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Review article

Natural and synthetic agents for the treatment of *Sarcoptes scabiei*: a review

Aditya SHIVEN[1], Afroze ALAM[2], Deepak N. KAPOOR[1]

[1]School of Pharmaceutical Sciences, Shoolini University, Bajhol, Solan, Himachal Pradesh, 173229, India
[2]School of Pharmacy, Al-Karim University, Katihar-Purnea road, Sirsa, Karim Bagh, Katihar, Bihar, 854105, India

Corresponding Author: Deepak N. KAPOOR; e-mail: deepakpharmatech@gmail.com

ABSTRACT. *Sarcoptes scabiei* is an ectoparasite known to infect different species of mammals. Mite is known to infect mankind since antiquity. Current scabicidal agents are becoming less effective due to resistance generated by the mite. The present review focuses on exploration of various herbal and non-herbal/synthetic agents that are proven to be efficient against scabies mite of different mammalian species. *In vitro* and *in vivo* acaricidal activities carried out for different dosage forms developed for these scabicidal agents are also discussed.

Keywords: *Sarcoptes scabiei*, acaricidal agents, dosage forms for scabies, natural products for scabies, synthetic products for scabies

Introduction

The name *Sarcoptes scabiei* is derived from the Greek word "sarx" (flesh) and "koptein" (to smite or to cut) and the Latin word "scabere" (to scratch). Scabies is an obligate ectoparasitic mite that cause mange in more than 100 mammalian species belonging to 27 families. The classic presentation of scabies include skin eruption consisting of papules, nodules, vesicles and generalized pruritus that is typically worse at night [1,2]. Scabies mite is barely visible to naked eye, mostly found in the burrows located at specific areas such as in the finger web, flexure of wrist, elbow, arm pits, on genitals and breast. However, their number is least in the area with a high density of pilosebaceous follicles [3]. Scabies is contagious which spread through person-to-person contact. However, mite can only survive for 24–36 h off host, thus infection is limited through fomites, such as clothing and bed lining [4]. Adult mites use odour and thermotaxis to identify a new host [5]. Scabies is often confused with other pruritic rashes such as eczema, impetigo, *Tinea corporis* (ringworm) and psoriasis [6].

Current scabicides and problems associated with their use

Permethrin is the most effective and safe topical scabicide drug [7,8]. Scabies mites are reported to develop resistance against permethrin in *in vitro* condition [9–11] however, *in vivo* resistance has not been confirmed.

Ivermectin is prescribed with an oral dose of 200μg, repeated 1 or 2 weeks apart because ivermectin lacks ovicidal properties [6]. Ivermectin was reported with 100% cure rates with repeated dose therapy [12]. Ivermectin use is not recommended for children less than 15 kg body weight and pregnant or lactating women [13]. Ivermectin is P-glycoprotein inhibitor, which can cause serious toxicity in conjugation with other therapies such as methotrexate, cyclosporine, digoxin, and some anticancer treatments [14,15].

Crotamiton 10% cream is less efficacious than permethrin [16]. It requires daily application for 5 days for best results [5,11,16,17]. Safety for the use of crotamiton in newborns and infants has not been well established. Also, high resistance rates have been reported after a single application for 8 to 12 hours [16,18].

Table 1. Natural plant based products for the treatment of scabies

Plant/plant part	Application	Outcome	References
Crude *Aloe vera* gel	Topical application on whole body for 3 consecutive days each week for 2 weeks	*Aloe vera* is effective in treating scabies in human	[29]
Colocynth tar from the seeds of *Citrullus colocynthis*	Topical application of tar	Effective in killing *S. scabiei* mite in camels	[30]
Tar from the seeds of *Colocynthis vulgaris*	Topical application of tar for 2 weeks	Two goats, 3 lambs and 2 donkeys showed complete removal of mites, nymphs, larvae or eggs	[31]
Oil from *Cedrus deodara*	Applied topically on adjacent days for 10 days	Complete termination of scabies mite in lambs	[32]
Pongamia pinnata seed oil mixed with sulfur	Applied topically for six times in three days interval	Complete termination of scabies mite in goats	[33]
Essential oil from *Elsholtzia densa* Benth	Scabies mite collected from rabbits exposed to 5 different concentrations of oil	Mite were killed at a dose of 16 mg/ml with LC_{50} and LT_{50} values of 0.981 mg/ml and 0.760 h respectively	[34]
Lemon oil	Scabies mite collected from rabbits exposed to 50 and 100% lemon oil	99% mites were killed after 1 hr exposure of 100% lemon oil	[35]
Crude watery extract of *Onobrychis ptolemaica*	Extract of 2.5-10 mg/ml applied topically for 14 days	10 mg/ml showed complete termination of scabies mite in sheep	[36]
Crude leaf extract of *Annona squamosa*	The extract was applied topically on alternate days for 20 days	Effective in killing dog scabies mite, with no side effects and recurrence	[37]
Methanolic extract of *Vitex negundo* dried stem and leaves	*In vitro*: extract was exposed to collected scabies mite *In vivo*: topically applied to goats, buffalos, camels, dogs and humans (n=10) once in every week for 5 weeks	*In vitro* showed 90% acaricidal activity *In vivo* showed 69, 73, 75, 77 and 78% acaricidal activity respectively	[38]
Methanolic extract of *Tecomella undulate* branches (30%)	*In vitro*: extract was exposed to collected scabies mite *In vivo*: topically applied to goats, buffalos, camels, humans and dogs (n=10) once in every week for 5 weeks	*In vitro* showed 80% acaricidal activity *In vivo* showed 73, 78, 78, 78 and 83% acaricidal activity respectively	[39]
Ethanolic extract of *Ligularia virgaurea*	Scabies mite collected from rabbits exposed to 2, 1, 0.5, and 0.25 g/ml of extract for 2h	Extract 2 g/ml killed all scabies mites with LT_{50} of 0.716	[40]
Leaf extract of *Acalypha indica*	Scabies mite collected from rabbits exposed to 6.25%, 12.5% and 25% of extract	25% leaf extract showed fastest mortality rate of 4.6 mite/h	[41]

Lindane is reported with 49% to 96% cure rate on single topical application however, treatment failures are attributed largely to resistance [19]. Lindane is highly neurotoxic drug associated with serious adverse effects such as irritability, vertigo, seizures, vomiting, diarrhoea, and syncope [6].

Benzyl benzoate is synthetic compound with higher miticidal activity than permethrin in *in vitro* conditions [10,20,21]. It is highly irritant compound and can cause contact dermatitis thus it should be diluted for application on children and pregnant or lactating women and should be washed off within 24 hr [22].

For more details on current scabicides and associated problems, reader are referred to review articles by Hengge et al. [6], Chandler and Fuller, [23], Banerji, [24], Golant and Levitt, [25], Walton and Currie, [26].

General mechanism of action drugs acting against *Sarcoptes scabiei*

The insecticidal/acaricidal activity is due to suppression in ecdysone hormone synthesis, and inhibition of cytochrome P450 mono-oxygenases. Ecdysone (20-hydroxyecdysone) is a major insect molting hormone and suppression of this hormone prevent the further growth of the insect causing

death of the insect. Cytochrome P450 mono-oxygenases is useful in detoxification by metabolizing the toxins due to which resistance occur in the mite against various insecticides. Some of the drugs inhibit the cytochrome P450 mono-oxygenase which leads to increase in the concentration of toxic drug in insect and ultimately causing death [27].

Alternate treatments available for scabies in various mammalian species

Scabies is a contagious but not zoonotic however, occasional inter-host cross-infestation occurs. Due to host specificity, testing of new drugs on humans is challenging. This review focuses on alternate herbal and synthetic compounds reported to be effective against different mammalian scabies mite which could be of great value in searching new remedies to treat human scabies. Some herbal preparations that are found to be effective against scabies infestation in humans are tea tree oil, *Lippia* oil, neem oil and extracts, clove oil, turmeric, camphor oil etc. [28]. Various plant based formulations and compounds derived from biological sources or synthesized chemically that are found to be effective against scabies of different species are discusses in the next section.

Natural herbal products for the treatment of scabies

Various medicinal plants have been reported with acaricidal activity against *S. scabiei*. Different plant derived product such as gels, tar, oil and extracts in different solvents were discussed here with a brief summary of these plants shown in Table 1.

Aloe vera gel has been reported to be effective against various skin disorders. The acaricidal activity of *Aloe vera* crude gel against *S. scabiei* was reported by Oyelami et al. [29]. Crude A*loe vera* gel was used to conduct 2 trails on human patients infested with scabies. Trail 1 involved 5 patients treated with topical application of crude *Aloe vera* gel on whole body for 3 consecutive days each week for 2 weeks. Trail 1 patients received an oral dose of co-trimoxazole twice daily. Trail 1 patients reported no itching and showed improved clinical symptoms. Trail 2 involved 30 scabies patients (18 adult and 12 children) from which 16 patients received crude *Aloe vera* gel and 14 patients received 25% benzyl benzoate (12.5% diluted benzyl benzoate for children) topical treatment. Total of 28 patients follow up with the study in which 3 out of 12 patients received benzyl benzoate reported itching while 2 out of 16 patients received crude *Aloe vera* gel reported itching. It was concluded from the results that crude gel of *Aloe vera* is as effective as benzyl benzoate in treating scabies in human.

Tar like distillate from the seeds of *Citrullus colocynthis* and *Colocynthis vulgaris* (water melon) have been reported with acaricidal activity against *S. scabiei*. Moson [30], tested colocynth tar extracted from the seeds of *Citrullus colocynthis*, was found to be effective in killing *S. scabiei* mite in camels and diminishing the clinical symptoms of scabies. Similarly, Mannan et al. [31] tested the tar from the seeds of water melon (*Colocynthis vulgaris*) in three different species of mammals infested with scabies. Two goats, 3 lambs and 2 donkeys were treated topically for 2 weeks. After 2 week treatment the skin scrapings of the animals, showed complete removal of mites, nymphs, larvae or eggs.

Oil from various plants have been reported with acaricidal activity against *S. scabiei*. Oil of *Cedrus deodara* was compared with benzyl benzoate for scabicidal potential in scabies infested lambs by Sharma et al. [32]. Twenty four lambs were divided into three groups i.e. group A (no treatment), group B (oil of *Cedrus deodara*), and group C (benzyl benzoate). *Cedrus deodara* oil was applied topically on adjacent days for 10 days while benzyl benzoate was applied 7 times on adjacent days for 14 days in order to achieve complete termination of scabies mite. Also, Mukerjee and Dasgupta [33] evaluated the comparative efficacy of three acaricides in scabies infested goats. One hundred and five goats were divided into three groups i.e. 25% benzyl-benzoate (n=48), γ-benzene-hexachloride (n=28) and sulfur-karanj (*Pongamia pinnata*) oil mixture (1:10; n=29). Each formulation was applied for six times in three days interval. The results concluded that γ-benzene-hexachloride was most effective in killing scabies mite followed by benzyl benzoate and then sulphur-karanja oil. However, sulphur-karanja oil mixture found to treat animals completely after the last application. An essential oil from *Elsholtzia densa* Benth contains 4-Pyridinol (28.16%) and thymol (26.58%) was extracted by Zhou et al. [34] using hydrodistillation. The *in vitro* acaricidal activity of the essential oil was evaluated on the scabies mites collected from infested rabbits.

The oil was diluted with liquid paraffin to prepare five different concentrations i.e. 1, 2, 4, 8, and 16 mg/ml. The concentrations 1, 2, 4, 8, and 16 mg/ml showed strong acaricidal activity with LT_{50} values of 16.637, 5.075, 2.884, 1.184, and 0.760 h respectively and LC_{50} values of 7.678, 4.623, 2.543, 1.502, 1.298, and 0.981 mg/ml at 1, 2, 4, 8, 16, and 24 h, respectively. Similarly, The *in vitro* evaluation of the effect of lemon oil as acaricidal agent againt *S. scabiei* was carried out by Aboelhadid et al. [35] on different concentrations of lemon oil prepared by diluting with water (2.5, 5, 10, 20, 50, and 100%). The killing efficacy of 50 and 100% lemon oil was found to be 96 and 99% respectively within one hour while, 20% lemon oil reported 100% mortality at 12 h.

Various extracts of different plant parts in different solvents have been evaluated for acaricidal activity against *S. scabiei*. A crude watery extract of *Onobrychis ptolemaica* was prepared by Shahatha [36] and evaluated for acaricidal activity against scabies infested goats. A total of 462 heads of sheep were examined for the infestation of scabies mite and found to be 34.6% prevalent. The extract with concentrations ranging from 2.5–10 mg/ml was applied topically to the infested sheep. The 10 mg/ml concentration of the extract was found to be potent enough to eliminate all scabies parasite on the 14th day of treatment. A crude leaf extract of *Annona squamosa* in white petroleum jelly was evaluated for acaricidal activity against *S. scabiei* by Roy et al. [37]. Twelve dogs infested with scabies were randomly divided into two groups i.e. treatment group and un-treated control group. The extract was applied locally on alternate days until complete recovery and found to be effective in killing all scabies mite in 20 days after application. The extract showed no side effects, dogs were monitored for three months and recurrence was not observed. The topical application of methanolic extract of *Vitex negundo* on different species of animals infested with scabies was carried out by Khan et al. [38]. Stem and leaves of *V. negundo* was dried and powdered and mixed in methanol for 20 days followed by filtering using cloth. Five treatment groups were formed of 10%, 20%, and 30% methanolic extract of *V. negundo*, ivermectin (0.2 mg/kg body weight) as standard drug and methanol as control for *in vitro* testing. Four treatment groups were formed of 10% and 20% methanolic extract of *V. negundo*, ivermectin (0.2 mg/kg body weight) as standard drug and methanol as control for *in vivo* testing. The *in vitro* results showed 90% acaricidal activity of 30% methanolic extract of *V. negundo* which was found to be higher than 85% acaricidal efficacy of standard ivermectin. *In vivo* evaluation involved topical application of 10% and 20% methanolic extract of *V. negundo* and standard ivermectine. The percent protection against scabies provided by 10% and 20% methanolic extract of *Vitex negundo* and standard ivermectine was found to be 46%, 75%, 84% respectively in camel (n=10); 43%, 73%, 81% respectively in buffalo (n=10); 42%, 69%, 81% respectively in goats (n=10); 42%, 77%, 83% respectively in dogs (n=10); and 61%, 78%, 84% respectively in humans (n=10). The topical application of methanolic extract of *Tecomella undulata* on different species of animals infested with scabies was carried out by Khan et al. [39]. Branches of *T. undulata* was dried and powdered and mixed in methanol for 20 days followed by filtering using cloth. Five treatment groups were formed of 10%, 20%, and 30% methanolic extract of *T. undulata*, ivermectin (0.2 mg/kg body weight) as standard drug and methanol as control for *in vitro* testing. Four treatment groups were formed of 10% and 20% methanolic extract of *T. undulata*, ivermectin (0.2 mg/kg body weight) as standard drug and methanol as control for *in vivo* testing. The *in vitro* results showed 45%, 65%, and 80% acaricidal activity of 10%, 20%, and 30% methanolic extract of *T. undulata* respectively, which was found to be slightly lower than 85% acaricidal efficacy of standard ivermectin. *In vivo* evaluation involved topical application of 10% and 20% methanolic extract of *T. undulata* and standard ivermectine once in every week for 5 weeks. The percent protection against scabies provided by 10% and 20% methanolic extract of *T. undulata* and standard ivermectine was found to be 64%, 78%, 82% respectively in camel (n=10); 64%, 78%, 82% respectively in buffalo (n=10); 58%, 73%, 81% respectively in goats (n=10); 62%, 83%, 85% respectively in dogs (n=10); and 61%, 78%, 80% respectively in humans (n=10). An ethanolic extract of *Ligularia virgaurea* was evaluated (*in vitro*) for its acaricidal efficacy against scabies mite collected from infested rabbits. Different concentrations of extract was tested viz. 2, 1, 0.5, and 0.25 g/ml with median lethal time (LT_{50}) of 0.716, 1.741, 2.968 and 4.838 h, respectively. The highest dose of 2 g/ml was found to kill all scabies mites within 2 h in *in vitro* conditions [40]. Leaf extract of *Acalypha indica* was prepared by Astuti et al. [41] and tested

against scabies mite collected from rabbits. Three different concentrations i.e. 6.25%, 12.5% and 25% were tested against scabies mite. In *in vitro* conditions, the fastest mortality rate was observed with 25% leaf extract of *A. indica* i.e. 4.6 mites/h followed by 12.5%, 3.1 mites/h and then 6.25%, 1.9 mites/h. The results concluded that leaf extract of *A. indica* has the potential to treat scabies and could be used as acaricidal therapy.

Chemicals for the treatment of scabies

Various chemicals derived from natural source or synthesised chemically have been reported with acaricidal activity are discussed in this section and a brief description of the chemicals is shown in Table 2.

The acaricidal activity of 2% aqueous solution of trichlorofon and 1% aqueous emulsion of creolin containing 2.5–3% gamma benzene hexachloride was carried out on Arctic fox (bred in captivity). Animals infested with scabies were dipped in treatment solution for 2–3 min twice at an interval of 7–8 days. Animals were fully treated with no side effects on fur [42]. Trichlorofon 0.1% w/v solution was evaluated for acaricidal activity against scabies infested dogs. Animal bodies were washed using shampoo to remove crust or debris then soaked in trichlorofon solution once a week up to 4 weeks. After 4 week dogs (n=16) were treated successfully with improved clinical symptoms and no sign of toxicity [43]. Eprinomectin was compared with ivermectin for acaricidal potential against *S. scabiei*. Twelve goats of either sex infested with scabies were randomly divided into 2 groups. Group A was poured topically with eprinomectin (500 µg/kg body weight) and group B was injected subcutaneously with ivermectin (200 µg/kg body weight). Eprinomectin was found to be effective in inhibiting scabies mites in all developmental stages and animals were free form mite, larvae, and nymphs/eggs after 14 days of application. However, some number of mite and eggs were observed in ivermectin treated group after 14 days [44]. Baishya et al. [45] evaluated the acaricidal potential of doramectin, diazinon and deltamethrin against *S. scabiei* infested pigs. Pigs were divided into three groups (n=30). Group A receive doramectin 300 µg/kg IM, group B animals were dipped in diazinon 20% (3 ml in 1 L) solution and group C animals were dipped in deltamethrin (4 ml in 1 L) solution. The efficacy of doramectin, diazinon and deltamethrin in treating *S. scabiei* infestation was found to be 100%, 86.67% and 76.67% respectively.

Table 2. Chemicals for the treatment of scabies

Chemical	Application	Outcome	References
Trichlorofon	Arctic fox (bred in captivity) dipped in 2% aqueous solution for 2-3 min twice at an interval of 7-8 days.	Animals were fully treated with no side effects on fur	[42]
Trichlorofon	Dogs dipped in 1% solution once a week up to 4 weeks	Animals were fully treated with no sign of toxicity	[43]
Eprinomectin	500 µg/kg b.w. was poured topically on goats for 14 days	Effective in inhibiting scabies mites in all developmental stages i.e mite, larvae, and nymphs/eggs	[44]
Doramectin	300 µg/kg IM injected to pigs	100% effective against scabies mite	[45]
Diazinon	Pigs were dipped in diazinon 20% (3 ml in 1 L) solution	86.67% effective against scabies mit	[45]
Deltamethrin	Pigs were dipped in deltamethrin (4 ml in 1 L) solution	76.67% effective against scabies mite	[45]
Carbaryl powder	Powder was dusted on infested rabbits on adjacent days until 21 days	Complete elimination of scabies mite	[46]
9-oxo-10,11-dehydroageraphorone (euptox A)	Scabies mite collected from rabbits exposed to 2, 3, and 4 mg/mL of euptox A	4 mg/ml showed LC_{50} of 1.068 mg/ml in 2h	[47]
octadecanoic acid-tetrahydrofuran-3,4-diyl ester	Scabies mite collected from rabbits exposed to 200 mg/ml	100% mortality of scabies mite at 4.5h	[48]
Thymol	Scabies mite collected from rabbits exposed to 16 mg/ml for 24 h	100% mortality of scabies mite	[49]

Table 3. Herbal formulations for the treatment of scabies

Formulation	Application	Outcome	References
Ointment (Olinall) contains: *Allium cepa, Citrus medica, Curcuma longa, Camphora offici-narum, Allium sativum, Derris indica* and sesame (*Sesamum indicum*) oil	Applied topically on buffalo calves for 7 to 15 days	Animals were fully treated with no side effects	[50]
Boiled decoction (Unani medicine) of *Fumaria indica* Pugsley, *Swertia chirayita* Roxb. Ex Flem. Karst, *Tephrosia purpurea* Linn. Pers., *Sphaeranthus indicus* Linn. and *Ziziphus jujuba* Mill. Paste (Unani medicine) of Sulphur, litharge (lead monoxide), *Cinnamomum camphora Linn*. mixed in coconut oil (*Cocos nucifera Linn*.)	The oral decoction was given to the human patients every morning on empty stomach and the paste was applied on the affected parts of patients for 15 days	Out of 30 patients 50% were relieved from itching, 40% healing in pruritic lesions, 33% cure from secondary infection, 43% relieved from burning sensation and 83% patients are negative in skin scrap test	[51]
Ectozee (herbal aerosol spray) containing *Cedrus deodara*, *Azadirachta indica* and *Embelia ribes*	Scabies mite collected from dogs exposed to 25% and 100% of ectozee	Killed scabies mite in 6 and 3 min respectively	[52]
Paste (Unani medicine) containing sulphur, *Psorelea corylifolia*, *Centratherum anthelminticum*, *Cassia tora* with *Sesamum indicum* L. oil	Paste was applied to whole body (except head and face) of human patients daily for 3 consecutive days	86.67% patients recovered from scabies	[53]
Lima beans (*Phaseolus lunatus*) leaf extract ointment	30% ointment applied topically to dogs twice a week for 8 weeks	100% effective in treating severely infected animals	[54]
Melon of Sao Caetano (*Momordica charantia*) ointment	Scabies infested rabbits were treated daily for 21 days	100% effective in treating infected animals	[55]
Paste of neem leaves with turmeric	Scabies infested camels were treated daily for 21 days	Effective against scabies and showed significant clinical improvement	[56]
Lotion of ethanolic extract of *Tinospora cordifolia*	Applied topically for 3 consecutive days per week for 2 weeks	Five week clinical assessment concluded that clearance time and cure rate of *T. cordifolia* lotion is equivalent to permethrin lotion	[57]

Dried carbaryl powder was evaluated for acaricidal activity against scabies infested rabbits. The animals were divided into 5 groups (n=4). Group 1 was treated subcutaneously with 400µg/kg body weight ivermectin on day 1 and 14. Group 2 was treated with carbaryl powder (lesions were wetted using liquid paraffin and dusted with powder carbaryl) on adjacent days until 21 days. Group 3 was treated with liquid paraffin for 21 days. Group 4 served as positive control and received only distilled water, Group 5 served as negative control containing non-infested rabbits. Complete elimination of scabies mite was found in two week post-treatment with carbaryl [46]. *In vitro* acaricidal activity of 9-oxo-10,11-dehydroageraphorone (euptox A) derived from *Eupatorium adenophorum* was carried out on scabies mite collected from rabbits. Liao et al. [47] prepared different concentrations of euptox A *i.e.* 2, 3, and 4 mg/ml. The *in vitro* acaricidal activity was strongest with 4 mg/ml concentration and the calculated median lethal concentration (LC_{50}) values was found to be 1.068 mg/ml for scabies mite in 2 h. Du et al. [48] extracted octadecanoic acid-tetrahydrofuran-3,4-diyl ester as an potent acaricidal compound from the chloroform extract of neem oil (*Azadirachta indica*). The compound was tested *in vitro* on the scabies mite collected from infested rabbit. The compound with 200 mg/ml showed 100% mortality of scabies mite at 4.5 h. The LC_{50} and LT_{50} values for the isolated compound was found to be 0.1 mg/ml at 24 h post-treatment and 15.3 h at a concentration of 7.5 mg/ml. The acaricidal activity of thymol was reported by Zhou et al. [49] against scabies mite collected from rabbits. Thymol at concentration of 16 mg/ml was found to be toxic to cause 100% mortality of scabies mite within 24 h in *in vitro* conditions.

Formulations for treatment of *Sarcoptes scabiei*

Herbal formulations for the treatment of scabies

Plant based formulation that have been reported with acaricidal activity against *S. scabiei* are

discussed under current section. A brief details of various herbal and polyherbal formulation discussed in this section are shown in Table 3.

An ointment (Olinall) manufactured by Wockherdt, India was tested for its acaricidal activity on *S. scabiei* infested buffalo calves [50]. Olinall is a botanical ointment consisting a mixture *Allium cepa*, *Citrus medica*, *Curcuma longa*, *Camphora officinarum*, *Allium sativum*, *Derris indica* and sesame (*Sesamum indicum*) oil along with small amounts of borax and beeswax to maintain its consistency as an ointment. The ointment (Oilnall) was applied topically on 9 buffalo calves for 7 to 15 days. No mites were present in the skin scarping taken on days 7, 15, and 30 days after treatment. All animals were found to be free from the clinical signs and symptoms of scabies after 15 days. The ointment was reported to be free from side effects. Thirty human patients infested with scabies were treated with poly-herbal Unani formulations including application of herbal paste and oral ingestion of herbal decoction [51]. Oral decoction was prepared by boiling *Fumaria indica*, *Swertia chirayita*, *Tephrosia purpurea*, *Sphaeranthus indicus* and *Ziziphus jujube* in water to get a viscous decoction which was then filtered using cloth. Topical paste was prepared by mixing powdered *Cinnamomum camphora*, sulphur, and lead monoxide in coconut oil. The oral decoction was given to the patients every morning on empty stomach and the paste was applied on the affected parts of patients for 15 days. After 15 days patients were examined for itching, pruritic lesions, secondary infection, burning sensation and skin scrap test. The results indicated that out of 30 patients 50% were relieved from itching, 40% healing in pruritic lesions, 33% cure from secondary infection, 43% relieved from burning sensation and 83% patients are negative in skin scrap test. Ectozee is herbal aerosol spray consisting of extracts of *Cedrus deodara*, *Azadirachta indica* and *Embelia ribes* was against scabies infested dogs. Maske and Bhilegaonkar, carried out *in-vitro* studies on two concentration of ectozee i.e. 25% and 100% that were found to kill scabies mite collected from infested dogs in 6 min and 3 min respectively [52]. A comparative evaluation of a herbo-mineral Unani formulation with benzyl benzoate was carried out by Rahman et al. [53] as acaricidal formulation against human scabies. The poly-herbal formulation was prepared by mixing dried seed powder of *Psorelea corylifolia*, *Centratherum anthelminticum*, *and Cassia tora* with sulphur previously soaked overnight in water. The paste was applied with *S. indicum* L. oil to whole body except head and face. A total of 66 patients infested with scabies were divided into 2 groups i.e. test (n=30) and control (n=30) groups. The Unani formulation was applied daily for 3 consecutive days was compared with 25% benzyl benzoate (control group) applied topically for 5 days. The results showed that out of 30 patients, 26 (86.67%) patients of test group and 27 (90%) patients of control group were treated successfully with no lesions on the skin. Lima beans (*Phaseolus lunatus*) were formulated into topical ointment by Tabije et al. [54] and evaluated for acaricidal activity against *S. scabiei* var *cannis*. Lima bean leaves were blended and filtered using cheese cloth to collect the extract. Beeswax and oil were heated together to form the ointment base to which 20, 25, and 30% lima bean leave extract was added. Twenty four dogs infested with scabies were divided in 4 groups i.e. Group 1 received plain ointment (containing water instead of extract in ointment base). Group 2 was treated with 20% lima bean ointment. Group 3 was treated with 25% lima bean ointment. Group 4 was treated with 30% lima bean ointment. All animals were treated topically with lima bean ointment twice a week for 8 weeks. The lima bean ointment was found effective in treating scabies in dogs however 30% lima bean ointment was found 100% effective in treating severely infected animals. Dantas et al. [55] evaluated the acaricidal efficacy of the ointment based on Melon of Sao Caetano (*Momordica charantia*) on scabies infested rabbits. Animals were treated daily for 21 days and found to be 100% effective in treating scabies. Acaricidal activity of a paste of neem leaves with turmeric was evaluated topically on scabies infested camels. Four infested animals were randomly grouped and treated with ivermectin 200 µg/kg body weight SC every week and daily application of paste. The paste was found to be effective against scabies and animal showed significant clinical improvement by the third week of therapy [56]. A comparative evaluation of acaricidal activity of permethrin lotion and *Tinospora cordifolia* lotion on *S. scabiei* var. *hominis*-infected paediatric patients was carried out. The *T. cordifolia* stems was percolated in ethanol to prepare the extract. The *T. cordifolia* lotion was prepared by mixing extract with 0.15g methyl paraben and 39.70g water to form water phase. 7.0g stearic acid, 2.5g tween 80, 0.5g lanolin, 0.15g

propyl paraben were triturated and mixed with water phase to form lotion. Patients diagnosed with scabies were divided into two groups i.e. test group (n=34) and control group (n=32). Both *T. cordifolia* lotion and permethrin lotion were applied topically for three consecutive days per week for two weeks. Five week clinical assessment concluded that clearance time and cure rate for both lotions did not differ [57].

Non-herbal formulations for the treatment of scabies

Some chemically synthesized compound that showed acaricidal activity against *S. scabiei* are discussed in this section. A brief mention of these non-herbal formulation is shown in Table 4.

A novel approach of treating *S. scabiei* infestation in pigs by feeding 2 ppm ivermectin in-feed was carried out by Primm et al. [58]. Pigs were divided into two groups (n=10 each) i.e. treatment group feed with ivermectin in-feed preparation for 7 days and control group receiving no treatment. On post-treatment day 14, animal's skin scrapings were taken and no mites were found in the treated animals similarly, Mercier et al. [59] incorporated 0.6% abamectin with the feed of pigs to treat scabies. Ten piglets infested with scabies were divided into 2 groups i.e. control group (n=4) and treatment group (n=6). The treatment group received in-feed formulation of abamectine for 7 days and was found effective in complete elimination of parasite for at-least 6 weeks. A study reported on the acaricidal activity of abamectin was carried out by Bal et al. [60]. Ten adult buffaloes were given 200 mg/kg subcutaneous injection of abamectine and found effective in treating buffalo scabies. Scabies in pigs was treated using 0.25% chlordane spray. Animals showed good recovery after one week and complete elimination of *S. scabiei* mite after two weeks of treatment [61]. Frontline spray formulation

Table 4. Non-herbal formulations for the treatment of scabies

Formulation	Application	Outcome	References
Ivermectin	Pigs feed with 2 ppm ivermectin in – feed for 7 days	Animals showed full recovery after 14 days of observation	[58]
Abamectin	Piglets feed with 0.6% abamectin in– feed for 7 days	Animals showed full recovery and no recurrence for at-least 6 weeks	[59]
Abamectin	200 mg/kg subcutaneous injection of abamectin on buffaloes	Animals showed full recovery	[60]
Chlordane	0.25% chlordane sprayed on scabies infested pigs for 14 days	Animals showed full recovery after 14 days of observation	[61]
Frontline spray (fipronil)	0.25% fipronil sprayed on scabies infested dogs for 14 days	Fipronil was well tolerated by dogs however, temporary diarrhoea and reddening of skin was observed in one dog	[62]
Gammatox (hexachlorocyclohexane)	Camels infested with sarcoptic mange were washed thrice with 0.1% hexachlorocyclohexane in 7 days	The results concluded that 6 days after 2nd wash with gammatox no alive mite were observed in skin scrapings	[63]
Aulin (solution of bisethylxanthogen in a mineral oil containing 52% sulphur)	Cattle infested with scabies were painted with aulin (0.5 lb) for 5 days repeated after 2 days interval	Animals showed full recovery	[64]
Tincture of tobacco	Tincture of tobacco (10%) was applied topically as a paint for 11 times in 3 days on infested goats	Animals showed full recovery	[65]
Amitraz	Amitraz (50 ml in 10 L) solution was applied topically for 4 weeks on alpacas	The amitraz solution found to be effective whereas, animals failed to respond topical applications of eprinomectin (0.5 mg/kg), and an injection of doramectin (0.2 mg/kg SC)	[66]
Ivermectin in combination with vitamin E and selenium	Injection of ivermectin (0.2 mg/kg) with 0.5 ml/kg intramuscular injection containing Vit. E (50 mg) + selenium (1.5 mg/ml)	Combinational therapy of ivermectin + Vit. E + selenium was more effective in improving the clinical symptoms than the conventional ivermectin	[67]
Propolis prepared by the bees (*Apis mellifera*)	Propolis ointment (10%) applied to scabies infested rabbits for 14 days	Full recovery from clinical symptoms and no scabies mite, larvae or eggs were found in the skin scrapings of animals after treatment	[68]

containing fipronil (0.25%) was used to treat scabies in dogs. Itoh and Muraoka [62] sprayed fipronil on the whole body surface of dogs (n=6) thrice in two weeks. Complete elimination of scabies was observed and no recurrence was noticed up to a period of four months. Fipronil was well tolerated by dogs however, temporary diarrhoea and reddening of skin was observed in one dog. Nayel and Samra [63] has reported the use of gammatox (hexachlorocyclohexane) in the treatment of camels infested with sarcoptic mange. Twenty camels showing viable mite in skin scrapings were washed twice with 15% salicylic acid in three days. Two days after salicylic acid wash animals were washed with soap and scrubbed with hard brush to remove scale and detritus. Then the animals were washed thrice with 0.1 % hexachlorocyclohexane in 7 days. The results concluded that 6 days after 2nd wash with gammatox no alive mite were observed in skin scrapings. Aulin is a solution of bisethylxanthogen in a mineral oil containing 52% sulphur. Cattle infested with scabies were painted with aulin for 5 days repeated after 2 days interval. Dose of 0.5 lb aulin was required for each animal and it is proved to be effective against scabies [64]. The acaricidal efficacy of tincture of tobacco, propetamphos (Blotic) and Scabiezma (of unstated composition) have been evaluated on scabies infested goats. Tincture of tobacco (10%) was applied topically as a paint for 11 times in 3 days. Propetamphos (0.035%) was used as body wash for 4 times in 7 days and Scabiezma was injected to infested animals. The results showed propetamphos was most effective in killing scabies mite followed by tobacco tincture. However, no acaricidal activity was observed with scabiezma [65].

Amitraz (50 ml in 10 L) solution was used to treat three alpacas with sarcoptic mange. Animals were washed with antibacterial or keratolytic shampoos before the topical application of amitraz solution once weekly. After 4 weeks of treatment only one eggs was found in one alpaca. The amitraz solution found to be effective in treating sarcoptic mange. Whereas, the animals failed to respond to repeated topical applications of eprinomectin (0.5 mg/kg), and an injection of doramectin (0.2 mg/kg SC) [66]. A combination of ivermectin with vitamin E and selenium has been investigated for the acaricidal efficacy in dogs infested with scabies. Dogs infested with scabies were divided into two treatment groups i.e. Group 1 (n=11) was given 0.2 mg/kg subcutaneous (SC) injection of ivermectin and Group 2 (n=11) was given with one subcutaneous injection of ivermectin (0.2 mg/kg) with 0.5 ml/kg intramuscular injection containing Vit. E (50 mg) + selenium (1.5 mg/ml). Author concluded that combinational therapy of ivermectin + Vit. E + selenium was more effective in improving the clinical symptoms than the conventional ivermectin because of the synergistic effect of Vit. E + selenium as anti-oxidant agents [67]. Propolis is a compound prepared by the bees (*Apis mellifera*) is tested against scabies by Metwally et al. [68]. Propolis ointment (10%) was prepared by heating propolis extract (5g) with petroleum jelly (45g). Forty infested rabbits were divided into 4 groups and 10 un-infested rabbits served as negative control. Treatment groups are as follows: T1 served as positive control group contains infested animals receive no treatment. T2 was treated with 10% propolis ointment, T3 was treated with ivermectin 400 µg/kg body weight SC on day 1 and 14 and T4 was treated with both ivermectin (SC) + propolis (topical). Group T2 and T4 resulting in full recovery from clinical symptoms and no scabies mite, larvae or eggs were found in the skin scrapings after 15 days of treatment.

Hemachandra [69] carried out the acaricidal activity of scabiezma injectable formulation on human patients. The formulation was found to be non-toxic by means monitoring blood urea, S.G.P.T and serum creatinine levels but due to lack of patient compliance author was able to summarize data from just 12 out of 24 patients. The efficacy of the formulation was not up to par when compared to the current acaricidal drugs.

Novel formulation for the treatment of scabies

Various novel formulation loaded with currently prescribed medicines are discussed in this section. These novel formulation have been reported with lesser side effects, higher bioavailability and better efficacy than the conventional formulations. This section explains the benefits of novel formulation over conventional formulations. However, these novel drug delivery approaches could be employed to some of the previously discussed herbal and non-herbal products which could lead to the advantages such as targeted delivery of drug, higher bioavailability and lesser side effects. Brief details of various novel formulations developed for the treatment of scabies are shown in Table 5.

Benzyl benzoate is well known irritant compound used for the treatment of scabies. A

Table 5. Novel formulations for the treatment of scabies

Drug	Formulations	Outcome	References
Benzyl benzoate	Microemulsion	Microemulsion was found non-irritant and released drug slowly as compared to conventional formulation	[70]
Benzyl benzoate	Lotion; emulsion; ointment; gel; emulsion based gel	All novel formulation showed better rheological properties and drug release when compared to conventional formulation	[71]
Permethrin	Proniosomal based emulsion-hydrogel	The niosomal loaded emulsion-hydrogel showed better efficacy than standard permethrin lotion in infested rabbits and goats	[72,73]
Ivermectin	Spray formulation using palmitoyl-glycine-histidine as gelling agent	0.1% ivermectin topical spray application to hairless rats was found to be more effective than standard oral ivermectin	[74]
Ivermectin	Liposomes	Liposomal formulation showed higher C_{max} of 33.33 ng/mL and lower T_{max} of 0.23 days when compared to conventional formulation	[75]
Ivermectin	Solid-lipid nanoparticles (SLN's)	SLN's showed excellent entrapment efficiency of 98.48% which facilitate the prolonged release and higher flux value of 2.37 μg/cm^2/h when compared to conventional formmulation	[76]

microemulsion of benzyl benzoate was prepared by Sharma et al. [70] and evaluated for its irritation potential and drug release kinetics. The release of benzyl benzoate was found to be slower in microemulsion than compare to conventional formulation and microemulsion was found to be non-irritant to skin. Similarly, Hamid et al. [71] prepared 5 different formulation of benzyl benzoate and evaluate them for rheological properties and *in-vitro* drug release. Benzyl benzoate 25% was used to prepare 5 formulations viz. lotion (25% of benzyl benzoate in olive oil), emulsion (25% of benzyl benzoate, 5% of Span 80, and 70% of water), ointment (25% of benzyl benzoate in soft paraffin), gel (25% of benzyl benzoate in methyl cellulose gel), and 3 emulgel (benzyl benzoate emulsion mixed with 10 g, 20 g, and 30 g of Carbopol 934 gel). The emulgel was prepared by adding organic phase (5% of Span 80 with benzyl benzoate) to aqueous phase (10 g, 20 g, and 30 g carbopol 934 in water).

Permethirn is currently prescribed medicine for the treatment of scabies. However, some disadvantages associated with its use as discussed earlier. Various novel formulation of permethrin have been developed to overcome the disadvantages. Badawi et al. [72] prepared 2 topical formulation containing proniosomes loaded with permethrin. The proniosomes were prepared by using slurry method and mixed factorial design and contains Brij 97, cholesterol, aerosil 200 and drug in different weight ratios, and using two different solvents. Similarly, a comparative clinical evaluation of the novel permethrin formulations with conventional formulation of permethrin has been carried out on scabies infested rabbits (n=10) and goats (n=2). The proniosomal based emulsion-hydrogel, proniosomal loaded topical powder and standard permethrin 5% lotion was compared for scabicidal activity. The topical proniosomal powder was not effective at all but the niosomal loaded emulsion-hydrogel showed better efficacy than standard permethrin lotion [73].

Ivermectin is also a currently prescribed medicine for the treatment of scabies. Various novel formulation of ivermectine were prepared and evaluated for superiority in case of bioavailability in comparison with conventional formulation. An ivermectin loaded spray formulation was prepeared by Dahlizar et al. [74] using palmitoyl-glycine-histidine as gelling agent. The results concluded that 0.1% ivermectin topical spray application to hairless rats was found to be more effective than standard oral ivermectin. A novel liposomal loaded ivermectin formulation was evaluated for it pharmacokinetic behivour in comparison with conventional ivermectin. Liposome loaded ivermectine was injected to scabies infested rabbits subcutaneously. The liposome based ivermectin formulation gave higher C_{max} of 33.33 ng/ml compared conventional ivermectin 20.82 ng/ml with significant faster absorption indicated by T_{max}

of 0.23 days for liposomal ivermectin formulation compared to T_{max} of 1.13 for conventional ivermectin [75]. Another novel solid lipid nanoparticles (SLN's) formulation of ivermectin was evaluated for its drug release kinetics in comparison to conventional ivermectin formulation. The solid lipid nanoparticles (SLN's) of ivermectin were prepared using homogenization followed by sonication. Method included mixing of melted palmitic acid and lipid to preheated aqueous phase containing polyvinyl alcohol 1%w/v. Ivermectin was loaded in SLN's with an excellent entrapment efficiency of 98.48% which facilitate the prolonged release. The *in vitro* release of ivermectin from SLN's showed higher flux value of 2.37 μg/cm^2/h than compared to the conventional ivermectin suspension 1.56 μg/cm^2/h [76].

Thus, it can be observed from the reports on novel formulations developed for the treatment of scabies that the interaction of drug is improved with affected site when applied in form of any nano-sized formulation. Although studies have not been reported but it is possible that nano-particles would also be able to penetrate the scabies mite more effectively as compared to plain drug/conventional formulation because of the better penetrating potential of nanoparticles.

In conclusions, scabies is a contagious parasite disease known to infect various species of mammals. Currently synthetic drugs are used to treat scabies which are known for their toxicity and side effects. The mite has the tendency to develop resistance against various drugs such as permethrin. Herbal natural products offer safe and equally effective alternative to currently utilized treatment options. The review included various plant based agents, synthetic and novel formulations that has been used for the treatment scabies in various species of mammals on the basis of reports from different researchers. There would be much research required for the development of novel formulations of various agents for the treatment of scabies. It has been proven earlier that novel formulation such as SLN's, liposomes, microemulsions etc improve the permeation of drugs. Since, scabies is a topical disorder of the skin therefore, it can be expected that novel formulations of natural or synthetic agents will improve the overall treatment efficacy. These findings will help in identifying potential scabicidal agents and designing their formulations with lesser side effects and higher efficiency.

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