posthemorrhoidectomy pain and wound healing: results of a randomized, blind, placebo-control study. J Altern Complement Med. 2010;16:647-50.
28. Phillips T, Ongenae K, Kanj L, Slaterfreedberg J. A randomized study of an aloe vera derivative gel dressing versus conventional treatment after shave biopsy excisions. Wounds. 1995;7:200-2.
29. Alamolhoda SH, Amir Ali Akbari S, Baghban AA, Esmaili S. Effects of Aloe vera gel on breast fissures in breastfeeding women. Pajoohandeh Journal. 2014;19:13-7. Persian.
30. Tafazoli M, Saeedi R, Gholami Robatsangi M, Mazloom R. Aloevera gel Vs. lanolin ointment in the treatment of nipple sore: a randomized clinical trial. Tehran University Medical Journal. 2010;67:699-704. Persian.
31. Avijgan M, Kamran A, Abedini A. Effectiveness of Aloe Vera Gel in Chronic Ulcers in Comparison with Conventional Treatments. Iran J Med Sci. 2016;41:S30. PubMed PMID: 27840496; PubMed Central PMCID: PMCPMC5103537.
32. Panahi Y, Izadi M, Sayyadi N, Rezaee R, Jonaidi-Jafari N, Beiraghdar F, et al. Comparative trial of Aloe vera/olive oil combination cream versus phenytoin cream in the treatment of chronic wounds. J Wound Care. 2015;24:459-60, 62-5. doi: 10.12968/jowc.2015.24.10.459. PubMed PMID: 26488737.
33. Rahmani N, Khademloo M, Vosoughi K, Assadpour S. Effects of Aloe vera cream on chronic anal fissure pain, wound healing and hemorrhaging upon defection: a prospective double blind clinical trial. Eur Rev Med Pharmacol Sci. 2014;18:1078-84. PubMed PMID: 24763890.
34. Choonhakarn C, Busaracome P, Sripanidkulchai B, Sarakarn P. A prospective, randomized clinical trial comparing topical aloe vera with 0.1% triamcinolone acetonide in mild to moderate plaque psoriasis. J Eur Acad Dermatol Venereol. 2010;24:168-72. doi: 10.1111/j.1468-3083.2009.03377.x. PubMed PMID: 19686327.
35. Thomas DR, Goode PS, LaMaster K, Tennyson T. Acemannan hydrogel dressing versus saline dressing for pressure ulcers. A randomized, controlled trial. Adv Wound Care. 1998;11:273-6. PubMed PMID: 10326343.
36. Syed TA, Cheema KM, Ahmad SA, Holt Jr AH. Aloe vera extract 0.5% in hydrophilic cream versus Aloe vera gel for the management of genital herpes in males. A placebo-controlled, double-blind, comparative study. J Eur Acad Dermatol Venereol. 1996;7:294-5.
37. Syed TA, Ahmad SA, Holt AH, Ahmad SA, Ahmad SH, Afzal M. Management of psoriasis with Aloe vera extract in a hydrophilic cream: a placebo-controlled, double-blind study. Trop Med Int Health. 1996;1:505-9. PubMed PMID: 8765459.
38. Williams MS, Burk M, Loprinzi CL, Hill M, Schomberg PJ, Nearhood K, et al. Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. Int J Radiat Oncol Biol Phys. 1996;36:345-9. PubMed PMID: 8892458.
39. Ghasemi Dehkordi A. Iranian herbal pharmacopeia (in Persian). Vol 1-2. Tehran: Ministry of Health, Treatment and Medical Training publication; 2002. p. 528-30.
40. Eshgizade M, Basiri Moghaddam M, Mohammadzadeh Moghaddam H, Mahmoudian A, Mesbah M. Comparison of the Effect of Olive Oil, Aloe Vera Extract and Breast Milk on Healing of Breast Fissure in Lactating Mothers: A Randomized Clinical Trial (Clinical Trial Article). Qom Univeresity of Medical Sciences. 2016;10:19-27. Persian.
41. Vazquez B, Avila G, Segura D, Escalante B. Antiinflammatory activity of extracts from Aloe vera gel. J Ethnopharmacol. 1996;55:69-75. PubMed PMID: 9121170.

This article has Continuous Medical Education (CME) credit for Iranian physicians and paramedics. They may earn CME credit by reading this article and answering the questions on page 83.

A review of the bioactivity and potential health benefits of chamomile tea (Matricaria recutita L.)

https://pubmed.ncbi.nlm.nih.gov/16628544/

Diane L McKay[1], Jeffrey B Blumberg

Affiliation

- [1]USDA Human Nutrition Research Center on Aging at Tufts University, 711 Washington Street, Boston, MA 02111, USA. diane.mckay@tufts.edu

- PMID: 16628544
- DOI: 10.1002/ptr.1900

Abstract

Chamomile (Matricaria recutita L., Chamomilla recutita L., Matricaria chamomilla) is one of the most popular single ingredient herbal teas, or tisanes. Chamomile tea, brewed from dried flower heads, has been used traditionally for medicinal purposes. Evidence-based information regarding the bioactivity of this herb is presented. The main constituents of the flowers include several phenolic compounds, primarily the flavonoids apigenin, quercetin, patuletin, luteolin and their glucosides. The principal components of the essential oil extracted from the flowers are the terpenoids alpha-bisabolol and its oxides and azulenes, including chamazulene. Chamomile has moderate antioxidant and antimicrobial activities, and significant antiplatelet activity in vitro. Animal model studies indicate potent antiinflammatory action, some antimutagenic and cholesterol-lowering activities, as well as antispasmotic and anxiolytic effects. However, human studies are limited, and clinical trials examining the purported sedative properties of chamomile tea are absent. Adverse reactions to chamomile, consumed as a tisane or applied topically, have been reported among those with allergies to other plants in the daisy family, i.e. Asteraceae or Compositae.

Chamomile: A herbal medicine of the past with a bright future (Review)

JANMEJAI K. SRIVASTAVA[1,2,4], ESWAR SHANKAR[1,2] and SANJAY GUPTA[1-3]

Department of Urology and Nutrition, [1]Case Western Reserve University; [2]University Hospitals Case Medical Center; [3]Case Comprehensive Cancer Center, Cleveland, OH 44106, USA

Received August 4, 2010; Accepted August 30, 2010

DOI: 10.3892/mmr.2010.377

Abstract. Chamomile is one of the most ancient medicinal herbs known to mankind. It is a member of the *Asteraceae/ Compositae* family and is represented by two common varieties, German Chamomile (*Chamomilla recutita*) and Roman Chamomile (*Chamaemelum nobile*). The dried flowers of chamomile contain many terpenoids and flavonoids, which contribute to its medicinal properties. Chamomile preparations are commonly used for many human ailments, including hay fever, inflammation, muscle spasms, menstrual disorders, insomnia, ulcers, wounds, gastrointestinal disorders, rheumatic pain and hemorrhoids. Essential oils of chamomile are used extensively in cosmetics and aromatherapy. Numerous preparations of chamomile have been developed, the most popular being in the form of herbal tea, of which more than one million cups are consumed every day. In this review, we describe the use of chamomile in traditional medicine with regard to evaluating its curative and preventive properties, and highlight recent findings that may contribute to its development as a therapeutic agent promoting human health.

Correspondence to: Dr Sanjay Gupta, Department of Urology, Case Western Reserve University, 10900 Euclid Avenue, Cleveland, OH 44106, USA
E-mail: sanjay.gupta@case.edu

Present address: [4]Amity Institute of Biotechnology (Mango Orchard Campus), Amity University, Lucknow Campus, Viraj Khand 5, Gomti Nagar, Lucknow, India

Abbreviations: ACTH, adrenocorticotropic hormone; ASA, American Society of Anesthesiologists; BDZ, benzodiazepine; CAM, complementary and alternative medicine; COX, cyclooxygenase; 5-FU, 5-fluorouracil; GABA, γ-aminobutyric acid; GAD, generalized anxiety disorder; LPS, lipopolysaccharide; SERMs, selective estrogen receptor modulators

Key words: chamomile, dietary agents, flavonoids, polyphenols, human health

Contents

1. Introduction

The effect of plants on human health has been documented for thousands of years (1-3). Herbs have been integral to both traditional and non-traditional forms of medicine dating back at least 5000 years (2,4-6). The enduring popularity of herbal medicines may be explained by the tendency of herbs to work slowly, usually with minimal toxic side effects. One of the most common herbs used for medicinal purposes is chamomile, whose standardized tea and herbal extracts are prepared from dried flowers of the *Matricaria* species. Chamomile is one of the oldest, most widely used and well-documented medicinal plants in the world, and has been recommended for a variety of healing applications (7). Chamomile is native to the Old World and is a member of the daisy family (*Asteraceae* or *Compositae*). The hollow, bright gold cones of the flowers are packed with disc or tubular florets, and are ringed with approximately fifteen white ray or ligulate florets. Chamomile is widely represented by two known varieties, German chamomile (*Matricaria chamomilla*) and Roman chamomile (*Chamaemelum nobile*) (8). In this review, we discuss the use and possible merits of chamomile, examining its historical use and recent scientific and clinical evaluations of its potential in the management of various human ailments.

2. Bioactive constituents of chamomile

Different classes of bioactive constituents are present in chamomile. These have been isolated and used as medicinal preparations and cosmetics (9). The plant contains 0.24-1.9% volatile oil, composed of a variety of separate oils. When exposed to steam distillation, the oil ranges in color from brilliant blue to deep green when fresh, but turns to dark yellow

after storage. Despite fading, the oil does not lose its potency. Approximately 120 secondary metabolites have been identified in chamomile, including 28 terpenoids and 36 flavonoids (10,11). The principal components of the essential oil extracted from the German chamomile flowers are the terpenoids α-bisabolol and its oxide azulenes, including chamazulene and acetylene derivatives. Chamazulene and bisabolol are very unstable and are best preserved in an alcoholic tincture. Essential oil of Roman chamomile contains less chamazulene and is mainly constituted from esters of angelic and tiglic acid. It also contains farnesene and α-pinene. Roman chamomile contains up to 0.6% of sesquiterpene lactones of the germacranolide type, mainly nobilin and 3-epinobilin. Both α-bisabolol and bisabolol oxides A and B, as well as chamazulene or azulenesse, farnesene and spiro-ether quiterpene lactones, glycosides, hydroxycoumarins, flavonoids (apigenin, luteolin, patuletin and quercetin), coumarins (herniarin and umbelliferone), terpenoids and mucilage are considered to be the major bioactive ingredients (12,13). Other major constituents of the flowers include several phenolic compounds, primarily the flavonoids apigenin, quercetin, patuletin as glucosides and various acetylated derivatives. Among the flavonoids, apigenin is the most promising compound. It is present in very small quantities as free apigenin, but predominantly exists in the form of various glycosides (14-18).

3. Healthcare preparations of chamomile

Chamomile preparations take various forms. Dry powder of chamomile flower is recommended and used by many individuals for traditionally established health problems. Medicinal ingredients are normally extracted from the dry flowers of chamomile using water, ethanol or methanol as solvents, with the corresponding extracts known as aqueous, ethanolic (alcoholic) and/or methanolic extracts. Optimum chamomile extracts contain approximately 50% alcohol. Normally, standardized extracts contain 1.2% apigenin, one of the most effective bioactive agents. Aqueous extracts, for example in the form of tea, contain quite low concentrations of free apigenin, but include high levels of apigenin-7-*O*-glucoside. Oral consumption of infusions of chamomile is recommended by the German Commission E (19,20). Chamomile tea is one of the world's most popular herbal teas. Roughly a million cups of chamomile tea are consumed each day. Chamomile tea bags containing chamomile flower powder, either pure or blended with other popular medicinal herbs, are readily available on the market. Chamomile tincture may also be prepared as one part chamomile flower in four parts of water having 12% grain alcohol, which is used to correct summer diarrhea in children and also used with purgatives to prevent cramping. Chamomile flowers are extensively used, either alone or in combination with crushed poppy-heads, as a poultice or hot foment for inflammatory pain or congestive neuralgia, and in cases of external swelling, such as facial swelling associated with underlying infection or abscess. The whole chamomile plant is used for making herbal beers, and also in lotions, for external application in cases of toothache, earache or neuralgia, and in cases of external swelling (20). It is also frequently used as a bath additive, recommended for soothing ano-genital inflammation (21). The tea infusion is used as a wash or gargle for inflammation of the mucous membranes of the mouth and throat (22,23). Inhalation of the vaporized essential oils derived from chamomile flowers is recommended to relieve anxiety and general depression. Chamomile oil is a popular ingredient in aromatherapy and hair care (24,25). Roman chamomile is widely used in cosmetic preparations and has a soothing and softening effect on the skin (26,27).

4. Traditional uses of chamomile

Traditionally, chamomile has been used for centuries as an anti-inflammatory, antioxidant, mild astringent and healing medicine (28). As a traditional medicine, it is used to treat wounds, ulcers, eczema, gout, skin irritations, bruises, burns, canker sores, neuralgia, sciatica, rheumatic pain, hemorrhoids, mastitis and other ailments (29,30). Externally, chamomile has been used to treat diaper rash, cracked nipples, chicken pox, ear and eye infections, disorders of the eyes including blocked tear ducts, conjunctivitis, nasal inflammation and poison ivy (31,32). Chamomile is widely used to treat inflammations of the skin and mucous membranes, and for various bacterial infections of the skin, oral cavity, gums, and respiratory tract. Chamomile in the form of an aqueous extract has been commonly used as a mild sedative to calm nerves and reduce anxiety to treat hysteria, nightmares, insomnia and other sleep problems (33). Chamomile has been valued as a digestive relaxant, and has been used to treat various gastrointestinal disturbances including flatulence, indigestion, diarrhea, anorexia, motion sickness, nausea and vomiting (34,35). Chamomile has also been used to treat colic, croup and fevers in children (36). Additionally, it has been used as an emmenagogue and a uterine tonic in women. It is also effective in alleviating arthritis, back pain, bedsores and stomach cramps.

5. Scientific evaluation of chamomile

Anti-inflammatory and antiphlogistic properties. The flowers of chamomile contain 1-2% volatile oils including α-bisabolol, α-bisabolol oxides A and B and matricin (usually converted to chamazulene) as well as other flavonoids that possess anti-inflammatory and antiphlogistic properties (12,19,35,36). A study in human volunteers demonstrated that chamomile flavonoids and essential oils penetrate below the skin surface into the deeper skin layers (37). This is key to their usefulnes as topical antiphlogistic (anti-inflammatory) agents. One of chamomile's anti-inflammatory activities involves the inhibition of lipopolysaccharide (LPS)-induced prostaglandin E_2 release and the attenuation of cyclooxygenase (COX-2) enzyme activity, without the constitutive form, COX-1, being affected (38).

Anticancer activity. Most evaluations of tumor growth inhibition by chamomile involve studies with apigenin, one of the bioactive constituents of chamomile. Studies using preclinical models of skin, prostate, breast and ovarian cancer have shown it to have promising growth inhibitory effects (39-43). In a recently conducted study, chamomile extracts were shown to have minimal growth inhibitory effects in normal cells, but showed a significant reduction in cell viability in various human cancer cell lines. Chamomile exposure induced apop-

tosis in cancer cells, but not in normal cells at similar doses (18). The efficacy of the novel agent TBS-101, a mixture of seven standardized botanical extracts including chamomile, has recently been tested. The results confirm it to have an outstanding safety profile with significant anticancer activities against androgen-refractory human prostrate cancer PC-3 cells, both *in vitro* and *in vivo* (44).

Common cold. Common cold (acute viral nasopharyngitis) is the most common human disease. It is a mild viral infectious disease of the upper respiratory system. Typically, a common cold is not life-threatening, although its complications (such as pneumonia) can lead to death, if not properly treated. Studies indicate that inhaling steam with chamomile extract has been helpful in relieving common cold symptoms (45); however, further research is needed to confirm these findings.

Cardiovascular conditions. It has been suggested that the regular use of flavonoids consumed in food may reduce the risk of death from coronary heart disease in elderly men (46). A study assessed the flavonoid intake of 805 men aged 65-84 years who were followed up for 5 years. Flavonoid intake (analyzed in tertiles) was significantly inversely associated with mortality from coronary heart disease and showed an inverse relation with the incidence of myocardial infarction. In another study (47) involving twelve patients with cardiac disease who underwent cardiac catheterization, hemodynamic measurements obtained prior to and 30 min after the oral ingestion of chamomile tea exhibited a small but significant increase in mean brachial artery pressure. No other significant hemodynamic changes were observed after chamomile consumption. Ten of the twelve patients fell into a deep sleep shortly after drinking the beverage. A large well-designed randomized controlled trial is needed to assess the potential value of chamomile in improving cardiac health.

Colic/diarrhea conditions. An apple pectin-chamomile extract may help shorten the course of diarrhea in children, as well as relieve symptoms associated with the condition (47). Two clinical trials have evaluated the efficacy of chamomile for the treatment of colic in children. In these trials, chamomile tea was combined with other herbs (German chamomile, vervain, licorice, fennel, balm mint) for administration. In a prospective randomized double-blind placebo-controlled study, 68 healthy term infants (2-8 weeks old) who had colic received either herbal tea or a placebo (glucose, flavoring). Each infant was offered treatment with every bout of colic, up to 150 ml/dose, no more than three times a day. After 7 days of treatment, parents reported that the tea eliminated the colic in 57% of the infants, whereas the placebo was helpful in only 26% ($P<0.01$). No adverse effects with regard to the number of nighttime awakenings were noted in either group (48). Another study examined the effects of a chamomile extract and apple pectin preparation in 79 children (aged 0.5-5.5 years) with acute non-complicated diarrhea who received either the chamomile/pectin preparation (n=39) or a placebo (n=40) for 3 days. Diarrhea ended sooner in children treated with chamomile and pectin (85%) than in the placebo group (58%) (49). These results indicate that chamomile can be used safely to treat infant colic disorders.

Eczema. Topical applications of chamomile have been shown to be moderately effective in the treatment of atopic eczema (50). It was found to be approximately 60% as effective as 0.25% hydrocortisone cream (51). Roman chamomile of the Manzana type in the cream Kamillosan® may ease discomfort associated with eczema. The Manzana type of chamomile is rich in active ingredients and does not exhibit chamomile-related allergenic potential. In a partially double-blind randomized study carried out as a half-side comparison, Kamillosan cream was compared with 0.5% hydrocortisone cream and a placebo consisting only of vehicle cream in patients suffering from medium-degree atopic eczema (52). After 2 weeks of treatment, Kamillosan cream showed a slight superiority over 0.5% hydrocortisone and a marginal difference as compared to the placebo. Further research is needed to evaluate the usefulness of topical chamomile in managing eczema.

Gastrointestinal conditions. Chamomile is traditionally used for the treatment of numerous gastrointestinal conditions, including digestive disorders, 'spasm' or colic, upset stomach, flatulence (gas), ulcers and gastrointestinal irritation (53). Chamomile is particularly helpful in dispelling gas, soothing the stomach, and relaxing the muscles that move food through the intestines. The protective effect of a commercial preparation (STW5, Iberogast), containing the extracts of bitter candy tuft, lemon balm leaf, chamomile flower, caraway fruit, peppermint leaf, liquorice root, Angelica root, milk thistle fruit and greater celandine herb against the development of gastric ulcers has been previously reported (54). STW5 extracts produced a dose-dependent anti-ulcerogenic effect associated with reduced acid output, increased mucin secretion, an increase in prostaglandin E_2 release and a decrease in leukotrienes. The results obtained demonstrated that STW5 not only lowered gastric acidity as effectively as a commercial antacid, but was more effective in inhibiting secondary hyperacidity (54).

Hemorrhoids. Studies suggest that chamomile ointment may improve hemorrhoids. Tinctures of chamomile can also be used in a sitz bath format. Tincture of Roman chamomile may reduce the inflammation associated with hemorrhoids (55,56).

Promotion of health. It has been claimed that consumption of chamomile tea boosts the immune system and helps fight infections associated with colds. The health promoting benefits of chamomile were assessed in a study involving fourteen volunteers who each drank five cups of the herbal tea daily for two consecutive weeks. Daily urine samples were taken and tested throughout the study, both before and after drinking chamomile tea. Drinking chamomile was associated with a significant increase in urinary levels of hippurate and glycine, which have been associated with increased antibacterial activity (57). In another study, chamomile relieved hypertensive symptoms and decreased systolic blood pressure significantly, increasing urinary output (58). Additional studies are required before a more definitive link between chamomile and its alleged health benefits can be established.

Inflammatory conditions. Inflammation is associated with many gastrointestinal complaints, such as esophageal reflux, diverticular disease and inflammatory disease (59-61). Studies in preclinical models suggest that chamomile inhibits *Helicobacter pylori*, the bacteria that contribute to stomach ulcers (60). Chamomile is believed to be helpful in reducing smooth muscle spasms associated with various gastrointestinal inflammatory disorders. Chamomile is often used to treat mild skin irritations, including sunburn, rashes, sores and even eye inflammations (62-65), but its value in treating these conditions has not been demonstrated through evidence-based research.

Mucositis. Mouth ulcers are a common condition with a variety of etiologies (66). Stomatitis is a major dose-limiting toxicity resulting from bolus 5-fluorouracil (5-FU)-based chemotherapy regimens. In a double-blind placebo-controlled clinical trial including 164 patients (22), patients were entered into the study at the time of their first cycle of 5-FU-based chemotherapy and were randomized to receive a chamomile or placebo mouthwash thrice daily for 14 days. There was no suggestion of any difference in the incidence of stomatitis between the patients randomized to either protocol group, nor any suggestion of toxicity. Similar results were obtained in another prospective trial on chamomile in this situation (23). Data obtained from these clinical trials did not support the pre-study hypothesis that chamomile decreases 5-FU-induced stomatitis. Thus it remains unclear whether chamomile is helpful in this situation.

Osteoporosis. Osteoporosis is a metabolic bone disease resulting from low bone mass (osteopenia) due to excessive bone resorption. Sufferers are prone to bone fractures from relatively minor trauma. Agents including selective estrogen receptor modulators or SERMs, biphosphonates and calcitonin are frequently used to prevent bone loss. To prevent bone loss that occurs with increasing age, chamomile extract was evaluated for its ability to stimulate the differentiation and mineralization of osteoblastic cells. Chamomile extract was shown to stimulate osteoblastic cell differentiation and to exhibit an anti-estrogenic effect, suggesting an estrogen receptor-related mechanism (67). However, further studies are required before it can be considered for clinical use.

Sleep aid/sedation. Traditionally, chamomile preparations such as tea and essential oil aromatherapy have been used to treat insomnia and to induce sedation (calming effects). Chamomile is widely regarded as a mild tranquillizer and sleep-inducer. Sedative effects may be due to the flavonoid apigenin, which binds to benzodiazepine receptors in the brain (68). Studies in preclinical models have shown anticonvulsant and CNS depressant effects, respectively. However, clinical trials are notably absent, although ten cardiac patients were reported to have immediately fallen into a deep sleep lasting for 90 min after drinking chamomile tea (47). Chamomile extracts exhibit benzodiazepine-like hypnotic activity (69). In another study, inhalation of the vapor of chamomile oil reduced a stress-induced increase in plasma adrenocorticotropic hormone (ACTH) levels. Diazepam co-administered with chamomile oil vapor further reduced ACTH levels, while flumazenile, a BDZ antagonist, blocked the effect of chamomile oil vapor on ACTH. According to Paladini *et al* (70), the separation index (ratio between the maximal anxiolytic dose and the minimal sedative dose) for diazepam is 3, while that of apigenin is 10. Compounds other than apigenin present in extracts of chamomile can also bind BDZ and GABA receptors in the brain and may be responsible for some sedative effect; however, many of these compounds have yet to be identified.

Anxiety and seizure. Chamomile has been studied in the treatment of generalized anxiety disorder (GAD). Though the reports have been contradictory, one suggested that German chamomile resulted in the significant inhibition of GAD activity (71). Recent results from a controlled clinical trial on chamomile extract for GAD suggests that it may have modest anxiolytic activity in patients with mild to moderate GAD (72). Extracts of chamomile (*M. recutita*) have notable effects on seizure induced by picrotoxin (73). Furthermore, apigenin has been shown to reduce latency in the onset of picrotoxin-induced convulsions and the reduction of locomotor activity, but did not demonstrate any anxiolytic, myorelaxant, or anti-convulsant activities (16).

Diabetes. Studies have suggested that chamomile ameliorates hyperglycemia and diabetic complications by suppressing blood sugar levels, increasing liver glycogen storage and inhibiting sorbitol in human erythrocytes (74). The pharmacological activity of chamomile extract was shown to be independent of insulin secretion (75), and studies further revealed a protective effect on pancreatic β cells due to the diminuation of hyperglycemia-related oxidative stress (76). Additional studies are required to evaluate the usefulness of chamomile in managing diabetes.

Sore throat/hoarseness. The efficacy of lubrication of the endotracheal tube cuff with chamomile before intubation on postoperative sore throat and hoarseness was determined in a randomized double-blind study. One hundred and sixty-one patients with an American Society of Anesthesiologists (ASA) physical status of I or II, undergoing elective surgical, orthopedic, gynecological or urological surgeries, were divided into two groups. The study group received 10 puffs of chamomile extract (Kamillosan M spray, total 370 mg of Chamomile extract) at the site of the cuff of the endotracheal tube for lubrication, while the control group did not receive any lubrication before intubation. Standard general anesthesia with tracheal intubations was applied in both groups. Forty-one of 81 patients (50.6%) in the chamomile group reported no post-operative incidences of sore throat in the post-anesthesia care unit, compared with 45 of 80 patients (56.3%) in the control group; therefore there was no statistical significance between postoperative cases of sore throat and hoarseness in either the post-anesthesia care unit or at 24 h post operation, indicating that lubrication of the endotracheal tube cuff with chamomile extract spray before intubation does not prevent postoperative sore throat and hoarseness (77). Similar results were obtained in another double-blind study (21).

Vaginitis. Vaginal inflammation is common in women of all ages. Vaginitis is associated with itching, vaginal discharge, or

pain with urination. Atrophic vaginitis most commonly occurs in menopausal and postmenopausal women, and its occurrence is often associated with reduced levels of estrogen. Chamomile douche may improve the symptoms of vaginitis with few side effects (78), yet there are insufficient research data to allow conclusions to be drawn concerning the possible potential benefits of chamomile in the treatment of this condition.

Wound healing. The efficacy of the topical use of chamomile to enhance wound healing was evaluated in a double-blind trial on 14 patients who underwent dermabrasion of tattoos. The effects on drying and epithelialization were observed, and chamomile was judged to be statistically efficacious in producing wound drying and in speeding epithelialization (79). The antimicrobial activity of the extract against various microorganisms was also assessed. The test group on day 15 exhibited a greater reduction in the wound area as compared to the controls (61 vs. 48%), faster epithelialization, and a significantly higher wound-breaking strength. In addition, wet and dry granulation tissue weight and hydroxyproline content were significantly higher. The increased rate of wound contraction, together with the increased wound-breaking strength, hydroxyproline content and histological observations, support the use of *M. recutita* in wound management (80). Recent studies suggest that chamomile caused faster complete wound healing than corticosteroids (81). However, further studies are needed before it can be considered for clinical use.

Quality of life in cancer patients. Essential oils obtained from Roman chamomile are the basic ingredients of aromatherapy. Clinical trials of aromatherapy in cancer patients have shown no statistically significant differences between treated and untreated patients (82). Another pilot study investigated the effects of aromatherapy massage on anxiety and self-esteem in Korean elderly women. A quasi-experimental control group pretest-posttest design included 36 elderly females: 16 in the experimental group and 20 in the control group. Aromatherapy massage using lavender, chamomile, rosemary and lemon was administered to the experimental group only. Each massage session lasted 20 min and was performed 3 times per week for 2 to 3-week periods with an intervening 1-week break. The intervention produced significant differences in anxiety and self-esteem. These results suggest that aromatherapy massage exerts positive effects on anxiety and self-esteem (83-85). However, more objective, clinical measures should be applied in a future study with a randomized placebo-controlled design.

6. Contraindications and safety issues with chamomile

A relatively low percentage of people are sensitive to chamomile and develop allergic reactions (86). People sensitive to ragweed and chrysanthemums or other members of the *Compositae* family are more prone to develop contact allergies to chamomile, particularly if they take other drugs that trigger the sensitization. A large-scale clinical trial was conducted between 1985 and 1991 in Hamburg, Germany, to study the development of contact dermatitis secondary to exposure to a mixture of components derived from the *Compositae* family. Twelve species of the *Compositae* family, including German chamomile, were selected and tested individually when the mixture induced allergic reactions. During the study, 3,851 individuals were tested using a patch with the plant extract (87). Of these patients, 118 (3.1%) experienced an allergic reaction. Further tests revealed that feverfew elicited the most allergic reactions (70.1% of patients) followed by chrysanthemums (63.6%) and tansy (60.8%). Chamomile fell in the middle range (56.5%). A study involving 686 subjects exposed to either a sesquiterpene lactone mixture or a mixture of *Compositae* extracts led to allergic reactions in 4.5% of the subjects (88). In another study, it was shown that eye washing with chamomile tea in hay fever patients who had conjunctivitis exacerbated the eye inflammation, whereas no worsening of eye inflammation was noted when chamomile tea was ingested orally (89). Chamomile is listed on the FDA's GRAS (generally recognized as safe) list. It is possible that some reports of allergic reactions to chamomile may be due to the contamination of chamomile by 'dog chamomile', a highly allergenic and bad-tasting plant of similar appearance. Evidence of cross-reactivity of chamomile with other drugs is not well documented, and further study of this issue is required prior to reaching conclusions. Safety in young children, pregnant or nursing women, or those with liver or kidney disease has not been established, although there have not been any credible reports of toxicity caused by this common tea beverage.

7. Conclusions

Chamomile has been used as a herbal medication since ancient times, is still popular today, and will probably continue to be used in the future, as it contains various bioactive phytochemicals that provide therapeutic effects. Chamomile can aid in improving cardiovascular conditions, stimulates the immune system and provides some protection against cancer. Establishing whether or not the therapeutic effects of chamomile are beneficial to patients requires further research and the generation of scientific evidence. There is a need for continued efforts that focus on pre-clinical studies with chamomile involving animal models of various diseases. These results may then be validated in clinical trials with the aim of developing chamomile as a promising therapeutic agent. Without such evidence, it remains unclear whether these untested and unproven medical treatments are truly beneficial. It can be concluded that the discriminate and proper use of chamomile preparations is safe and provides therapeutic benefits; however, its indiscriminate or improper use may be unsafe and harmful.

Acknowledgements

The original work from the laboratory of the authors outlined in this review was supported by US Public Health Service grants RO1 AT002709 and RO1 CA108512.

References

1. Newman DJ, Cragg GM and Snader KM: Natural products as sources of new drugs over the period 1981-2002. J Nat Prod 66: 1022-1037, 2003.
2. Koehn FE and Carter GT: The evolving role of natural products in drug discovery. Nat Rev Drug Discov 4: 206-220, 2005.

3. Jones WP, Chin YW and Kinghorn AD: The role of pharmacognosy in modern medicine and pharmacy. Curr Drug Targets 7: 247-264, 2006.
4. Philip RB: Herbal remedies: the good, the bad, and the ugly. J Comp Integ Med 1: 1-11, 2004.
5. Fabricant DS and Farnsworth NR: The value of plants used in traditional medicine for drug discovery. Environ Health Perspect 109: 69-75, 2001.
6. Hadley SK and Petry JJ: Medicinal herbs: a primer for primary care. Hosp Pract 34: 105-116, 1999.
7. Astin JA, Pelletier KR, Marie A and Haskell WL: Complementary and alternative medicine use among elderly persons: one year analysis of Blue Shield medicare supplement. J Gerontol 55: M4-M9, 2000.
8. Hansen HV and Christensen KI: The common chamomile and the scentless may weed revisited. Taxon 58: 261-264, 2009.
9. Der MA and Liberti L: Natural Product Medicine: A Scientific Guide to Foods, Drugs, Cosmetics. George F. Stickley Co., Philadelphia, 1988.
10. Mann C and Staba EJ: Herbs, spices and medicinal plants: recent advances in botany. In: Horticulture and Pharmacology. Craker E and Simon JE (eds). Oryx Press, Phoenix, pp235-280, 1986.
11. McKay DL and Blumberg JB: A review of the bioactivity and potential health benefits of chamomile tea (*Matricaria recutita* L.). Phytother Res 20: 519-530, 2000.
12. Lemberkovics E, Kéry A, Marczal G, Simándi B and Szöke E: Phytochemical evaluation of essential oils, medicinal plants and their preparations. Acta Pharm Hung 68: 141-149, 1998.
13. Baser KH, Demirci B, Iscan G, *et al*: The essential oil constituents and antimicrobial activity of *Anthemis aciphylla* BOISS. Var. *discoidea* BOISS. Chem Pharm Bull 54: 222-225, 2006.
14. Babenko NA and Shakhova EG: Effects of *Chamomilla recutita* flavonoids on age-related liver sphingolipid turnover in rats. Exp Gerontol 41: 32-39, 2006.
15. Redaelli C, Formentini L and Santaniello E: Reversed-phase high-performance liquid chromatography analysis of apigenin and its glucosides in flowers of *Matricaria chamomilla* and chamomile extracts. Planta Med 42: 288-292, 1981.
16. Avallone R, Zanoli P, Puia G, Kleinschnitz M, Schreier P and Baraldi M: Pharmacological profile of apigenin, a flavonoid isolated from *Matricaria chamomilla*. Biochem Pharmacol 59: 1387-1394, 2000.
17. Svehliková V, Bennett RN, Mellon FA, *et al*: Isolation, identification and stability of acylated derivatives of apigenin 7-O-glucoside from chamomile (*Chamomilla recutita* [L.] Rauschert). Phytochemistry 65: 2323-2332, 2004.
18. Srivastava JK and Gupta S: Antiproliferative and apoptotic effects of chamomile extract in various human cancer cells. J Agric Food Chem 55: 9470-9478, 2007.
19. Carnat A, Carnat AP, Fraisse D, Ricoux L and Lamaison JL: The aromatic and polyphenolic composition of Roman camomile tea. Fitoterapia 75: 32-38, 2004.
20. Hamon N: Herbal medicine. The chamomiles. Can Pharm J 612, 1989.
21. Kyokong O, Charuluxananan S, Muangmingsuk V, Rodanant O, Subornsug K and Punyasang W: Efficacy of chamomile-extract spray for prevention of post-operative sore throat. J Med Assoc Thai 85: 180-185, 2002.
22. Fidler P, Loprinzi CL, O'Fallon JR, Leitch JM, Lee JK, Hayes DL, Novotny P, Clemens-Schutjer D, Bartel J and Michalak JC: Prospective evaluation of a chamomile mouthwash for prevention of 5-FU induced oral mucositis. Cancer 77: 522-525, 1996.
23. Mazokopakis EE, Vrentzos GE, Papadakis JA, Babalis DE and Ganotakis ES: Wild chamomile (*Matricaria recutita* L.) mouthwashes in methotrexate-induced oral mucositis. Phytomedicine 12: 25-27, 2005.
24. Anderson C, Lis-Balchin M and Kirk-Smith M: Evaluation of massage with essential oils on childhood atopic eczema. Phytother Res 14: 452-456, 2000.
25. Wilkinson S, Aldridge J, Salmon I, Cain E and Wilson B: An evaluation of aromatherapy massage in palliative care. Palliat Med 13: 409-417, 1999.
26. Scala G: Acute, short-lasting rhinitis due to chamomile-scented toilet paper in patients allergic to *Compositae*. Int Arch Allergy Immunol 139: 330-333, 2006.
27. Thornfeldt C: Cosmeceuticals containing herbs: fact, fiction, and future. Dermatol Surg 7: 873-880, 2005.
28. Weiss RF: Herbal Medicine. Arcanum AB (ed). Beaconsfield Publishers, Beaconsfield, pp22-28, 1988.
29. Rombi M: Cento Piante Medicinali. Nuovo Instituto d'Arti Grafiche, Bergamo, Italy pp63-65, 1993.
30. Awang DVC: Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals. Taylor and Francis Group, CRC Press, New York, 2006.
31. Martens D: Chamomile: the herb and the remedy, J Chiropract Acad Homeo 6: 15-18, 1995.
32. Newall CA, Anderson LA and Phillipson JD: Herbal Medicine: A Guide for Health Care Professionals. Pharmaceutical Press, London, pp296, 1996.
33. Forster HB, Niklas H and Lutz S: Antispasmodic effects of some medicinal plants. Planta Med 40: 309-319, 1980.
34. Crotteau CA, Wright ST and Eglash A: Clinical inquiries; what is the best treatment for infants with colic? J Fam Pract 55: 634-636, 2006.
35. Sakai H and Misawa M: Effect of sodium azulene sulfonate on capsaicin-induced pharyngitis in rats. Basic Clin Pharmacol Toxicol 96: 54-55, 2005.
36. Peña D, Montes de Oca N and Rojas S: Anti-inflammatory and anti-diarrheic activity of *Isocarpha cubana* Blake. Pharmacol Online 3: 744-749, 2006.
37. Merfort I, Heilmann J, Hagedorn-Leweke U and Lippold BC: In vivo skin penetration studies of camomile flavones. Pharmazie 49: 509-511, 1994.
38. Srivastava JK, Pandey M and Gupta S: Chamomile, a novel and selective Cox-2 inhibitor with anti-inflammatory activity. Life Sci 85: 663-669, 2009.
39. Way TD, Kao MC and Lin JK: Apigenin induces apoptosis through proteasomal degradation of HER2/neu in HER2/neu-overexpressing breast cancer cells via the phosphatidylinositol-3'-kinase/Akt-dependent pathway. J Biol Chem 279: 4479-4489, 2004.
40. Birt DF, Mitchell D, Gold B, Pour P and Pinch HC: Inhibition of ultraviolet light induced skin carcinogenesis in SKH-1 mice by apigenin, a plant flavonoid. Anticancer Res 17: 85-91, 1997.
41. Patel D, Shukla S and Gupta S: Apigenin and cancer chemoprevention: progress, potential and promise. Int J Oncol 30: 233-245, 2007.
42. Gates MA, Tworoger SS, Hecht JL, De Vivo I, Rosner B and Hankinson SE: A prospective study of dietary flavonoid intake and incidence of epithelial ovarian cancer. Int J Cancer 121: 2225-2232, 2007.
43. Shukla S, Mishra A, Fu P, MacLennan GT, Resnick MI and Gupta S: Up-regulation of insulin-like growth factor binding protein-3 by apigenin leads to growth inhibition and apoptosis of 22Rv1 xenograft in athymic nude mice. FASEB J 19: 2042-2044, 2005.
44. Evans S, Dizeyi N, Abrahamsson PA and Persson J: The effect of a novel botanical agent TBS-101 on invasive prostrate cancer in animal models. Anticancer Res 10: 3917-3924, 2009.
45. Saller R, Beschomer M and Hellenbrecht D: Dose dependency of symptomatic relief of complaints by chamomile steam inhalation in patients with common cold. Eur J Pharmacol 183: 728-729, 1990.
46. Hertog MG, Feskens EJ, Hollman PC, Katan MB and Kromhout D: Dietary antioxidant flavonoids and risk of coronary heart disease: the Zutphen Elderly Study. Lancet 342: 1007-1011, 1993.
47. Gould L, Reddy CV and Gomprecht RF: Cardiac effects of chamomile tea. J Clin Pharmacol 11: 475-479, 1973.
48. Gardiner P: Complementary, holistic, and integrative medicine: chamomile. Pediatr Rev 28: 16-18, 2007.
49. Kell T: More on infant colic. Birth Gaz 13: 3, 1997.
50. Nissen HP, Blitz H and Kreyel HW: Prolifometrie, eine methode zur beurteilung der therapeutischen wirsamkeit kon Kamillosan®-Salbe. Z Hautkr 63: 84-90, 1988.
51. Albring M, Albrecht H, Alcorn G and Lüker PW: The measuring of the anti-inflammatory effect of a compound on the skin of volunteers. Meth Find Exp Clin Pharmacol 5: 75-77, 1983.
52. Patzelt-Wenczler R and Ponce-Pöschl E: Proof of efficacy of Kamillosan® cream in atopic eczema. Eur J Med Res 5: 171-175, 2000.
53. Kroll U and Cordes C: Pharmaceutical prerequisites for a multitarget therapy. Phytomedicine 5: 12-19, 2006.
54. Khayyal MT, Seif-El-Nasr M, El-Ghazaly MA, Okpanyi SN, Kelber O and Weiser D: Mechanisms involved in the gastroprotective effect of STW 5 (Iberogast) and its components against ulcers and rebound acidity. Phytomedicine 13: 56-66, 2006.

55. Lyseng-Williamson KA and Perry CM: Micronised purified flavonoid fraction: a review of its use in chronic venous insufficiency, venous ulcers, and haemorrhoids. Drugs 63: 71-100, 2003.
56. Misra MC and Parshad R: Randomized clinical trial of micronized flavonoids in the early control of bleeding from acute internal haemorrhoids. Br J Surg 87: 868-872, 2000.
57. Wang Y, Tang H, Nicholson JK, Hylands PJ, Sampson J and Holmes E: A metabonomic strategy for the detection of the metabolic effects of chamomile (*Matricaria recutita* L.) ingestion. J Agric Food Chem 53: 191-196, 2005.
58. Zeggwagh NA, Moufid A, Michel JB and Eddouks M: Hypotensive effect of *Chamaemelum nobile* aqueous extract in spontaneously hypertensive rats. Clin Exp Hypertens 31: 440-450, 2009.
59. Ramos-e-Silva M, Ferreira AF, Bibas R and Carneiro S: Clinical evaluation of fluid extract of *Chamomilla recutita* for oral aphthae. J Drugs Dermatol 5: 612-617, 2006.
60. Wu J: Treatment of rosacea with herbal ingredients. J Drugs Dermatol 5: 29-32, 2006.
61. Graf J: Herbal anti-inflammatory agents for skin disease. Skin Ther Lett 5: 3-5, 2000.
62. Weseler A, Geiss HK, Saller R and Reichling JA: Novel colorimetric broth microdilution method to determine the minimum inhibitory concentration (MIC) of antibiotics and essential oils against *Helicobacter pylori*. Pharmazie 60: 498-502, 2005.
63. Fugh-Berman A: Herbal supplements: indications, clinical concerns, and safety. Nutr Today 37: 122-124, 2002.
64. Wechselberger G, Schoeller T, Otto A, Obrist P, Rumer A and Deetjen H: Total gluteal pouching with pseudoanus caused by burn injury: report of a case. Dis Colon Rectum 41: 929-931, 1998.
65. Tubaro A, Zilli C, Redaelli C and Della Loggia R: Evaluation of antiinflammatory activity of a chamomile extract after topical application. Planta Med 50: 359, 1984.
66. Gonsalves WC, Wrightson AS and Henry RG: Common oral conditions in older persons. Am Fam Physician 78: 845-852, 2008.
67. Kassi E, Papoutsi Z, Fokialakis N, Messari I, Mitakou S and Moutsatsou P: Greek plant extracts exhibit selective estrogen receptor modulator (SERM)-like properties. J Agric Food Chem 52: 6956-6961, 2004.
68. Avallone R, Zanoli P, Corsi L, Cannazza G and Baraldi M: Benzodiazepine compounds and GABA in flower heads of *Matricaria chamomilla*. Phytother Res 10: 177-179, 1996.
69. Shinomiya K, Inoue T, Utsu Y, Tokunaga S, Masuoka T, Ohmori A and Kamei C: Hypnotic activities of chamomile and passiflora extracts in sleep-disturbed rats. Biol Pharm Bull 28: 808-810, 2005.
70. Paladini AC, Marder M, Viola H, Wolfman C, Wasowski C and Medina JH: Flavonoids and the central nervous system: from forgotten factors to potent anxiolytic compounds. J Pharm Pharmacol 51: 519-526, 1999.
71. Awad R, Levac D, Cybulska P, Merali Z, Trudeau VL and Arnason JT: Effects of traditionally used anxiolytic botanicals on enzymes of the gamma-aminobutyric acid (GABA) system. Can J Physiol Pharmacol 85: 933-942, 2007.
72. Amsterdam JD, Li Y, Soeller I, Rockwell K, Mao JJ and Shults J: A randomized, double-blind, placebo-controlled trial of oral *Matricaria recutita* (Chamomile) extract therapy for generalized anxiety disorder. J Clin Psychopharmacol 29: 378-382, 2009.
73. Herdari MR, Dadollahi Z, Mehrabani M, Mehrabi H, Pourzadeh-Hosseini M, Behravan E and Etemad L: Study of antiseizure effects of *Matricaria recutita* extract in mice. Ann NY Acad Sci 1171: 300-304, 2009.
74. Kato A, Minoshima Y, Yamamoto J, Adachi I, Watson AA and Nash RJ: Protective effects of dietary chamomile tea on diabetic complications. J Agric Food Chem 56: 8206-8211, 2008.
75. Eddouks M, Lemhadri A, Zeggwah NA and Michel JB: Potent hypoglycaemic activity of the aqueous extract of *Chamaemelum nobile* in normal and streptozotocin-induced diabetic rats. Diabetes Res Clin Pract 67: 189-195, 2005.
76. Cemek M, Kaga S, Simsek N, Buyukokuroglu ME and Konuk M: Antihyperglycemic and antioxidative potential of *Matricaria chamomilla* L. in streptozotocin-induced diabetic rats. J Nat Med 62: 284-293, 2008.
77. Charuluxananan S, Sumethawattana P, Kosawiboonpol R, Somboonviboon W and Werawataganon T: Effectiveness of lubrication of endotracheal tube cuff with chamomile-extract for prevention of postoperative sore throat and hoarseness. J Med Assoc Thai 87: 185-189, 2004.
78. Benetti C and Manganelli F: Clinical experiences in the pharmacological treatment of vaginitis with a camomile-extract vaginal douche. Minerva Ginecol 37: 799-801, 1985.
79. Glowania HJ, Raulin C and Swoboda M: Effect of chamomile on wound healing – a clinical double-blind study. Z Hautkr 62: 1267-1271, 1987.
80. Nayak BS, Raju SS and Rao AV: Wound healing activity of *Matricaria recutita* L. extract. J Wound Care 16: 298-302, 2007.
81. Martins MD, Marques MM, Bussadori SK, Martins MA, Pavesi VC, Mesquita-Ferrari RA and Fernandes KP: Comparative analysis between *Chamomilla recutita* and corticosteroids on wound healing. An in vitro and in vivo study. Phytother Res 23: 274-278, 2009.
82. Wilcock A, Manderson C, Weller R, Walker G, Carr D, Carey AM, Broadhurst D, Mew J and Ernst E: Does aromatherapy massage benefit patients with cancer attending a specialist palliative care day centre? Palliat Med 18: 287-290, 2004.
83. Soden K, Vincent K, Craske S, Lucas C and Ashley S: A randomized controlled trial of aromatherapy massage in a hospice setting. Palliat Med 18: 87-92, 2004.
84. Graham PH, Browne L, Cox H and Graham J: Inhalation aromatherapy during radiotherapy: results of a placebo-controlled double-blind randomized trial. J Clin Oncol 21: 2372-2376, 2003.
85. Hadfield N: The role of aromatherapy massage in reducing anxiety in patients with malignant brain tumours. Int J Palliat Nurs 7: 279-285, 2001.
86. Budzinski JW, Foster BC, Vandenhoek S and Arnason JT: An in vitro evaluation of human cytochrome P450 3A4 inhibition by selected commercial herbal extracts and tinctures. Phytomedicine 7: 273-282, 2000.
87. Hausen BM: A 6-year experience with a *Compositae* mix. Am J Contact Dermat 7: 94-99, 1996.
88. Paulsen E, Andersen KE and Hausen BM: *Compositae* dermatitis in a Danish dermatology department in one year (I). Results of routine patch testing with the sesquiterpene lactone mix supplemented with aimed patch testing with extracts and sesquiterpene lactones of *Compositae* plants. Contact Dermatitis 29: 6-10, 1993.
89. Subiza J, Subiza JL, Alonso M, Hinojosa M, Garcia R, Jerez M and Subiza E: Allergic conjunctivitis to chamomile tea. Ann Allergy 65: 127-132, 1990.

In vivo skin penetration studies of camomile flavones

https://pubmed.ncbi.nlm.nih.gov/8073060/

I Merfort[1], J Heilmann, U Hagedorn-Leweke, B C Lippold

Affiliation

- [1]Institut für Pharmazeutische Biologie, Heinrich-Heine Universität Düsseldorf.

- PMID: 8073060

Abstract

In vivo skin penetration studies of the Camomile flavones apigenin, luteolin and apigenin 7-O-beta-glucoside were carried out with nine healthy, female volunteers. During seven hours the decline of flavonoid concentration in a saturated aqueous alcoholic solution filled in glass application chambers were repeatedly measured by spectrophotometry at fixed time periods. The maximal fluxes were calculated. From the graph of the maximal flux values as a function of time it was concluded, that the flavonoids are not only adsorbed at the skin surface, but penetrate into deeper skin layers. This is important for their topical use as antiphlogistic agents.

Green tea and skin

S K Katiyar[1], N Ahmad, H Mukhtar
Affiliations collapse

Affiliation

- [1]Department of Dermatology, Case Western Reserve University, Cleveland, OH 44106, USA.

- PMID: 10926734

- DOI: 10.1001/archderm.136.8.989

Abstract

Objective: To discuss the current knowledge of polyphenolic compounds present in green tea as anti-inflammatory, antioxidant, and anticarcinogenic in skin.

Data sources: References identified from bibliographies of pertinent articles, including our work in related fields.

Study selection and data extraction: Articles were selected based on the use of green tea or its polyphenolic constituents for prevention against inflammation and cancer in the skin. Also discussed is the possible use of green tea to treat various inflammatory dermatoses.

Data synthesis: The polyphenolic compounds from green tea were tested against chemical carcinogenesis and photocarcinogenesis in murine skin. These green tea polyphenols were found to afford protection against chemical carcinogenesis as well as photocarcinogenesis in mouse skin. A few experimental studies were conducted in human skin in our laboratory. Analysis of published studies demonstrates that green tea polyphenols have anti-inflammatory and anticarcinogenic properties. These effects appear to correlate with antioxidant properties of green tea polyphenols.

Conclusions: The outcome of the several experimental studies suggests that green tea possess anti-inflammatory and anticarcinogenic potential, which can be exploited against a variety of skin disorders. Although more clinical studies are needed, supplementation of skin care products with green tea may have a profound impact on various skin disorders in the years to come. Arch Dermatol. 2000;136:989-994

Green Tea for Your Skin

Rich with antioxidants and nutrients, green tea is considered by many to have benefits for a variety of health issues.

A 2018 study showed the major polyphenolic compound present in green tea, EGCG (epigallocatechin-3-gallate), was found to exhibit a wide range of therapeutic properties, including:

- anti-oxidant
- anti-inflammatory
- anti-atherosclerosis
- anti-myocardial infarction
- anti-diabetes

In a 2012 study, these plant polyphenols were shown to also offer cancer-prevention effects when used to protect the skin and immune system support.

Green tea and acne

According to a 2016 reviewTrusted Source, the EGCG in green tea has antioxidant, anti-inflammatory, and antimicrobial properties. They have shown improvement in treating acne and oily skin.

Oily skin

Acne is the result of excess sebum clogging pores and stimulating bacterial growth.

EGCG is anti-androgenic and lowers lipid levels. This makes it effective at reducing sebum excretions in the skin. By reducing sebum, EGCG can slow or stop the development of acne.

- Sebum is an oily substance that your sebaceous glands secrete to moisturize your skin and hair.
- Androgens are hormones that your body produces. If you have high or fluctuating levels of androgen, it can cause your sebaceous glands to produce greater amounts of sebum.

Green tea and skin cancer

According to a 2003 studyTrusted Source, the polyphenols in green tea can be used as pharmacological agents for the prevention of solar UVB light-induced skin disorders in animals and humans, including:

- melanoma skin cancer
- nonmelanoma skin cancers
- photoaging

Green tea extract and your skin

A 2012 reviewTrusted Source of 20 studies indicated that green tea extract has been shown to be potentially effective when applied to the skin and taken as a supplement for:

- acne
- androgenetic alopecia
- atopic dermatitis
- candidiasis

genital warts

- keloids
- rosacea

Acne

Consider green tea extract as part of your acne regimen.

In a 2016 study, participants took 1,500 mg of green tea extract for 4 weeks. At the conclusion of the study, participants showed a significant reduction in the red skin bumps acne causes.

Aging

Drinking green tea and applying it to your skin can help your skin handle the aging process better.

- A small 2005 studyTrusted Source of 80 women showed an improvement of skin elasticity in participants treated with a combination regimen of topical and oral green tea.
- A long-term 2013 studyTrusted Source of 24 people showed that skin damage caused by sun exposure was reduced with the topical application of cosmetics containing green tea extract. Researchers suggested cosmetic formulations including green tea extract have improved skin microrelief and have pronounced moisturizing effects.

Green tea and the skin around your eyes

If you're experiencing swelling around your eyes, this green tea home remedy for puffy eyes may provide relief. It's a simple method.

Here are the steps:

1. Steep or soak two green tea bags for tea to drink.
2. Squeeze the bags to remove excess liquid.
3. Put the tea bags in the refrigerator for 10 to 20 minutes.
4. Place the tea bags on your closed eyes for up to 30 minutes.

Advocates for this treatment suggest that the combination of caffeine and a cold compress will help alleviate the puffiness.

Although clinical research does not support this method, the Mayo Clinic recommends using a cool compress (washcloth and cool water).

Also, according a 2010 article in the Journal of Applied Pharmaceutical Science, the caffeine in green tea can constrict the blood vessels to reduce swelling and inflammation.

Precautions

The area around your eyes is sensitive, so before attempting this remedy, consider:

- washing your hands and face
- removing makeup

- removing contact lenses
- keeping liquid out of your eyes
- avoiding tea bags with staples

As with any home remedy, talk with your doctor before trying it. Also, stop using it if you experience any pain or irritation.

Takeaway

There are many research studies that show that both drinking green tea and applying it topically can have benefits for your skin.

Not only can green tea and green tea extract help with acne and help your skin look younger, but it also has the potential for helping to prevent melanoma and nonmelanoma skin cancers.

Healthline has strict sourcing guidelines and relies on peer-reviewed studies, academic research institutions, and medical associations. We avoid using tertiary references. You can learn more about how we ensure our content is accurate and current by reading our editorial policy.

https://www.healthline.com/health/benefits-of-green-tea-for-skin#takeaway

- Amnuaikit T, et al. (2011). Evaluation of caffeine gels on physicochemical characteristics and in vivo efficacy in reducing puffy eyes. japsonline.com/admin/php/uploads/20_pdf.pdf

- Chacko SM, et al. (2010). Beneficial effects of green tea: A literature review. DOI: 10.1186/1749-8546-5-13

- Chatterjee P, et al. (2012). Evaluation of anti-inflammatory effects of green tea and black tea: A comparative in vitro study. DOI: 10.4103/2231-4040.97298

- Chiu AE, et al. (2005). Double-blinded, placebo-controlled trial of green tea extracts in the clinical and histologic appearance of photoaging skin. ncbi.nlm.nih.gov/pubmed/16029678

- Eng QY, et al. (2018). Molecular understanding of Epigallocatechin gallate (EGCG) in cardiovascular and metabolic diseases. DOI: 10.1016/j.jep.2017.08.035

- Gianeti MD, et al. (2013). The use of green tea extract in cosmetic formulations: Not only an antioxidant active ingredient. DOI: 10.1111/j.1529-8019.2013.01552.x

- Katiyar SK. (2003). Skin photoprotection by green tea: Antioxidant and immunomodulatory effects. ncbi.nlm.nih.gov/pubmed/12871030

- Lu PH, et al. (2016). Does supplementation with green tea extract improve acne in post-adolescent women? A randomized, double-blind, and placebo-controlled clinical trial. DOI: 10.1016/j.ctim.2016.03.004

- Mayo Clinic Staff. (2018). Arteriosclerosis / atherosclerosis. mayoclinic.org/diseases-conditions/arteriosclerosis-atherosclerosis/symptoms-causes/syc-20350569

- Mayo Clinic Staff. (2018). Bags under eyes. mayoclinic.org/diseases-conditions/bags-under-eyes/diagnosis-treatment/drc-20369931

- OyetakinWhite P, et al. (2012). Protective mechanisms of green tea polyphenols in skin. DOI: 10.1155/2012/560682

- Pazyar N, et al. (2012). Green tea in dermatology. ncbi.nlm.nih.gov/pubmed/23346663

- Saric S, et al. (2017). Green tea and other tea polyphenols: Effects on sebum production and acne vulgaris. DOI: 10.3390/antiox6010002

Green tea in dermatology

Nader Pazyar[1], Amir Feily, Afshin Kazerouni
Affiliations collapse
Affiliation

- [1]Department of Dermatology, Jahrom University of Medical Sciences, Jahrom, Iran.

- PMID: 23346663

Abstract

The purpose of this brief review is to summarize all in vitro, in vivo, and controlled clinical trials on green tea preparations and their uses in dermatology. An extensive literature search was carried out to identify in vivo and in vitro studies as well as clinical trials. Twenty studies were assessed and the results suggest that oral administration of green tea can be effective in the scavenging of free radicals, cancer prevention, hair loss, and skin aging plus protection against the adverse effects associated with psoralen-UV-A therapy. Topical application of green tea extract should be potentially effective for atopic dermatitis, acne vulgaris, rosacea, androgenetic alopecia, hirsutism, keloids, genital warts, cutaneous leishmaniasis, and candidiosis. There are promising results with the use of green tea for several dermatologic conditions; however, the efficacy of oral and topical green tea has not always been confirmed.

Identification of *Magnolia officinalis* L. Bark Extract as the Most Potent Anti-Inflammatory of Four Plant Extracts

Joel M. Walker, Amarnath Maitra, Jessica Walker, Miriam M. Ehrnhoefer-Ressler, Taichi Inui and Veronika Somoza
https://doi.org/10.1142/S0192415X13500389

Abstract

This study was designed to compare the anti-inflammatory potential of a *Magnolia officinalis* L. bark extract solely or in combination with extracts prepared from either *Polygonum aviculare* L., *Sambucus nigra* L., or *Isodon japonicus* L. in bacterial lipopolysaccharide (LPS) stimulated human gingival fibroblasts (HGF-1) and human U-937 monocytes, as cell models of periodontal disease. HGF-1 and U-937 cells were incubated with LPS from either *Porphyromonas gingivalis* or *Escherichia coli* together with the four plant extracts alone or in combination. Secretion of anti-inflammatory cytokines from HGF-1 and U-937 cells was measured by means of a multiplexed bead assay system. *Magnolia officinalis* L. bark extract, at concentrations of 1 μg/mL and 10 μg/mL, reduced interleukin 6 (IL-6) and interleukin-8 (IL-8) secretion from HGF-1 cells to 72.5 ± 28.6% and reduced matrix metalloproteinase 2 (MMP-2) and matrix metalloproteinase 9 (MMP-9) secretion from U-937 cells to 8.87 ± 7.97% compared to LPS-treated cells (100%). The other three extracts also reduced secretion of these inflammatory markers but were not as effective. Combination of 9 μg/mL *Magnolia officinalis* L. extract with 1 μg/mL of each of the other extracts maintained the anti-inflammatory effect of *Magnolia officinalis* L. extract. Combination of 5 μg/mL *Magnolia officinalis* L. extract with 5 μg/mL *Isodon japonicus* L. extract also maintained the anti-inflammatory potential of the *Magnolia officinalis* L. extract, whereas increasing concentrations of any of the other plant extracts in the combination experiments reduced the *Magnolia officinalis* L. extract efficacy in U-937 cells.

References

- T. Ara et al. , *J. Periodontal Res.* **44** , 21 (2009) . Crossref, Medline, ISI, Google Scholar
- G. Campus et al. , *Caries Res.* **45** , 393 (2011) . Crossref, Medline, ISI, Google Scholar
- C. Chaussain-Miller et al. , *J. Dent. Res.* **85** , 22 (2006) . Crossref, Medline, ISI, Google Scholar
- R. P. Darveau et al. , *Infect Immun.* **72** , 5041 (2004) . Crossref, Medline, ISI, Google Scholar
- J. Detert et al. , *Arthritis Res. Ther.* **12** , 218 (2010) . Crossref, Medline, ISI, Google Scholar
- G. P. Garlet , *J. Dent. Res.* **89** , 1349 (2010) . Crossref, Medline, ISI, Google Scholar

- M. Gonzalez Begne et al. , *J. Ethnopharmacol.* **74** , 45 (2001) . Crossref, Medline, ISI, Google Scholar
- M. Greenberg , P. Urnezis and M. Tian , *J. Agric. Food Chem.* **55** , 9465 (2007) . Crossref, Medline, ISI, Google Scholar
- E. Harokopakis et al. , *J. Periodontol.* **77** , 271 (2006) . Crossref, Medline, ISI, Google Scholar
- C. Hayashi et al. , *Mol. Oral Microbiol.* **25** , 305 (2010) . Crossref, Medline, ISI, Google Scholar
- S. Held , P. Schieberle and V. Somoza , *J. Agric. Food Chem.* **55** , 8040 (2007) . Crossref, Medline, ISI, Google Scholar
- B. Y. Hwang et al. , *Planta Med.* **67** , 406 (2001) . Crossref, Medline, ISI, Google Scholar
- H. Inaba and A. Amano , *J. Pharmacol. Sci.* **113** , 103 (2010) . Crossref, Medline, ISI, Google Scholar
- L. N. Jackson et al. , *Am. J. Chin. Med.* **36** , 953 (2008) . Link, ISI, Google Scholar
- S. Jain and R. P. Darveau , *Periodontology 2000* **54** , 53 (2010) . Crossref, Medline, ISI, Google Scholar
- S. Jaric et al. , *J. Ethnopharmacol.* **111** , 160 (2007) . Crossref, Medline, ISI, Google Scholar
- S. Y. Kim et al. , *Immunopharmacol. Imunotoxicol.* **26** , 273 (2004) . Crossref, Medline, ISI, Google Scholar
- J. Lee et al. , *Planta Med.* **71** , 338 (2005) . Crossref, Medline, ISI, Google Scholar
- A. C. Morandini et al. , *J. Periodontol.* **81** , 310 (2010) . Crossref, Medline, ISI, Google Scholar
- T. Mosmann , *J. Immunol. Methods* **65** , 55 (1983) . Crossref, Medline, ISI, Google Scholar
- T. Ogawa et al. , *Int. Immunol.* **14** , 1325 (2002) . Crossref, Medline, ISI, Google Scholar
- J. Park et al. , *Eur. J. Pharmacol.* **496** , 189 (2004) . Crossref, Medline, ISI, Google Scholar
- I. Paur et al. , *Cancer Prev. Res (Phila).* **3** , 653 (2010) . Crossref, Medline, ISI, Google Scholar
- B. L. Pihlstrom , B. S. Michalowicz and N. W. Johnson , *Lancet* **366** , 1809 (2005) . Crossref, Medline, ISI, Google Scholar
- S. S. Socransky et al. , *J. Clin. Periodontol.* **25** , 134 (1998) . Crossref, Medline, ISI, Google Scholar
- P. Souza et al. , *J. Dent. Res.* **89** , 802 (2010) . Crossref, Medline, ISI, Google Scholar
- W. S. Speidl et al. , *FASEB J.* **18** , 603 (2004) . Crossref, Medline, ISI, Google Scholar
- C. Sundstrom and K. Nilsson , *Int. J. Cancer* **17** , 565 (1976) . Crossref, Medline, ISI, Google Scholar
- A. K. Tse et al. , *Mol. Immunol.* **44** , 2647 (2007) . Crossref, Medline, ISI, Google Scholar
- J. E. Vlachojannis , M. Cameron and S. Chrubasik , *Phytother. Res.* **24** , 1 (2010) . Crossref, Medline, ISI, Google Scholar
- H. Wagner and G. Ulrich-Merzenich , *Phytomedicine* **16** , 97 (2009) . Crossref, Medline, ISI, Google Scholar
- A. P. West , A. A. Koblansky and S. Ghosh , *Annu. Rev. Cell Dev. Biol.* **22** , 409 (2006) . Crossref, Medline, ISI, Google Scholar

- X. N. Wu et al. , *J. Ethnopharmacol.* **134** , 191 (2011) . Crossref, Medline, ISI, Google Scholar
- Z. Zakay-Rones et al. , *J. Altern. Complement. Med.* **1** , 361 (1995) . Crossref, Medline, Google Scholar
- Z. Zakay-Rones et al. , *J. Int. Med. Res.* **32** , 132 (2004) . Crossref, Medline, ISI, Google Scholar
- C. Zhao et al. , *Bioorg. Med. Chem.* **18** , 2388 (2010) . Crossref, Medline, ISI, Google Scholar