

Table 1. Different formulation of *A. vera* in the management of dermal or topical diseases and results obtained from different studies.

S. No.	Disease	Remedies	Outcome	Reported by
1	Various infections including skin transmitted infections	<i>A. vera</i> extracts	Maximum antibacterial activities and antifungal activity were observed in acetone extracts	Arunkumar [24]
2	Scabies	Crude gel of <i>A. vera</i>	The scabietic lesions virtually disappeared in all patients	Oyelami [25]
3	Burne wound	<i>A. vera</i> gel	Early epithelialization in the treated aloe vera gel area.	Visuthikosol [26]
4	Chronic pruritic skin lesions	<i>A. vera</i> /olive oil combination cream	<i>A. vera</i> /olive oil cream was at least as effective as betamethasone 0.1% in the treatment of sulfur mustard-induced chronic skin complications	Panahi [27]
5	Oral aphthous ulceration	Acemannan, a polysaccharide extracted from <i>A. vera</i>	Acemannan can be used for the treatment of oral aphthous ulceration in patients who wish to avoid the use of steroid medication	Bhalang [28]
6	Atopic dermatitis	Microencapsulation of copper enriched Aloe gel garment	Control of skin disease through medicated textiles.	Krishnaveni [29]
7	Atopic Eczema	<i>A. vera</i> gel	Dose dependent anti-inflammatory activity <i>A. vera</i> gel	Afzal [30]
8	Venous Eczema	Medical Moisture Retention Cream of <i>A. vera</i> (ALHYDRAN®),	Effective, safe, and feasible in the treatment of venous eczema	Rondas [31]

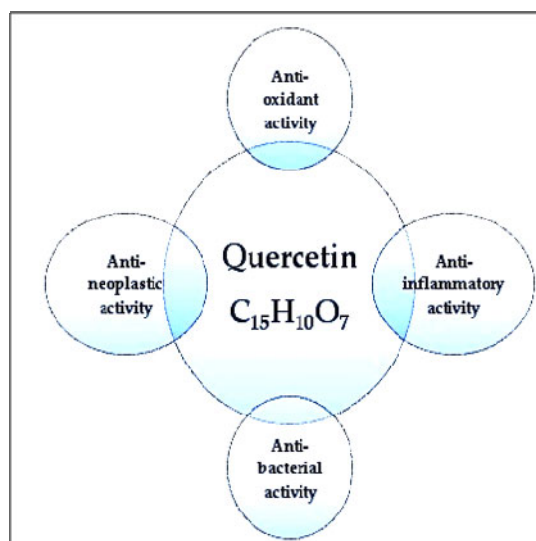


Figure 2. Quercetin: A natural flavanol with multifunctional therapeutic properties.

Source: Gupta [8]

NOVEL TOPICAL FORMULATIONS IN THE MANAGEMENT OF ECZEMA

Therapeutics is applied dermally to the skin especially for their local or site-specific action. Even though, the dermal delivery of the drug can also be applicable for systemic activity. Over the previous years, dermal delivery of drugs has given rise to more and more attention, of which, systemic side effects can be minimized in comparison to parenteral or oral drug delivery. Dermal delivery of the drug circumvents hepatic first-pass metabolism and extensive fluctuations of drug-plasma levels caused by repeated oral administration of rapidly eliminated drugs. Based on the characteristics of the ingredients and on the condition of the skin to be applied, a dispensing medium to provide a stable physicochemical environment that protects the active compound from chemical and enzymatic degradation should be developed, that can be a liquid or semi-solid, monophasic or multiphasic (dispersed systems). Inflammation of hypertrophic scar on the eczematous lesions forms a strong barrier for the skin permeation of medicaments through dermal route. To overcome this challenge, various novel topical formulations such as hydrogels, microemulsions, solid lipid nanoparticles, liposomes, dendrimers, and microsponges, nanogels, organogels etc. [37] have been explored for the penetration enhancement and prolonged release actions. These preparations are depicted to be applied not only as “drug carriers”, but also play a role in “drug depots” for releasing active ingredients over a sustained period of time.

SCOPE OF PHYTO-CHEMICAL IN NOVEL TOPICAL FORMULATION

Dermal applications of drugs, herbal or others are applied with a diversity of desired effects, including the targeting of

local tissues for dermal consequences, to the targeting of deeper strata, to the seeking out of a broader systemic influence. The history of the dermal application of plant-based medicines is over the prolonged period of time with documentations within traditional medicinal systems [38]. Herbal medicines are used in the management of a wide variety of conditions extending from dermatitis and psoriasis to dermal infections to dermal malignancies. However, the skin does provide an alarming barrier and novel drug delivery systems are being revolve to as a means to enhance dermal absorption. It is the incorporation of herbal medicines into such novel drug delivery systems. The key novel formulations that have been more specifically utilized for the dermatological and transdermal applications of herbal medicines are polymeric nanoparticles, liposomes, ethosomes, nano-emulsions, transferosomes, phytosomes and novel gels (Table 2). All these are reserving much interest to aggravate the therapeutic efficacy of phytochemicals [39].

CONCLUSIONS

Eczema is characterized by dry, rough and broken topmost layer of the skin known as stratum corneum. Several medicinal plant species applied to treat dermal ailments was investigated and documented since ancient time. Several investigated species are claimed very useful. However, these medicinal floras demanding a phytochemical screening for active moieties, biological properties and clinical studies are of universal significance. Using natural constituents in different novel topical formulations for skin care are very popular today. Moreover, one such type of natural plant; *A. vera* contain a lot of constituents which can be useful for dermal care. It is reported that *A. vera* possesses anti-aging and wrinkles reducing properties, moisturizing and cooling responses on the skin without allergic reaction, and burned

wound healing effects on the skin. Their potential is still undefined and need more investigations. Indeed, more research trials and clinical evidences are needed. It was shown that using only one natural constituent is not enough for skin care. Maybe, combination of several different

natural components is a right solution. Quercetin along with *A. vera* might be useful in the management of eczema due to its antioxidant and anti-inflammatory activity. Also, it is necessary to find out in which novel formulation the selected combination is stable and showing the best results.

Table 2. Phyto-chemical in different novel topical formulation to manage the various dermal diseases and ailments.

S. No.	Formulation	Merits	Therapeutic properties	Reported by
1	Quercetin liposomes	Enhanced skin permeation	Antioxidant and protective against UV β - radiation	Liu [40]
2	Mixed liposomes of quercetin and curcumin	Enhanced skin penetration	Anti-oxidant	Di Marzio [41]
3	<i>A. vera</i> liposomes	Enhanced bioavailability of AGE	Increased proliferation and synthesis of collagen in human skin cell line	Takahashi [42]
4	Quercetin nanoparticles	Enhanced skin uptake	Antioxidant	Tan [43]
5	Curcumin nanoparticles	Increased cellular uptake, better <i>in vitro</i> and <i>in vivo</i> bioavailability	Wound healing	Krausz [44]
6	Silver nanoparticles of <i>Citrullus colocynthis</i> extract	Enhanced penetration	wound healing	Satyavani [45]
7	Solid lipid nanoparticles of <i>Kaempferia parviflora</i> extract	Enhancement in skin permeability	Anti-inflammatory	Sutthanut [46]
8	Poly-herbal phytocomplex of <i>Trichosanthes curcumerina</i> extract and <i>Abrus precatorius</i> extract	Enhanced hair growth promoting effect	Anti-alopecia	Sandhya [47]
9	Genistein nanoemulsion	Enhancement of skin penetration	Anti-inflammatory	Momenkiaei [48]
10	Curcumin transferosome gel	Improvement in skin penetration	Antipsoriatic	Patel [49]
11	<i>Withania somnifera</i> niosomes	Improved delivery of withaferin A and withanolide A to the epidermis and dermis	Anti-melanoma	Chinembiri [50]

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

REFERENCES

- Wollenberg A, Barbarot S, Bieber T, Christen-Zaech S, Deleuran M, et al. (2018) Consensus-based European guidelines for treatment of atopic eczema (atopic dermatitis) in adults and children: Part I. *J Eur Acad Dermatol Venereol* 32(5): 657-682.
- Maan AA, Nazir A, Khan MKI, Ahmad T, Zia R, et al. (2018) The therapeutic properties and applications of Aloe vera: A review. *J Herb Med* 12: 1-10.
- Kumar R, Singh AK, Gupta A, Bishayee A, Pandey AK (2019) Therapeutic potential of Aloe vera - A miracle gift of nature. *Phytomedicine* 60: 152996.
- Gao Y, Kuok KI, Jin Y, Wang R (2019) Biomedical applications of Aloe vera. *Crit Rev Food Sci Nutr* 59(sup1): S244-S256.
- Ulusoy HG, Sanlier N (2020) A mini review of quercetin: From its metabolism to possible mechanisms of its biological activities. *Crit Rev Food Sci Nutr* 60(19): 3290-3303.
- Polerà N, Badolato M, Perri F, Carullo G, Aiello F (2019) Quercetin and its natural sources in wound

- healing management. *Curr Med Chem* 26(31): 5825-5848.
7. Pivetta TP, Silva LB, Kawakami CM, Araujo MM, Del Lama MPF, et al. (2019) Topical formulation of quercetin encapsulated in natural lipid nanocarriers: Evaluation of biological properties and phototoxic effect. *J Drug Deliv Sci Technol* 53: 101148.
 8. Gupta V, Dhote V, Paul BN, Trivedi P (2014) Development of novel topical drug delivery system containing cisplatin and imiquimod for dual therapy in cutaneous epithelial malignancy. *J Liposome Res* 24(2): 150-162.
 9. Manasiya M, Sawarkar S, Bajaj A (2019) Topical Vitamin A Delivery: Challenges, Overview of Novel Approaches. *Indian Drugs* 56: 7-19.
 10. Tizek L, Schielein MC, Seifert F, Biedermann T, Böhner A, et al. (2019) Skin diseases are more common than we think: Screening results of an unreferral population at the Munich Oktoberfest. *J Eur Acad Dermatol Venereol* 33(7): 1421-1428.
 11. Bell DC, Brown SJ (2017) Atopic eczema treatment now and in the future: Targeting the skin barrier and key immune mechanisms in human skin. *World J Dermatol* 6(3): 42-51.
 12. Zari ST, Zari TA (2015) A review of four common medicinal plants used to treat eczema. *J Med Plant Res* 9(24): 702-711.
 13. Rahmani R, Gharanfoli M, Gholamin M, Darroudi M, Chamani J, et al. (2020) Plant-mediated synthesis of superparamagnetic iron oxide nanoparticles (SPIONs) using aloe vera and flaxseed extracts and evaluation of their cellular toxicities. *Ceram Int* 46(3): 3051-3058.
 14. Sánchez M, González-Burgos E, Iglesias I, Gómez-Serranillos MP (2020) Pharmacological update properties of Aloe vera and its major active constituents. *Molecules* 25(6): 1324.
 15. Surjushe A, Vasani R, Sable DG (2008) Aloe vera: A short review. *Indian J Dermatol* 53(4): 163-166.
 16. West DP, Zhu YF (2003) Evaluation of aloe vera gel gloves in the treatment of dry skin associated with occupational exposure. *Am J Infect Control* 31(1): 40-42.
 17. Sahu PK, Giri DD, Singh R, Pandey P, Gupta S, et al. (2013) Therapeutic and medicinal uses of Aloe vera: A review. *Pharmacol Pharm* 4(8): 599.
 18. Fox LT, Du Plessis J, Gerber M, Van Zyl S, Boneschans B, et al. (2014) In Vivo skin hydration and anti-erythema effects of Aloe vera, Aloe ferox and Aloe marlothii gel materials after single and multiple applications. *Pharmacogn Mag* 10(Suppl 2): S392-S403.
 19. Haddad P, Amouzgar-Hashemi F, Samsami S, Chinichian S, Oghabian MA (2013) Aloe vera for prevention of radiation-induced dermatitis: A self-controlled clinical trial. *Curr Oncol* 20(4): e345-e348.
 20. Byeon SW, Pelley RP, Ullrich SE, Waller TA, Bucana CD, et al. (1998) Aloe barbadensis extracts reduce the production of interleukin-10 after exposure to ultraviolet radiation. *J Invest Dermatol* 110(5): 811-817.
 21. Rudolph KL, Chang S, Lee HW, Blasco M, Gottlieb GJ, et al. (1999) Longevity, stress response, and cancer in aging telomerase-deficient mice. *Cell* 96(5): 701-712.
 22. Grace OM, Simmonds MSJ, Smith GF, Van Wyk AE (2008) Therapeutic uses of Aloe L. (Asphodelaceae) in southern Africa. *J Ethnopharmacol* 119(3): 604-614.
 23. Miroddi M, Navarra M, Calapai F, Mancari F, Giofrè SV, et al. (2015) Review of clinical pharmacology of Aloe vera L. in the treatment of psoriasis. *Phytother Res* 29(5): 648-655.
 24. Arunkumar S, Muthuselvam M (2009) Analysis of phytochemical constituents and antimicrobial activities of Aloe vera L. against clinical pathogens. *World J Agric Res* 5(5): 572-576.
 25. Oyelami OA, Onayemi A, Oyediji OA, Adeyemi LA (2009) Preliminary study of effectiveness of Aloe vera in scabies treatment. *Phytother Res* 23(10): 1482-1484.
 26. Visuthikosol V, Chowchuen B, Sukwanarat Y, Sriurairatana S, Boonpucknavig V (1995) Effect of aloe vera gel to healing of burn wound a clinical and histologic study. *J Med Assoc Thai* 78(8): 403-409.
 27. Panahi Y, Davoudi SM, Sahebkar A, Beiraghdar F, Dadjo Y, et al. (2012) Efficacy of Aloe vera/olive oil cream versus betamethasone cream for chronic skin lesions following sulfur mustard exposure: A randomized double-blind clinical trial. *Cutan Ocul Toxicol* 31(2): 95-103.
 28. Bhalang K, Thunyakitpisal P, Rungsirisatean N (2013) Acemannan, a polysaccharide extracted from Aloe vera, is effective in the treatment of oral aphthous ulceration. *J Altern Complement Med* 19(5): 429-434.
 29. Krishnaveni V, Aparna B (2014) Microencapsulation of copper enriched Aloe gel curative garment for atopic dermatitis. NISCAIR-CSIR, India. *Indian J Tradit Know* 13(4): 795-803.
 30. Afzal I, Zia S, Kausar S, Hazrat A, Jan T, et al. (2020) Dose Response Relationship of Aloe vera to Cure Atopic Dermatitis in Rats. *Dermatol Ther* 33(4): e13376-e13376.
 31. Rondas AALM, Schols JMGA (2017) Application of Medical Moisture Retention Cream (ALHYDRAN®), A

- New Option in the Treatment of Venous Eczema. *J Gerontol Geriatr Res* 6(395): 2.
32. Saija A, Tomaino A, Trombetta D, Pellegrino ML, Tita B, et al. (2003) 'In vitro' antioxidant and photoprotective properties and interaction with model membranes of three new quercetin esters. *Eur J Pharm Biopharm* 56(2): 167-174.
 33. Chondrogianni N, Kapeta S, Chinou I, Vassilatou K, Papassideri I, et al. (2010) Anti-ageing and rejuvenating effects of quercetin. *Exp Gerontol* 45(10): 763-771.
 34. Vicentini FT, Simi TR, Del Ciampo JO, Wolga NO, Pitol DL, et al. (2008) Quercetin in w/o microemulsion: In vitro and in vivo skin penetration and efficacy against UVB-induced skin damages evaluated in vivo. *Eur J Pharm Biopharm* 69(3): 948-957.
 35. Vicentini FTMC, He T, Shao Y, Fonseca MJ, Verri Jr WA, et al. (2011) Quercetin inhibits UV irradiation-induced inflammatory cytokine production in primary human keratinocytes by suppressing NF- κ B pathway. *J Dermatol Sci* 61(3): 162-168.
 36. Choquenot B, Couteau C, Papisaris E, Coiffard LJ (2008) Quercetin and rutin as potential sunscreen agents: Determination of efficacy by an in vitro method. *J Nat Prod* 71(6): 1117-1118.
 37. Silverberg JI, Nelson DB, Yosipovitch G (2016) Addressing treatment challenges in atopic dermatitis with novel topical therapies. *J Dermatolog Treat* 27(6): 568-576.
 38. Escobar-Chávez JJ, Díaz-Torres R, Rodríguez-Cruz IM, Domínguez-Delgado CL, Morales RS, et al. (2012) Nanocarriers for transdermal drug delivery. *Res Rep Transdermal Drug Deliv* 1: 3-17.
 39. Jeevanandam J, San Chan Y, Danquah MK (2016) Nanoformulations of drugs: recent developments impact and challenges. *Biochimie* 128: 99-112.
 40. Liu D, Hu H, Lin Z, Chen D, Zhu Y, et al. (2013) Quercetin deformable liposome: Preparation and efficacy against ultraviolet B induced skin damages in vitro and in vivo. *J Photochem Photobiol B* 127: 8-17.
 41. Di Marzio L, Ventura CA, Cosco D, Paolino D, Di Stefano A, et al. (2016) Nanotherapeutics for anti-inflammatory delivery. *J Drug Deliv Sci Technol* 32: 174-191.
 42. Takahashi M, Kitamoto D, Asikin Y, Takara K, Wada K (2009) Liposomes encapsulating Aloe vera leaf gel extract significantly enhance proliferation and collagen synthesis in human skin cell lines. *J Oleo Sci* 58(12): 643-650.
 43. Tan Q, Liu W, Guo C, Zhai G (2011) Preparation and evaluation of quercetin-loaded lecithin-chitosan nanoparticles for topical delivery. *Int J Nanomedicine* 6: 1621-1630.
 44. Krausz AE, Adler BL, Cabral V, Navati M, Doerner J, et al. (2015) Curcumin-encapsulated nanoparticles as innovative antimicrobial and wound healing agent. *Nanomedicine* 11(1): 195-206.
 45. Satyavani K, Ramanathan T, Gurudeeban S (2011) Plant mediated synthesis of biomedical silver nanoparticles by using leaf extract of *Citrullus colocynthis*. *Res J Nansci Nanotechnol* 1(2): 95-101.
 46. Sutthanut K, Lu X, Sripanidkulchai B, Yenjai C, Jay M (2009) Solid liquid nanoparticles for transdermal delivery of *Kaempferia parviflora* extracts. *J Biomed Nanotechnol* 5(2): 224-232.
 47. Sandhya S, Chandra SJ, Vinod KR, Rao KNV, Banji D (2012) Preclinical studies of a novel polyherbal phyto-complex hair growth promoting cream. *Asian Pac J Trop Biomed* 2(1): S296-S304.
 48. Momenkiaei F, Raofie F (2019) Preparations of *Curcuma longa* L. extract nanoparticles using supercritical solution expansion. *J Pharm Sci* 108(4): 1581-1589.
 49. Patel RD, Singh SK, Singh S, Sheth NR, Gendle R (2009) Development and characterization of curcumin loaded transfersome for transdermal delivery. *J Pharm Sci Res* 1(4): 71.
 50. Chinembiri TN, Gerber M, Du Plessis LH, Du Preez JL, Hamman JH, et al. (2017) Topical delivery of *Withania somnifera* crude extracts in niosomes and solid lipid nanoparticles. *Pharmacogn Mag* 13(Suppl 3): S663-S671.