Original Article

A New Herbal Medicine Formulation with Potential Anti-scabies Properties to Treat Demodex and Sarcoptes Parasites

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ABSTRACT

Scabies is considered an external parasite notorious for its high prevalence causing severe and contagious skin lesions in humans and animals worldwide. This study has introduced a medicine to treat dogs infested with scabies (variants of Demodex, Sarcoptes, Psoroptes, Otodectes, etc.). The present study offers a no-side-effect herbal formulation to treat dogs infested with scabies. Unlike oral and injectable medicines, which take the form of an ointment and are topically applied on-site, this medicinal formulation can be easily used without concerns over its side effects or consumption dosages. This medicinal formulation requires no skin rinsing due to its herbal and high skin absorption properties, as recovery may take less than a month with a maximum of two times of application. To carry out the experiment, 25 sick dogs with various breeds and ages suspected of scabies were gathered. Following accurate morphological examinations of all the samples, a deep skin chip of the lesion site was provided, which was examined by a microscope. Then, 13 dogs (Mix, Terrier, Pug, Husky, Spitz) were infested with Demodex scabies and 12 dogs (Pittbull, Mix, Shih Tzu, Terrier, Boxer, Setter) with Sarcoptic scabies. The prepared product was topically administered at a constant 2% dosage to the bodies of all the samples. To prepare the ointment, 1 g of Borax ($Na_2 B_4 O_7 \cdot 10H_2 O$) was first dissolved in 35 g deionized water and heated to 70°C. Then, 45 g of liquid paraffin (C_nH_{2n+2}) was mixed with 1 g of Carvacrol ($C_{10}H_{14}O$) and 1 g of geranium ($C_{10}H_{18}O$) and stirred well to become a phase. Later, 17 g of the melted beeswax ($C_{15}H_{31}COOC_{30}H_{61}$) was added to the liquid paraffin compound. In the end, the aqueous phase was added to the oil phase, and the mixture process immediately began in one direction with a glass stirrer and continued until the product cooled down. Essential oils (EO) was obtained by steam distillation of fresh Thyme and Rose-Acented Geranium in a stainless steel distillation apparatus (alembic) for 3 h. The main components of the essential oils used in the formulation were performed using a Hewlett-Packard GC system interfaced with a mass spectrometer equipped with an HP5-MS capillary column (30 m, 0.32 mm, 0.25 µm film thicknesses). For GC–MS detection, electron ionization with ionization energy of 70 eV was used. To examine the presence of scabies, weekly skin sampling was performed, and the treatment continued until 30 days, when no skin chip of the scabies was noted. The findings revealed that the formulation developed no side effects and removed the daily use, as it could be administered once or twice a week. Also, complete recovery of scabies in all the breeds was found to be less than a month at most. This medicinal formulationcan be easily used without concerns over its side effects or consumption dosages. This study introduced a herbal formulation with effective herbal ingredients without any side effects to treat the sarcoptes and demodex parasites; unlike other chemical compounds, this medicinal formulation has no side effects, while some other formulations could develop side effects.

Keywords: Anti-scabies, Demodex, Essential oils (EO), Formulation, Sarcoptes, Herbal Medicine

1. Introduction

Scabies is considered an external parasite notorious for its high prevalence, causing severe and contagious skin lesions in humans and animals worldwide [1-6]. Several species of scabies, including *Demodex*, *Sarcoptes*, *Psoroptes*, and *Otodectes*, infect hosts, including humans and animals (e.g., dogs, cats, and rabbits) [7-10]. When it settles on the skin, it burrows and forms channels in the skin causing hair loss, itching, pustules, skin inflammation, and dark skin color [11-16]. Nowadays, in order to eliminate and control the population of these microscopic organisms, chemical poisons, such as carbamates, organophosphates, and pyrethroid compounds, are used [17-19], which not only require daily and long-term application but also cause some side effects, such as itching, urticaria, angioedema, poisoning, central nervous system stimulation, depression, coma, and even death in some breeds, which has led to the prohibition of the use of some of these agents in some countries [20]. In addition, the disproportionate use of these poisons has led to widespread resistance. The use of potentially safe botanicals to replace injectable and oral drugs, sprays, synthetic insecticides, and pesticides without worrying about dosage would help protect the environment and is a practical step for the health of other living things [21-23].

In recent years, numerous techniques have been employed to eliminate and control populations of microscopic organisms, such as scabies, which not only required daily and long-term applications but also caused side effects and even death in some breeds. Some studies on this topic are presented below:

In 2000, a study evaluated the efficacy of bovine-specific injectable 1% moxidectin in dogs and rabbits infested with sarcoptic, demodictic, and psoroptic mites. Twenty-two dogs infested with generalized demodicosis were treated orally with 0.4 mg/kg moxidectin daily. Forty-one dogs affected by sarcoptic scabies were treated orally or subcutaneously with 0.2-0.25 mg/kg moxidectin three to six times per week. In addition, seven rabbits were administered 0.2 mg/kg moxidectin orally twice within ten days. Of the 22 dogs with demodicosis, treatment was discontinued due to side effects, another 14% were lost, and 72% were treated (mean treatment duration was 2.4 months) [13].

In another study, Fourie et al. randomly assigned 16 dogs diagnosed with generalized demodictic scabies into two groups. One group was given Bravecto™ chewable tablets orally once, at a minimum dose of 25 mg fluralaner per kg of body weight. In contrast, the second group was treated topically with Advocate® three times at 28-day intervals, with a minimum dose of 10 mg imidacloprid per kg of body weight and 2.5 mg of moxidectin per kg of body weight. After a single oral administration of Bravecto™ chewable tablets, mite counts in skin scrapings were reduced by 99.8% on day 28 and 100% on days 56 and 84. In dogs treated topically with Advocate® three times 28 days apart, mite counts also decreased by 98.0%, 96.5%, and 94.7% on days 28, 56, and 84, respectively [7].

In another study, Fourie et al. compared the efficacy of two topical drugs (i.e., fluralaner and a combination of imidacloprid and moxidectin) against naturally acquired generalized demodicosis in dogs. In this study, 16 dogs with naturally acquired generalized demodicosis were randomly divided into two groups. After the administration of fluralaner, the antimicrobial effects were obtained at 99.7%, > 99.9%, and 100% on days 28, 56, and 84, respectively. In dogs treated topically with a combination of imidacloprid and moxidectin, efficacy was 9.8%, 45.4%, and 0% on days 28, 56, and 84, respectively [11].

In a 2020 study, 134 dogs diagnosed with generalized demodicosis were registered. The dogs were randomly assigned in a 2:2:1 ratio for treatment with fluralaner chewable tablets, topical fluralaner, or topical imidacloprid-moxidectin. Of the 124 dogs that participated in the study, 57 were diagnosed with juvenile form and 67 with adult form. A single treatment with oral or spot- administration of

fluralaner was effective, eliminating 98% of the mites in treated dogs on days 56 and 84 [12].

In 2021, Beck et al. used a topical solution of selamectin and sarolaner in their study and found that selamectin was effective against scabies infestation in dogs as a dosage of 6 mg/kg within a week was also confirmed for the treatment of sarcoptic scabies (caused by *Sarcoptes scabiei*) [1].

The present study provides a side-effect-free herbal formulation for the treatment of animals infested with scabies. Unlike oral and injectable drugs, which take the form of an ointment and are applied on the spot, this drug can be easily used without worrying about its side effects or consumption doses. Due to its herbal properties and high absorption through the skin, the drug does not need to be rinsed off, as healing can take less than a month with a maximum of two applications.

2. Materials and Methods

2.1. Materials

Table 1 lists the ingredients and the amounts of effectively combined substances in the formulation, while figure 1 illustrates the process of formulation preparation. Borax, liquid kerosene, and beeswax used in this study were trademarks of the German company Merck. To prepare carvacrol ($C_{10}H_{14}O$), the essential oil (EO) of the thyme plant was used as follows: Thyme EO was obtained by water distillation, which finally contributed to the extraction of carvacrol. To identify the extracted carvacrol, a gas chromatography-mass spectrometry (GC-MS) device was used. To produce geranium ($C_{10}H_{18}O$), the EO of the plant was obtained by water distillation, which finally produced geranium. To identify the extracted geranium, the GC-MS device was used.

Table 1: Ingredients and amounts of effectively combined substances in the formulation

Ingredients and combined substances in the formulation	Amounts of effective substance used in the whole formulation
Borax ($Na_2 B_4 O_7 \cdot 10H_2 O$)	1 g
Liquid paraffin (C_nH_{2n+2})	45 g
Carvacrol ($C_{10}H_{14}O$)	1 g
Geranium ($C_{10}H_{18}O$)	1 g
Beeswax ($C_{15}H_{31}COOC_{30}H_{61}$)	17 g

2.2. Methods

2.2.1. Plant material and essential oils extraction

Thyme and rose geranium were grown in the herbarium of the Faculty of Pharmacy (Tabriz University of Medical Sciences, Tabriz, Iran). The aerial parts of the plant were collected in September 2021. The identification of the plant was confirmed by the National Institute of Agriculture of Iran and the pharmacognosy expert of the Faculty of Pharmacy.

Essential oils were obtained by steam distillation of fresh plant material (thyme and rose geranium) in a stainless steel distillation apparatus (still) for 3 h. The process consisted of passing steam at low pressure through a tank containing the aromatic parts of the plant. The steam captured the oil, which was trapped in micro-pockets in the plant tissue. The vapor was then passed through a serpentine cooled with cold water, where it condensed to liquid. At the exit, the collected liquid was a mixture of oil and floral water, which could be easily separated using a Florentine vase. The EO of rose geranium (RGEO) thus obtained was dried over anhydrous sodium sulfate, filtered, and stored at +4°C until tested. The same method and steps were performed to extract the EO of carvacrol from thyme.

2.2.2. Gas Chromatography-Mass Spectrometry analyzes

GC-MS analyses were performed using a Hewlett-Packard gas chromatograph (HP, Palo Alto, CA, USA) equipped with a flame ionization detector and an HP5-MS capillary column (30 m, 0.32 mm, and 0.25 µm film thickness). The oven temperature was

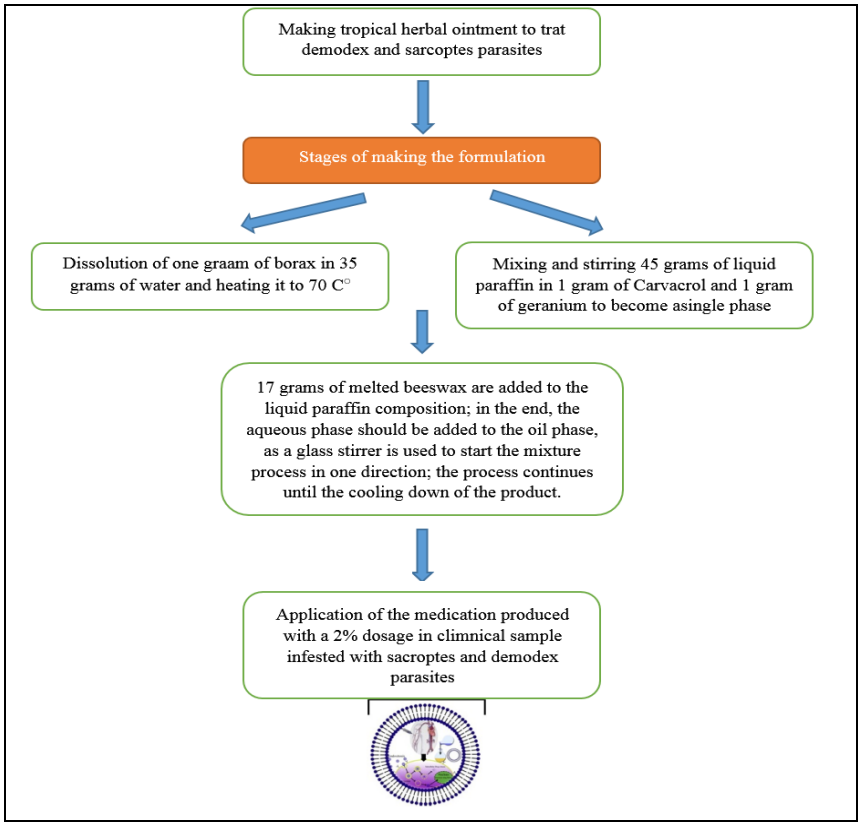

Figure 1. Flowchart of the formulation preparation process

programmed isothermally to 45°C for 8 min and then to 45-240°C at 2°C/min for 15 min. Injector and detector temperatures were set at 250°C and 280°C, respectively. Carrier gas was nitrogen at a flow rate of 1.2 ml/min in split mode 1:70 with an injection volume of 1 µl. The composition of RGEO was calculated from the GC-MS peak areas using the normalization method.

GC-MS analyses were performed using a Hewlett-Packard GC-MS system connected to a mass spectrometer and equipped with an HP5-MS capillary column (30 m, 0.32 mm, 0.25 µm path length). Electron ionization with an ionization energy of 70 eV was used for GC-MS detection. The carrier gas was helium with a flow rate of 1.2 ml/min and an injection volume of 1 µl. The injector and detector temperatures were set at 250°C and 280°C, respectively. The constituents of rose geranium and thyme EOs were identified by matching the recorded mass spectra with the mass spectra database (Wiley 7N and NIST 2002 libraries) and comparing their retention indices relative to a range of hydrocarbons (C7-C28) with literature values.

2.2.3. Formulation

To prepare the ointment, 1 g of borax ($Na_2 B_4 O_7 \cdot 10H_2 O$) was first dissolved in 35 g of deionized water and heated to 70°C. Following that, 45 g of liquid kerosene (C_nH_{2n+2}) was mixed with 1 g of carvacrol ($C_{10}H_{14}O$) and 1 g of geranium ($C_{10}H_{18}O$) and stirred well to form a phase. Later, 17 g of melted beeswax ($C_{15}H_{31}COOC_{30}H_{61}$) was added to the liquid kerosene compound. Finally, the aqueous phase was added to the oil phase, and the mixing process started immediately with a glass stirrer in one direction and continued until the product cooled.

To perform the experiment, 25 infected dogs of different breeds and ages with suspected scabies were collected. After a detailed morphological examination

of all specimens, a deep skin incision was made, which was examined with a microscope. Subsequently, 13 dogs with Demodex scabies (demodicosis) and 12 others with Sarcoptes scabies were infected. The prepared product was topically administered at a constant dosage of 2% to the bodies of all samples. This treatment method was continued twice weekly for three weeks and then once weekly until recovery. To investigate the presence of scabies, skin samples were taken weekly, and the treatment was continued for up to 30 days when no more rash of scabies was detected.

All samples treated with the manufactured drug were quarantined separately at the veterinary hospital for two months, and microscopic and morphological examinations (e.g., recurrence of parasites, itching, inflammation, abscesses, blisters, sores, fever, and hair loss at the site where the topical drug was applied) were observed and studied. In addition to microscopic examinations, morphological examinations were performed on all samples before and after the treatment.

3. Results and Discussion

Tables 2 and 3 show GC-MS results for thyme and rose-scented geranium plants.

Table 2. Volatile compounds in Rose Geranium essential oil identified by GC-MS analysis

Chemical Name	R.T[a]	Content (%)
β-Myrcene	9.99	0.11±0.04
β-Ocimene	11.32	0.12±0.02
Linalool oxide cis	12.00	0.18±0.01
Linalool	12.91	4.23±0.06
Rose oxide B	13.17	3.86±0.07
Isopulegol	14.23	0.1±0.06
p-Menthone	14.49	2.18±0.03
L-menthal one	14.87	5.2±0.04
p- Menth-1-en-8-ol	15.6	0.97±0.2
α - Citronellol	16.43	0.94±0.06
Citronellol	17.11	30.68±0.09
Geraniol	17.77	9.68±0.07
Citronellyl formate	18.15	9.90±0.4
Geraniol formate	18.80	2.72±0.03
Oxiranemethanol	19.74	0.56±0.4
6-Octen-1-ol	20.14	1.07±0.26
1,7-Octanediol	20.41	0.2±0.09
2,6-Octadien-1-ol	20.98	1.86±0.07
2,6,10-Dodecatrien-1-ol	21.30	0.24±0.06
α-Gurjunene	21.83	2.32±0.03
Caryophyllene	22.12	1.66±0.32
Citronellyl propionate	22.54	3.21±0.02
Neryl acetate	22.77	0.1±0.05
α -Humulene	22.97	0.62±0.02
Geranyl propionate	23.32	1.75±0.03
Azulene	23.42	0.37±0.05
β -Selinene	23.82	0.22±0.06
α-Selinene	24.01	0.34±0.03
Ledol	24.24	0.15±0.17
Citronellyl butyrate	24.68	3.47±0.22
Geranyl butyrate	25.45	2.44±0.04
Phenylethyl tiglate 2	26.14	2.6±0.38
Caryophyllene oxide	26.82	0.2±0.09
2-Dodecenal	27.09	0.16±0.13
Citronellyl propionate	27.94	2.1±0.02
Thiogeraniol	33.60	0.07±0.01
Geranyl tiglate	28.73	2.76±0.61

Table 3. Chemical content in Thyme plant identified by GC-MS analysis

Chemical Name	R.T[a]	Content (%)
α-Thujene	7.38	2.2±0.08
α -pinene	7.28	18.75±0.04
Camphene	7.95	14.39±0.09
β-pinene	9.56	8.43±0.03
Myrecene	9.93	6.41±0.05
α -terpinen	10.12	0.60±0.03
P-cymene	10.45	2.38±0.04
1,8-cineol	10.78	10.95±0.02
Trans- β -ocimene	10.96	0.18±0.02
δ-terpinene	11.24	1.05±0.07
Cis-sabinene hydrate	11.38	0.92±0.01
Camphenilone	11.67	0.62±0.01
α -terpinolene	11.96	0.22±0.02
Linalool	12.18	0.28±0.08
Camphor	12.65	22.24±0.07
Terpinene-4-ol	13.42	4.42±0.02
P-cymen-8-ol	13.56	0.56±0.01
α -terpineol	13.87	1.04±0.05
carveol	14.12	0.44±0.01
Carvacrol methyl ethyl	13.58	0.56±0.06
Bornyl acetate	14.87	0.80±0.02
Thymol	15.51	85.12±0.09
α -copaene	16.45	0.60±0.03
α -elemene	17.21	0.44±0.04
δ-cadinene	17.63	8.98±0.03
β-oplepenone	19.44	6.15±0.04

After detailed morphological examinations of the specimens, a deep skin chip was prepared from all the samples of 13 infested dogs of 5 different breeds, aged four months to 13 years, and they were investigated under a microscope. The examinations revealed the diagnosis of the *Demodex* (demodicosis) parasitic disease. The prepared product was applied topically at a dosage of 2% to the bodies of 13 infested samples. The results indicated that the prepared topical product had a potential efficacy of less than one month on all samples and helped the *Demodex*-parasite-infested samples to recover without any side effects. Table 4 presents the test results, and figure 2 illustrates the treatment of the samples before and after the treatment. After detailed morphological examinations of the samples, a deep skin chip of all samples was made from the 12 infested dogs of 6 different breeds, aged from 1.5 to 13 years, and examined under the microscope. Based on the examinations, the *Sarcoptes* parasitic disease was diagnosed. The prepared product was applied topically at a dosage of 2% to the bodies of the 12 infested samples. The results indicated that the prepared topical product had a potential efficacy of less than one month on all samples and helped the *Sarcoptes*-parasite-infested samples to recover without side effects. Table 5 tabulates the test results, and figure 3 displays the before-and-after ratio of the treatment in the sample.

Table 4. Results of scabies infestation tests, the dosage used, length of treatment in dogs of various ages and breeds infested with Demodex (Demodicosis) parasite

Row	Breed	Age	Diagnosis	Ointment percentage	Manner of administration	Length of treatment	Result	Side effects
1	Mix	Four months	Demodex	2%	Topical	Three weeks	Full recovery	-
2	Terrier	11 months	Demodex	2%	Topical	One month	Full recovery	-
3	Mix	Two years	Demodex	2%	Topical	One month	Full recovery	-
4	Mix	Two years	Demodex	2%	Topical	One month	Full recovery	-
5	Pug	4.5 years	Demodex	2%	Topical	1.5 months	Full recovery	-
6	Husky	Nine months	Demodex	2%	Topical	One month	Full recovery	-
7	Husky	11 months	Demodex	2%	Topical	One month	Full recovery	-
8	Mix	13 years	Demodex	2%	Topical	1.5 months	Full recovery	-
9	Mix	Ten years	Demodex	2%	Topical	Two months	Full recovery	-
10	Mix	Eight years	Demodex	2%	Topical	Three weeks	Full recovery	-
11	Mix	11 years	Demodex	2%	Topical	One month	Full recovery	-
12	Mix	Six years	Demodex	2%	Topical	One month	Full recovery	-
13	Spitz	Seven months	Demodex	2%	Topical	One month	Full recovery	-

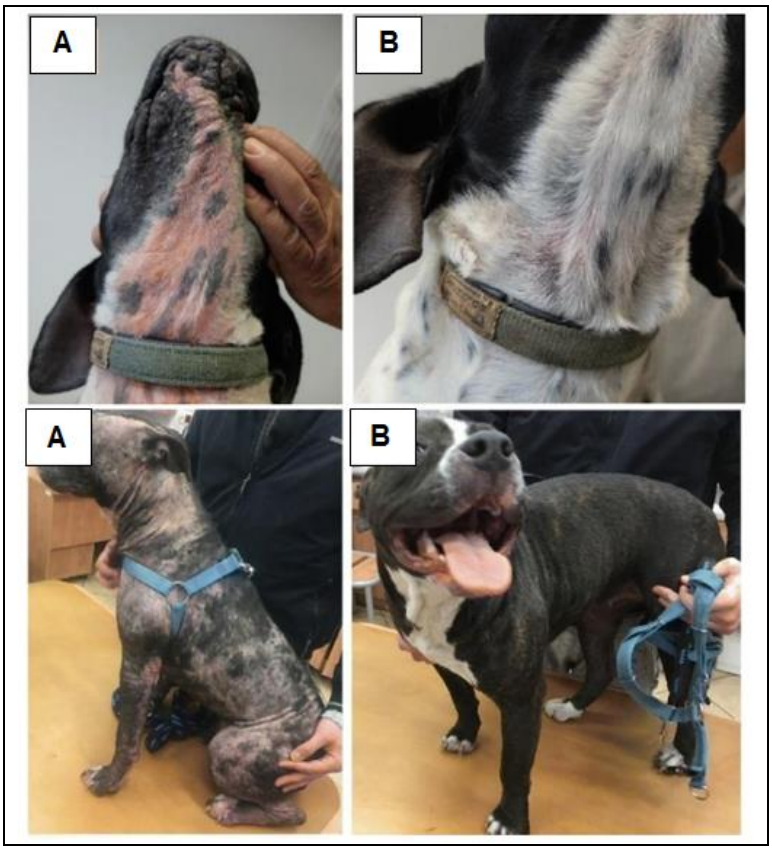

Figure 2. Before the treatment (A) and after the treatment (B) with the ointment produced for the Demodex (Demodicosis) parasite

This study presented a new herbal formulation with effective herbal ingredients that can effectively treat Sarcoptes and Demodex parasites without any side effects. Unlike other chemical compounds, this drug is free of side effects, while some other formulations may develop some side effects [24]. This ointment is cost-effective and easily accessible due to its preparation and application [25]. This is noteworthy because some drugs prescribed for *Demodex* and *Sarcoptes* parasites are costly or need to be injected.

Table 5. Results of scabies infestation tests, the dosage used, length of treatment in dogs of various ages and breeds infested with Sarcoptes parasite

Row	Breed	Age	Diagnosis	Percentage of ointment	Manner of administration	Length of treatment	Result	Side effects
1	Pittbull	Three years	Sarcoptes	2%	Topical	One month	Full recovery	-
2	Mix	Seven years	Sarcoptes	2%	Topical	One month	Full recovery	-
3	Mix	13 years	Sarcoptes	2%	Topical	One month	Full recovery	-
4	Shih Tzu	2.5 years,	Sarcoptes	2%	Topical	1.5 months	Full recovery	-
5	Terrier	six years	Sarcoptes	2%	Topical	One month	Full recovery	-
6	Pittbull	1.5 years	Sarcoptes	2%	Topical	1.5 months	Full recovery	-
7	Boxer	Two years	Sarcoptes	2%	Topical	Three weeks	Full recovery	-
8	Boxer	Four years	Sarcoptes	2%	Topical	One month	Full recovery	-
9	Setter	2.5 years	Sarcoptes	2%	Topical	Three weeks	Full recovery	-
10	Mix	Ten years	Sarcoptes	2%	Topical	One month	Full recovery	-
11	Mix	Ten years	Sarcoptes	2%	Topical	Two months	Full recovery	-
12	Mix	Eight years	Sarcoptes	2%	Topical	Three weeks	Full recovery	-

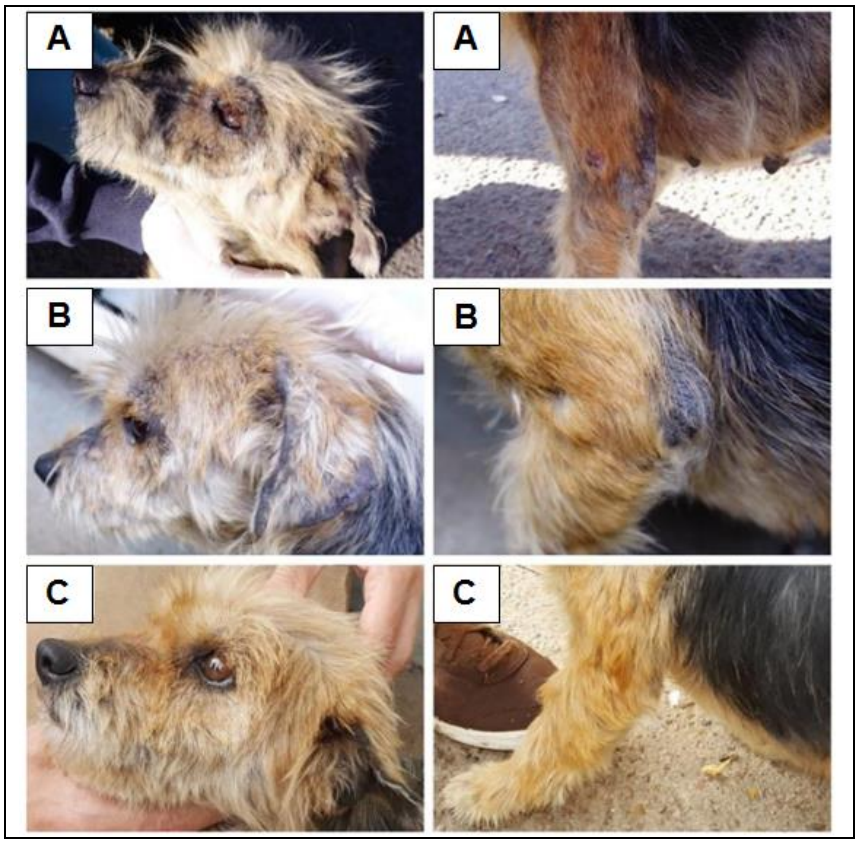

Figure 3. Before the treatment (A,B) and after the treatment (C) with the ointment produced for the Sarcoptes parasite

[25-27]. The ease of application of this ointment and the fact that the site does not need to be rinsed may be a distinctive feature of this formulation. Some of the medications are not very effective against scabies; however, this formulation has been shown to be able to eliminate scabies that are resistant to available injectable and oral medications as well as sprays and insecticides [11, 28]. Due to the high content of geranium substances and carvacrol in the formulation, the medicinal formulation is characterized by its healing, anti-inflammatory, antipruritic, and

antimicrobial properties [1, 11]. As shown in the studies, some formulations require daily ingestion of the drugs to achieve sufficient efficacy. However, the formulation presented in this study does not require daily drug intake, as application once or twice a week resulted in complete recovery in less than one month. In addition, the production of this ointment is simple with existing equipment and has no harmful environmental effects caused by chemical insecticides. One of the problems with injectable and oral drugs is their sensitivity to the dose taken [26, 29]; this formulation has resolved this problem as well.

This article introduced an herbal medicine for the treatment of dogs infested with scabies (*Demodex*, *Sarcoptes*, *Psoroptes*, and *Otodectes*). A total of 25 infected dogs (including 13 dogs from Mix, Terrier, Pug, Husky, and Spitz breeds affected by *Demodex* scabies and another 12 dogs from Pittbull, Mix, Shih Tzu, Terrier, Boxer, and Setter breeds with *Sarcoptic* scabies) in different ages with suspected scabies were collected. The prepared product was applied topically to the bodies of all samples at a constant dosage of 2%. The treatment was continued until the 30th day when no rash of scabies was detected. The healing, anti-inflammatory, and antipruritic properties of this product for the animal's skin are its main advantages. This product can be used to treat dogs affected by scabies, both those living at home and those living in crowded areas, such as breeding centers and animal shelters. This medical formulation has won the satisfaction of dog owners for its potential effect and the absence of the need for daily and long-term use. Unlike oral and injectable medicines, which take the form of an ointment and are applied on the spot, this drug formulation can be used easily without worrying about its side effects or consumption doses.

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Authors' Contribution

Study concept and design: H. A. and P. T. and M. M., Acquisition of data: H. A., Analysis and interpretation of data: T. S. and A. H. N., Drafting of the manuscript: P. T. and A. H. N, Critical revision of the manuscript for important, Intellectual content: H. A. and A. H. N. and M. M., Statistical analysis: H. A. and T. S, Administrative, technical, and material support: H. A.

Ethic

The current study was approved by and carried Tabriz University of Medical Sciences, (Tabriz, Iran). All experiments involving animals were approved by the Committee for Conducting Animal Experiments at the Araz Pharmed Pet Hospital, (Tabriz, Iran).

Conflict of Interest

The authors declare that they have no conflict of interest. This study not supported by any grant money from a pharmaceutical company or for-profit organization.

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