



ISSN : 2347 - 2243

Indo - American Journal of Life Sciences and Biotechnology



<https://iajlb.org>

Email : editor@iajlb.com or iajlb.editor@gmail.com



Evaluation of Wound-Healing Activity of an Aloe vera Gel Formulation in an Excision Wound Model

Pawel Sobczak¹, Dimitrios Papadakis², Aparna Kamath³

¹Professor, Department of Pharmaceutics, Kashubian Institute of Medical Sciences, Kartuzy, Poland.

²Associate Professor, Department of Pharmacology, Epirus Institute of Biomedical Sciences, Ioannina, Greece.

³Professor, Department of Pharmacology, Tungabhadra Institute of Biotechnology, Hospet, India.

Email: ¹p.sobczak@kims.edu.pl, ²d.papadakis@eibs.gr, ³a.kamath@tib.ac.in

ORCID: ¹0000-0001-2418-0833, ²0000-0001-0925-0995, ³0000-0001-0129-6569

Received: June 9, 2013 Accepted: November 2, 2013 Published: February 25, 2014

DOI: [10.62644/iajlb.2014.v11.i1.pp11-18](https://doi.org/10.62644/iajlb.2014.v11.i1.pp11-18)

ABSTRACT

Aloe vera leaf gel is among the most widely used botanical materials for skin care, and a steady stream of reports describes faster closure of excision wounds in rodents treated with gel formulations. This narrative review asks what that body of work can and cannot tell a reader. It draws on published literature on the composition of the gel, the biology of cutaneous repair, the excision wound model and the design and reporting of animal experiments, and it reports no new data and no local study. The gel contains polysaccharides, glycoproteins, phenolic compounds and minerals that could plausibly act on inflammation, moisture balance, fibroblast activity and oxidative stress, but most proposed mechanisms rest on in vitro work or on a few small animal reports. Human trials are few, small and mixed in their findings. Composition varies with plant part, processing and storage, and many animal reports omit the details needed to repeat them: the base used, the control group, how wounds were measured and who was blinded. Rodent wounds also close mainly by contraction, which limits translation to people. The review concludes that benefit is plausible but unproven for any particular formulation, and it sets out what a convincing excision wound study of an Aloe vera gel would need to report.

Keywords: Aloe vera; Wound healing; Excision wound model; Topical gel; Narrative review

Citation: Sobczak, Papadakis and Kamath [2014]. Evaluation of Wound-Healing Activity of an Aloe vera Gel Formulation in an Excision Wound Model. *Indo-Am. J. Life Sci. Biotechnol.* 11(1):11-18. DOI: [10.62644/iajlb.2014.v11.i1.pp11-18](https://doi.org/10.62644/iajlb.2014.v11.i1.pp11-18)

Article Class: Narrative Review

1. Introduction

Few plants are as familiar in household medicine as Aloe vera. The clear mucilaginous gel from the inner leaf has been smeared on burns, grazes and sore skin for centuries, and it now turns up in creams, dressings, drinks and cosmetics (1, 2). Against that background it is not

surprising that wound healing has become one of the most frequently tested claims for the gel, and that a topical gel formulation applied to an excision wound in a rat or mouse is one of the commonest designs in the pharmacology literature (3, 4). The design is popular because it is quick and inexpensive, though popularity



is not the same as reliability.

A full-thickness excision wound is cheap to make and gives several numbers at once, yet a result that is simple to generate is not simple to interpret, and the animal reports sit alongside human trials that are small and conflicting (5, 6).

This article reviews what the published literature says about the wound-healing activity of Aloe vera gel formulations and about the excision wound model used to test them. It is a narrative review that reports no new experiment, no animal data and no local study; every statement is drawn from published work. We describe what the gel contains, how skin repairs itself, where the excision model informs and where it misleads, and what a study would have to report to be trusted. The aim is a fair account of what has been shown and what has merely been repeated.

2. Literature Review

2.1 Composition of the Gel

Aloe vera gel is the colourless tissue at the centre of the leaf, and it is mostly water. The solid fraction includes polysaccharides, notably acetylated mannans and glucomannans, together with proteins, amino acids, lipids, sterols, organic acids, vitamins and minerals (7, 8). Table 1 lists the main classes and the roles proposed for them. The polysaccharides attract most attention because they bind water and have been reported to influence fibroblasts and immune cells in culture (8). Composition is not constant. Polysaccharide structure differs between leaf tissues and between preparations (9), and processing changes what finally reaches the wound (8, 11). The yellow latex just beneath the leaf rind carries irritant anthraquinones, and a gel carelessly separated from the rind is not the same material as a carefully filleted one (12). This is one reason the same plant

can look excellent in one report and unremarkable in the next.

Table 1. Reported constituents of Aloe vera leaf gel and the roles proposed for them.

Constituent class	Examples	Proposed relevance
Polysaccharides	Acetylated mannans, glucomannans (8, 9)	Water binding; effects on fibroblasts
Glycoproteins and proteins	Lectin-like fractions (8)	Possible signalling roles
Phenolic compounds	Anthraquinones, chromones (7, 10)	Antioxidant; irritant if latex remains
Sterols and organic acids	Plant sterols, salicylic acid (7)	Possible effects on inflammation
Minerals and vitamins	Zinc, magnesium, vitamins C and E (2, 8)	Cofactors for repair enzymes

Note: Roles are hypotheses drawn from the cited literature; composition varies with species, plant part and processing.

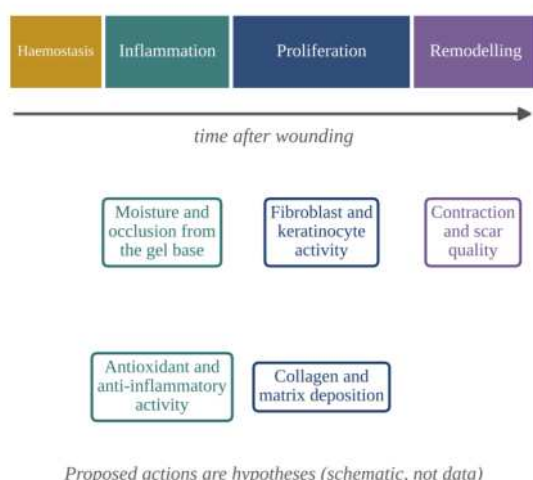
2.2 How Skin Repairs Itself

Cutaneous repair is usually described in overlapping phases: haemostasis, inflammation, proliferation and remodelling (13, 14). Platelets and fibrin seal the wound first; neutrophils and macrophages then clear debris, and macrophages release the signals that start the next phase (15). Over the following days keratinocytes migrate across the wound, fibroblasts lay down new matrix, and new vessels grow in (16, 17). Months later the matrix is remodelled, though the scar never fully matches uninjured skin (18).

Growth factors and cytokines coordinate these steps (19). Figure 1 shows the phases and the places where Aloe vera has been proposed to act. They are proposals, not established mechanisms. Anti-inflammatory activity has been reported for gel extracts in experimental



systems (20, 21), antioxidant activity has been measured in extracts in the test tube (10), and effects on fibroblast activity and collagen have been suggested (8). How much of this occurs in a living wound is far less clear.



Proposed actions are hypotheses (schematic, not data)

Figure 1. Phases of cutaneous repair and the points at which Aloe vera gel has been proposed to act (schematic, not data).

There is one mechanism that needs no special chemistry. Wounds that stay moist re-cover with epithelium faster than wounds left to dry, a point made decades ago for pig and human skin (22, 23). Any water-rich gel may therefore speed closure partly through the moisture it provides, so a benefit seen against an untreated control may owe something to the vehicle, and only a base-only control can show how much.

2.3 The Excision Wound Model

In the excision model a defined piece of full-thickness skin is removed, usually from the back of a rat or mouse, and the open wound is left to heal under observation. Detailed protocols exist for mice (24) and the surgical variants have been compared (25).

The model has a well-known limitation. In loose-skinned rodents most closure comes from contraction by the panniculus muscle,

whereas human wounds close more by re-epithelialisation and granulation (26, 27, 28). Splinting the wound edge with a ring reduces contraction and makes the mouse wound behave more like a human one (27). Pig skin is closer to ours (29). Many plant studies use unsplinted wounds, so faster closure may reflect contraction more than regeneration. A wound that is left alone behaves differently from one that is dressed, measured and re-dressed every other day.

2.4 Clinical and Experimental Evidence for Aloe vera

Experimental reports on Aloe vera and wounds are numerous. Gel applied to excisional wounds has been reported to speed closure in rodents (30, 31), and extracts of other Aloe species have been tested in similar models (32). Plant extract studies in excision wounds usually pair a treated group with an untreated group and a reference drug (33), and reviews note how varied and loosely reported these designs are (3, 4).

Human evidence is thinner. A systematic review of burn wounds concluded that Aloe vera may shorten healing time, while noting the small size and variable quality of the trials (6), and one randomised comparison with silver sulfadiazine in second-degree burns reported favourable results for the gel (34). For acute and chronic wounds as a group, the Cochrane review judged the evidence inconclusive (5). The burn trials used different comparators and outcome definitions, which makes pooling them difficult (6). A trial of the gel to prevent radiation-induced skin damage found no benefit (35). Figure 2 summarises the picture: promise without proof. That is a modest claim, and it is the one the evidence will currently bear. Consistent reporting of dose, vehicle and comparator would make the next review easier to write.



3. Materials and Methods

3.1 Scope

This is a narrative synthesis. The question was what the literature establishes about the wound-healing activity of Aloe vera gel formulations, and how reliable the excision model is for testing them. No new experiments were done.

3.2 Literature Assembly

Sources were gathered by reading and by following citations from review articles, not by a formal systematic search, and no protocol was registered. The review therefore carries the risks of any narrative approach, chiefly that the selection reflects what the authors knew or found, and cannot be called exhaustive. Only works published up to 2013 were used. Reviews of this kind are more useful when they say where the evidence stops than when they smooth it over.

3.3 Appraisal Framework

Each source was read against the questions in Table 2, which draw on published reporting guidance for animal research (36, 37). The questions were applied qualitatively, without scores. None of these steps is difficult, but each is easy to skip when a result looks promising.

4. Results

4.1 What Is Measured, and What It Means

Table 3 sets out the measures that recur in excision wound studies. Wound area is the simplest, but it merges contraction and epithelialisation, and in an unsplinted rodent wound contraction dominates (24, 27). Hydroxyproline is an amino acid abundant in collagen, and its content in tissue is measured by established chemistry (40). It tells us how much collagen is present, not how well it is organised.

Table 2. Appraisal framework used to read each source.

Domain	Question asked	Why it matters
Material	Is the plant part, species and processing stated?	Composition varies widely (9, 12)
Vehicle	Is a base-only control included?	Gel base is itself moist and occlusive (22)
Animals	Strain, sex, age, number and housing?	Needed to repeat the work (36)
Wound	Site, size, splinting, dressing, observer blinding?	Contraction dominates in rodents (27)
Outcomes	Which measures and what time points?	Different measures answer different questions
Analysis	Unit of analysis and handling of multiple outcomes?	Small groups give unstable estimates (38, 39)

Note: Domains were applied qualitatively; no scores were calculated.

Table 3. Outcome measures common in excision wound studies and their main caveats.

Measure	What it reflects	Main caveat
Wound area over time	Contraction plus epithelialisation (24)	Cannot separate the two processes
Epithelialisation period	Days to full re-covering	Depends on how closure is defined
Hydroxyproline content	Collagen deposition (40)	Reflects amount, not quality of collagen
Histology	Cell infiltrate, vessels, matrix (17)	Scoring is subjective unless blinded
Tensile strength	Mechanical recovery (41)	Usually measured on incision, not excision, wounds

Note: Listed are measures that appear in the cited methodological and experimental literature.

Tensile strength tests mechanical recovery, as in the classic rat work (41), but it is



usually done on incision wounds. Histology adds detail on vessels, cells and matrix (17), but its value falls if the slides are scored by someone who knows the treatment. The same extract can thus look strong on one measure and unremarkable on another.

4.2 Weight of Evidence by Setting

Figure 2 summarises the literature by wound setting. The largest body of work is in rodent excision wounds, the setting least able to predict what happens in people (42, 43). Human work is concentrated in burns, where trials are small, and results for other wound types and for prevention of radiation damage are unclear or negative (5, 35).

Small groups give unstable estimates, and the studies that reach print are often those with striking results (38, 44). Surveys of animal research also find that randomisation and blinding are often not reported (37). Seen this way, a null result in a small group is not evidence that nothing happens.

Wound setting	Animal reports	Human trials
Rodent excision	Many, small	Not applicable
Burns	Some	Few, small, favourable
Chronic wounds	Few	Unclear
Surgical wounds	Few	Mixed
Radiation skin injury	Little	No benefit shown

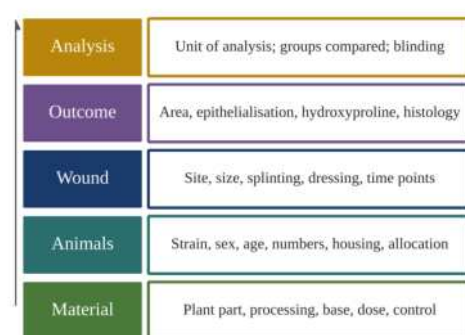
Qualitative summary, not data; shading shows weight of evidence only

Figure 2. Qualitative map of the evidence for Aloe vera by wound setting (schematic summary of the cited literature, not data).

4.3 What a Convincing Study Would Report

Figure 3 lays out the layers of information a reader needs. The first is the material

itself: the Aloe species and plant part, how the gel was prepared, whether latex was removed, what base and preservatives were used, and the dose or concentration applied (8, 12). The second is the animals, with strain, sex, age, number per group and how they were allocated (36, 39). The third is the wound: site, size, splinting, dressing and who measured it (27).



Each layer must be stated for the result above it to be judged (schematic)

Figure 3. Layers of information a reader needs to judge an excision wound study (schematic, not data).

The remaining layers are the outcome measures and the analysis. Analysis with the animal as the unit, and a stated plan for several outcomes, would remove much ambiguity (39). Because the base is moist and occlusive, a base-only group should accompany every comparison (22, 23). A reader of such a report needs to know one thing above all: would this result survive a repeat in another laboratory?

5. Discussion

5.1 Interpretation

The literature supports a cautious reading. Aloe vera gel is plausibly useful for wounds, and the reasons are not mysterious: it is mostly water, it contains substances with reported biological activity, and a moist environment aids repair (8, 22). What is missing is evidence that a specific formulation, tested in a well-designed study, produces a benefit beyond what its base would give.



Positive effects in animals do not reliably predict positive effects in people, and the gap is not unique to wound care (42, 43). Faster closure in an unsplinted rat wound does not show that the gel would help a person with a chronic leg ulcer.

5.2 Limitations

The review was not systematic, so relevant studies may have been missed and the balance skewed toward studies that are easy to find. The constituent roles in Table 1 rest largely on laboratory work whose relevance to a gel on a wound is untested. It is also confined to work published up to 2013. The point is not that a study is poor, only that its result travels less far than its abstract suggests.

5.3 Future Work

The most useful next step is not another unreplicated rodent study but a well-reported one: a characterised gel, a base-only control, splinted wounds or a species with human-like healing, blinded measurement and adequate numbers (27, 29, 36). Human trials should address time to closure and scarring, and the gel under test should be described well enough for a second group to make the same preparation. It is a habit worth keeping even when the expected answer is already obvious.

6. Conclusion

Aloe vera gel is a plausible wound dressing material, and the excision wound model is a convenient way to test it. Neither the plausibility nor the convenience amounts to proof. The published evidence does not show that any particular gel formulation heals wounds faster than a comparable moist base, and human trials remain small and mixed. A convincing study would describe its material, animals, wounds, outcomes and analysis fully enough to be repeated, and until such studies accumulate, claims of

strong wound-healing activity should be read with caution.

7. Acknowledgements

The authors thank colleagues who commented on earlier drafts of this review.

8. Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

P.S. conceived the review and wrote the sections on formulation and gel composition. D.P. wrote the sections on wound biology and the experimental model. A.K. wrote the sections on evidence appraisal and study design. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No animals or human participants were involved and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

13. References

1. Grindlay, D., & Reynolds, T. (1986). The *Aloe vera* phenomenon: A review of the properties and modern uses of the leaf parenchyma gel. *Journal of Ethnopharmacology*, 16(2–3), 117–151. DOI: [10.1016/0378-8741\(86\)90085-1](https://doi.org/10.1016/0378-8741(86)90085-1)
2. Surjushe, A., Vasani, R., & Saple, D. G. (2008). *Aloe vera*: A short review. *Indian Journal of Dermatology*, 53(4), 163–166. DOI: [10.4103/0019-5154.44785](https://doi.org/10.4103/0019-5154.44785)
3. Kumar, B., Vijayakumar, M., Govindarajan, R., & Pushpangadan, P. (2007). Ethnopharmacological approaches to wound healing—exploring medicinal plants of India. *Journal of Ethnopharmacology*, 114(2), 103–113. DOI:



- [10.1016/j.jep.2007.08.010](https://doi.org/10.1016/j.jep.2007.08.010)
4. Thakur, R., Jain, N., Pathak, R., & Sandhu, S. S. (2011). Practices in wound healing studies of plants. *Evidence-Based Complementary and Alternative Medicine*, 2011, 438056. DOI: [10.1155/2011/438056](https://doi.org/10.1155/2011/438056)
 5. Dat, A. D., Poon, F., Pham, K. B. T., & Doust, J. (2012). Aloe vera for treating acute and chronic wounds. *Cochrane Database of Systematic Reviews*, (2), CD008762. DOI: [10.1002/14651858.CD008762.pub2](https://doi.org/10.1002/14651858.CD008762.pub2)
 6. Maenthaisong, R., Chaiyakunapruk, N., Niruntraporn, S., & Kongkaew, C. (2007). The efficacy of aloe vera used for burn wound healing: A systematic review. *Burns*, 33(6), 713–718. DOI: [10.1016/j.burns.2006.12.007](https://doi.org/10.1016/j.burns.2006.12.007)
 7. Reynolds, T., & Dweck, A. C. (1999). Aloe vera leaf gel: A review update. *Journal of Ethnopharmacology*, 68(1–3), 3–37. DOI: [10.1016/S0378-8741\(99\)00085-9](https://doi.org/10.1016/S0378-8741(99)00085-9)
 8. Hamman, J. H. (2008). Composition and applications of Aloe vera leaf gel. *Molecules*, 13(8), 1599–1616. DOI: [10.3390/molecules13081599](https://doi.org/10.3390/molecules13081599)
 9. Femenia, A., Sánchez, E. S., Simal, S., & Rosselló, C. (1999). Compositional features of polysaccharides from *Aloe vera* (*Aloe barbadensis* Miller) plant tissues. *Carbohydrate Polymers*, 39(2), 109–117. DOI: [10.1016/S0144-8617\(98\)00163-5](https://doi.org/10.1016/S0144-8617(98)00163-5)
 10. Hu, Y., Xu, J., & Hu, Q. (2003). Evaluation of antioxidant potential of aloe vera (*Aloe barbadensis* Miller) extracts. *Journal of Agricultural and Food Chemistry*, 51(26), 7788–7791. DOI: [10.1021/jf034255i](https://doi.org/10.1021/jf034255i)
 11. Eshun, K., & He, Q. (2004). Aloe vera: A valuable ingredient for the food, pharmaceutical and cosmetic industries—a review. *Critical Reviews in Food Science and Nutrition*, 44(2), 91–96. DOI: [10.1080/10408690490424694](https://doi.org/10.1080/10408690490424694)
 12. Boudreau, M. D., & Beland, F. A. (2006). An evaluation of the biological and toxicological properties of *Aloe barbadensis* (Miller), *Aloe vera*. *Journal of Environmental Science and Health, Part C*, 24(1), 103–154. DOI: [10.1080/10590500600614303](https://doi.org/10.1080/10590500600614303)
 13. Singer, A. J., & Clark, R. A. F. (1999). Cutaneous wound healing. *New England Journal of Medicine*, 341(10), 738–746. DOI: [10.1056/NEJM199909023411006](https://doi.org/10.1056/NEJM199909023411006)
 14. Gurtner, G. C., Werner, S., Barrandon, Y., & Longaker, M. T. (2008). Wound repair and regeneration. *Nature*, 453(7193), 314–321. DOI: [10.1038/nature07039](https://doi.org/10.1038/nature07039)
 15. Koh, T. J., & DiPietro, L. A. (2011). Inflammation and wound healing: The role of the macrophage. *Expert Reviews in Molecular Medicine*, 13, e23. DOI: [10.1017/S1462399411001943](https://doi.org/10.1017/S1462399411001943)
 16. Martin, P. (1997). Wound healing—aiming for perfect skin regeneration. *Science*, 276(5309), 75–81. DOI: [10.1126/science.276.5309.75](https://doi.org/10.1126/science.276.5309.75)
 17. Tonnesen, M. G., Feng, X., & Clark, R. A. F. (2000). Angiogenesis in wound healing. *Journal of Investigative Dermatology Symposium Proceedings*, 5(1), 40–46. DOI: [10.1046/j.1087-0024.2000.00014.x](https://doi.org/10.1046/j.1087-0024.2000.00014.x)
 18. Diegelmann, R. F., & Evans, M. C. (2004). Wound healing: An overview of acute, fibrotic and delayed healing. *Frontiers in Bioscience*, 9, 283–289. DOI: [10.2741/1184](https://doi.org/10.2741/1184)
 19. Werner, S., & Grose, R. (2003). Regulation of wound healing by growth factors and cytokines. *Physiological Reviews*, 83(3), 835–870. DOI: [10.1152/physrev.2003.83.3.835](https://doi.org/10.1152/physrev.2003.83.3.835)
 20. Vázquez, B., Avila, G., Segura, D., & Escalante, B. (1996). Antiinflammatory activity of extracts from *Aloe vera* gel. *Journal of Ethnopharmacology*, 55(1), 69–75. DOI: [10.1016/S0378-8741\(96\)01476-6](https://doi.org/10.1016/S0378-8741(96)01476-6)
 21. Davis, R. H., Donato, J. J., Hartman, G. M., & Haas, R. C. (1994). Anti-inflammatory and wound healing activity of a growth substance in *Aloe vera*. *Journal of the American Podiatric Medical Association*, 84(2), 77–81. DOI: [10.7547/87507315-84-2-77](https://doi.org/10.7547/87507315-84-2-77)
 22. Winter, G. D. (1962). Formation of the scab and the rate of epithelization of superficial wounds in the skin of the young domestic pig. *Nature*, 193(4812), 293–294. DOI: [10.1038/193293a0](https://doi.org/10.1038/193293a0)
 23. Hinman, C. D., & Maibach, H. (1963). Effect of air exposure and occlusion on experimental human skin wounds. *Nature*, 200(4904), 377–378. DOI: [10.1038/200377a0](https://doi.org/10.1038/200377a0)
 24. Dunn, L., Prosser, H. C. G., Tan, J. T. M., Vanags, L. Z., Ng, M. K. C., & Bursill, C. A. (2013). Murine model of wound healing. *Journal of Visualized Experiments*, (75), e50265. DOI: [10.3791/50265](https://doi.org/10.3791/50265)
 25. Wong, V. W., Sorkin, M., Glotzbach, J. P., Longaker, M. T., & Gurtner, G. C. (2011). Surgical approaches to create murine models of human wound healing. *Journal of Biomedicine and Biotechnology*, 2011, 969618. DOI: [10.1155/2011/969618](https://doi.org/10.1155/2011/969618)
 26. Davidson, J. M. (1998). Animal models for wound repair. *Archives of Dermatological Research*, 290(Suppl 1), S1–S11. DOI: [10.1007/PL00007448](https://doi.org/10.1007/PL00007448)
 27. Galiano, R. D., Michaels, J., Dobryansky, M., Levine, J. P., & Gurtner, G. C. (2004). Quantitative and reproducible murine model of excisional wound healing. *Wound Repair and Regeneration*, 12(4), 485–492. DOI: [10.1111/j.1067-1927.2004.12404.x](https://doi.org/10.1111/j.1067-1927.2004.12404.x)



28. Hinz, B. (2007). Formation and function of the myofibroblast during tissue repair. *Journal of Investigative Dermatology*, 127(3), 526–537. DOI: [10.1038/sj.jid.5700613](https://doi.org/10.1038/sj.jid.5700613)
29. Sullivan, T. P., Eaglstein, W. H., Davis, S. C., & Mertz, P. (2001). The pig as a model for human wound healing. *Wound Repair and Regeneration*, 9(2), 66–76. DOI: [10.1046/j.1524-475x.2001.00066.x](https://doi.org/10.1046/j.1524-475x.2001.00066.x)
30. Heggors, J. P., Kucukcelebi, A., Listengarten, D., Stabenau, J., Ko, F., Broemeling, L. D., ... Winters, W. D. (1996). Beneficial effect of Aloe on wound healing in an excisional wound model. *Journal of Alternative and Complementary Medicine*, 2(2), 271–277. DOI: [10.1089/acm.1996.2.271](https://doi.org/10.1089/acm.1996.2.271)
31. Tarameshloo, M., Norouzian, M., Zarein-Dolab, S., Dadpay, M., Mohsenifar, J., & Gazor, R. (2012). Aloe vera gel and thyroid hormone cream may improve wound healing in Wistar rats. *Anatomy & Cell Biology*, 45(3), 170–177. DOI: [10.5115/acb.2012.45.3.170](https://doi.org/10.5115/acb.2012.45.3.170)
32. Jia, Y., Zhao, G., & Jia, J. (2008). Preliminary evaluation: The effects of *Aloe ferox* Miller and *Aloe arborescens* Miller on wound healing. *Journal of Ethnopharmacology*, 120(2), 181–189. DOI: [10.1016/j.jep.2008.08.008](https://doi.org/10.1016/j.jep.2008.08.008)
33. Nayak, B. S., & Pereira, L. M. P. (2006). *Catharanthus roseus* flower extract has wound-healing activity in Sprague Dawley rats. *BMC Complementary and Alternative Medicine*, 6, 41. DOI: [10.1186/1472-6882-6-41](https://doi.org/10.1186/1472-6882-6-41)
34. Khorasani, G., Hosseinimehr, S. J., Azadbakht, M., Zamani, A., & Mahdavi, M. R. (2009). Aloe versus silver sulfadiazine creams for second-degree burns: A randomized controlled study. *Surgery Today*, 39(7), 587–591. DOI: [10.1007/s00595-008-3944-y](https://doi.org/10.1007/s00595-008-3944-y)
35. Williams, M. S., Burk, M., Loprinzi, C. L., Hill, M., Schomberg, P. J., Nearhood, K., ... Christensen, J. C. (1996). Phase III double-blind evaluation of an aloe vera gel as a prophylactic agent for radiation-induced skin toxicity. *International Journal of Radiation Oncology, Biology, Physics*, 36(2), 345–349. DOI: [10.1016/S0360-3016\(96\)00320-3](https://doi.org/10.1016/S0360-3016(96)00320-3)
36. Kilkenny, C., Browne, W. J., Cuthill, I. C., Emerson, M., & Altman, D. G. (2010). Improving bioscience research reporting: The ARRIVE guidelines for reporting animal research. *PLoS Biology*, 8(6), e1000412. DOI: [10.1371/journal.pbio.1000412](https://doi.org/10.1371/journal.pbio.1000412)
37. Kilkenny, C., Parsons, N., Kadyszewski, E., Festing, M. F. W., Cuthill, I. C., Fry, D., ... Altman, D. G. (2009). Survey of the quality of experimental design, statistical analysis and reporting of research using animals. *PLoS ONE*, 4(11), e7824. DOI: [10.1371/journal.pone.0007824](https://doi.org/10.1371/journal.pone.0007824)
38. Button, K. S., Ioannidis, J. P. A., Mokrysz, C., Nosek, B. A., Flint, J., Robinson, E. S. J., & Munafò, M. R. (2013). Power failure: Why small sample size undermines the reliability of neuroscience. *Nature Reviews Neuroscience*, 14(5), 365–376. DOI: [10.1038/nrn3475](https://doi.org/10.1038/nrn3475)
39. Festing, M. F. W., & Altman, D. G. (2002). Guidelines for the design and statistical analysis of experiments using laboratory animals. *ILAR Journal*, 43(4), 244–258. DOI: [10.1093/ilar.43.4.244](https://doi.org/10.1093/ilar.43.4.244)
40. Reddy, G. K., & Enwemeka, C. S. (1996). A simplified method for the analysis of hydroxyproline in biological tissues. *Clinical Biochemistry*, 29(3), 225–229. DOI: [10.1016/0009-9120\(96\)00003-6](https://doi.org/10.1016/0009-9120(96)00003-6)
41. Levenson, S. M., Geever, E. F., Crowley, L. V., Oates, J. F., Berard, C. W., & Rosen, H. (1965). The healing of rat skin wounds. *Annals of Surgery*, 161(2), 293–308. DOI: [10.1097/0000658-196502000-00019](https://doi.org/10.1097/0000658-196502000-00019)
42. Perel, P., Roberts, I., Sena, E., Wheble, P., Briscoe, C., Sandercock, P., ... Khan, K. S. (2007). Comparison of treatment effects between animal experiments and clinical trials: Systematic review. *BMJ*, 334(7586), 197. DOI: [10.1136/bmj.39048.407928.BE](https://doi.org/10.1136/bmj.39048.407928.BE)
43. Hackam, D. G., & Redelmeier, D. A. (2006). Translation of research evidence from animals to humans. *JAMA*, 296(14), 1731–1732. DOI: [10.1001/jama.296.14.1731](https://doi.org/10.1001/jama.296.14.1731)
44. Ioannidis, J. P. A. (2005). Why most published research findings are false. *PLoS Medicine*, 2(8), e124. DOI: [10.1371/journal.pmed.0020124](https://doi.org/10.1371/journal.pmed.0020124)