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Original Research

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Therapeutic Management, Clinicopathological, Molecular and Cost Studies on *Sarcoptes scabiei* Infestation in Rabbit

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Abstract

Sarcoptic Mange is a highly contagious parasitic disease that can cause huge economic losses to rabbit producers and has the potential to infect humans. This study aimed to perform molecular characterization and phylogenetic analysis of *Sarcoptes scabiei*, assess redox and inflammatory state, evaluate the cost and efficacy of a single dose of a commercially available ivermectin with a topical application of sulfur ointment for control of this issue. Skin scraping was collected from infested rabbits in Ismailia governorate, Egypt, and submitted for parasitological examination. The mite specimens were identified based on ITS2 PCR gene. Forty-four adult rabbits naturally infected with mange and 5 free animals were divided into three groups, group 1, 1% ivermectin was injected subcutaneously once, the affected area was soaked with 1% deltamethrin, and sulfur ointment 10% was applied every 2 days. Group 2 received two injections of ivermectin with an interval of 2 weeks while group 3 was non-infested rabbits. Skin scraping and serum samples were taken for parasitological and clinicopathological examination and the cost of each treatment was calculated. A high degree of sequence variation was observed between our sequence sample and some other *Sarcoptes scabiei* sequences from Egypt and different geographic areas. MDA and IL-6 levels were significantly increased, and TAC was significantly decreased in the infected groups compared with the uninfected group. On the 28th day of treatment, hair growth and complete skin recovery were observed in both treated groups. A single dose of 1% ivermectin with topical treatment is sufficient to eliminate *Sarcoptes scabiei* but is costly.

KEYWORDS
Ivermectin, Mange costs, Molecular, Rabbits, *Sarcoptes scabiei*

INTRODUCTION

Sarcoptic mange is a common dermatological problems in rabbits which is a highly contagious disease condition caused by the deep burrow mite *Sarcoptes scabiei* (*S. scabiei*) (Kumar, A. *et al*., 2018) causing severe itching, pruritus, dermatitis, crust production, scar formation, thickening of affected skin, mainly on the ears, nose, and feet (Kachhawa *et al*., 2013), leading to severe losses (Bhardwaj *et al*., 2012). In Egypt, mange is a major disease problem of both sexes of all rabbit breeds throughout the year (Elshahawy *et al*., 2016) as well as affects the skin of a variety of mammals including humans (Abo-Elhassan, 2020). Mite infestation is usually transmitted between rabbits through direct skin contact or through contact with the environment (Panigrahi and Gupta, 2013). Increasing housing density and a poor hygienic environment are the most critical predisposing factors for infestation (McCarthy *et al*., 2004). Research on molecular identification of scabies is limited, possibly because it is difficult to obtain sufficient amounts of mite genetic material (Walton *et al*., 2004). However, molecular identification is an alternative and necessary tool for the accurate identification of mites (Abo-Elhassan, 2020).

Sarcoptic mange infestation, if left untreated, can lead to high morbidity and severe economic losses in livestock. Scabies in rabbits can be effectively treated with chemotherapeutic drugs such as ivermectin and sulfur-based compounds (Ulutas *et al*., 2005). Subcutaneous injection is an effective route of administration of ivermectin in the treatment of sarcoptic mite infestation in rabbits (Panigrahi *et al*., 2016). However, repeated use generates free radicals, leading to liver damage and degenerative changes ranging from mild to complete necrosis of spermatogenic cells and loss of spermatozoa (Nayak *et al*., 1996; GabAllh *et al*., 2017). What's more, their extensive use can lead to environmental pollution and drug resistance (Coles and Dryden, 2014), Consequently, ivermectin needs a synergistic product to quickly treat infested animals. The combined use of ivermectin and deltamethrin is more effective and has a stronger killing effect on mites (Mohamed *et al*., 2020). This study focused on the molecular characterization and phylogenetic analysis of *S. scabiei* infestation and its relationship to other *S. scabiei* sequences, evaluating redox and inflammatory state in the infected rabbits, as well a trial for in vivo control using a single dose of a commercially available ivermectin with a topical application of sulfur ointment

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and assessing the cost relevance.

MATERIALS AND METHODS

Ethical approval

The present material and protocol were approved by the Scientific Research Ethics Committee of the Faculty of Veterinary Medicine, Suez Canal University, Ismailia, Egypt, Approval No (2023010).

Rabbit examination and treatment

A private rabbit farm in Ismailia, Egypt with adult and growing rabbits was inspected for the manifestation of mange in 2021. Forty-four adult rabbits (10 males and 34 females) were naturally infested with mange and another 5 were free. Improper hygienic measures were noticed in the animal environment. Infested rabbits were grouped into two groups. In group 1, 1% ivermectin (El-Naser pharmaceutical chemicals co.) 0.2 mg/kg b.wt was injected subcutaneously once, the affected area was soaked with 1% deltamethrin (Butox® 50 EC, Intervet, France), and sulfur ointment 10% (Mega Pharma) was applied every 2 days. Group 2 received two injections of 1% ivermectin 0.2 mg/kg bwt with an interval of 2 weeks. Group 3 consisted of rabbits without mange infestation (control non-infested group). Vitamin AD3E supplements were administered in drinking water as a supportive therapy. During treatment, cages and the surrounding environment was carefully cleaned and disinfected. Rabbits were examined on the 14th and 28th day of treatment and observed for 3 months. Skin scrapings and ear scab samples were collected from rabbits on day 0 (the start of the treatment day) then on day 14, and the last sampling was done on day 28.

Parasitological examination and skin scraping

The suspected rabbits were selected for parasitological investigation after clinical examination. Skin scrapings were obtained from the peripheral of the clinical lesions from the ears, the scraping varied from 1 to 2.5 cm^2, until the skin was bleeding slightly. The scraped samples were treated with 5 ml of 10% of potassium hydroxide (KOH) to dissolve hairs and tissue material and heated for 5-10 min. After that, samples were centrifuged at 1500 rpm for 4-5 min, then the sediment was spread on a glass slide and examined, microscopically under 10x magnification, identification of mites was carried out with the help of morphological characteristics according to Soulsby (1968).

Molecular identification

Following morphological identification, the DNA of mites was extracted utilizing QIAamp DNA Mini Kit (Qiagen) according to manufacturer's instruction. Genomic DNA was stored at − 20 °C until use. PCR amplification of the ITS- 2 was done using primers RIB-18 and RIB-3 as described by Zahler *et al.* (1999). The PCR was running following the cycling condition: initial denaturation at 95ºC for 5 minutes followed by 10 cycles of 92ºC for 1min, 48ºC for 1 minute and 72ºC for 90 seconds. This step was followed by additional 32 cycles of 92ºC for 1 minute, 54ºC for 35 seconds and 72ºC for 90 seconds, this was followed by a final extension at 72ºC for 7 minutes. The amplification products from ITS-2 were separated on 1.6% agarose gel containing 0.4 µg/ml of ethidium bromide (Bio-Rad Laboratoies Inc., Hercules, CA) at 90 volts for 40-60 minutes, The PCR products were sent for sequencing. Sequences were amplified using primers the upstream primer RIB-18 5' -GGG CTG CAG TAT CCG ATG GCT TCG T-3'. and RIB-3 5 '- CGG GAT CCT TC (A,G) CTC GCC G(C,T)T ACT- 3'.

Sequencing and sequence analysis

Sanger sequencing was performed by SolgentCo. Ltd (South Korea). DNA sequence files were visualized and checked for quality in Chromas 2.6.6 (Technelysium Pty Ltd, Queensland, Australia). Sequences were then analyzed using BLAST® (Johnson *et al*., 2008).

Phylogenetic analysis

Phylogenetic analysis was performed based on the ITS- 2 sequences from several closely related mite species. A phylogenetic tree was constructed in MEGA X (Kumar, S. *et al*., 2018).

Blood sampling

At zero day, two and four weeks later, blood was drawn from each rabbit's ear vein and centrifuged at 3000 rpm for ten minutes. The serum was then separated and stored at -20 ºC for analysis of serum biochemical parameters. Serum samples were analyzed for Malonaldialdehyde (MDA) levels using a commercial kit provided by Cell Biolabs, Inc. (USA) in accordance with Armstrong and Browne (1994) The total antioxidant capacity and interleukin 6 were estimated by Labor Diagnostika Nord GmbH & Co. KG, (Germany) and CUSABIO (USA) respectively according to the manufacturer's directives.

Prevalence of skin infestations and cost analysis

Analyzing both the number of treated cases of skin infestations throughout Ismailia and Egypt based on data obtained from CAPMAS (2015-2019), Ministry of Agriculture and Directorate of Veterinary Medicine of Ismailia, was performed.

Direct disease cost per head (LE) was calculated according to the following equation: L=T + D, where L is the direct monetary loss, T is the monetary value of treatment cost (ivermectin conc%), and D is the cost of disinfectant (butox conc%) (Bennett *et al*., 1999). The actual market prices were used in calculating relevant costs. The cost of each treatment was calculated by multiplying the cost of medication dose used by the frequency and the number of days. The value of other monetary losses was not calculated because losses were either non-specific, their prevention cost has a generalized benefit, or because of their implicit values.

Statistical analysis

The obtained data were statistically analyzed by one-way analysis of variance using IBM SPSS software computer program version 25. P values of less than 0.05 were considered significant. The data were represented as Mean ± Standard error (Landau and Everitt, 2003)

RESULTS

Clinical observations and treatment efficacy trial

Before treatment, infested rabbits suffered from thickened raised crusts on the ear, dry scabs distributed on the face around eye, nose, and mouth, and in the toes of the feet with a patchy loss of hair (Fig. 1). Many other complications appeared in infest-

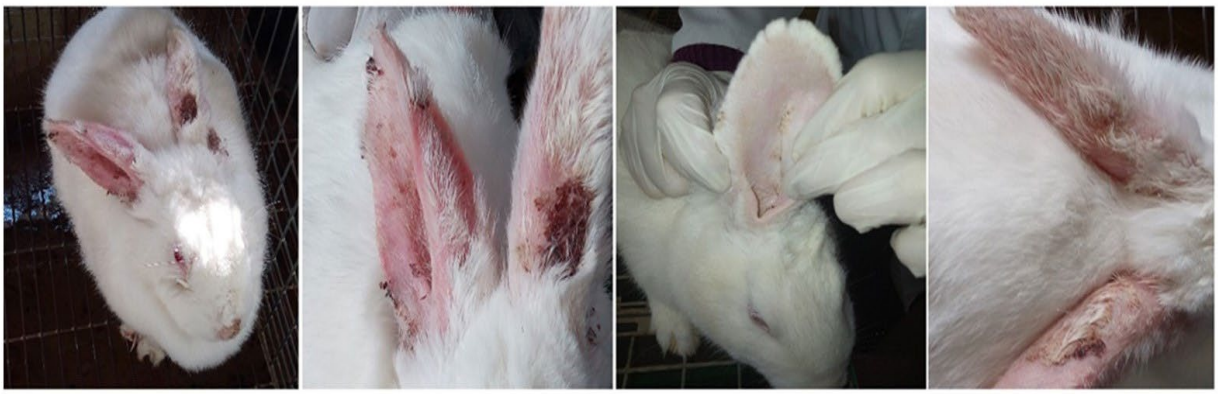

Fig. 1. Infested rabbits had thickened raised crusts on the ears and dry scabs around the nose and eyes with patchy hair loss.

ed rabbits such as anorexia, diarrhea, and reproductive problems. There were heavy infestations in both males and females over 6 months of age, while no infections were recorded in rabbits under 3 months of age. Examination of the skin on the 14th day after treatment revealed marked clinical improvement in the affected part. Lesions on the ears, face and legs started to decrease, raised and dry scabs started to disappear, healing and skin texture was improved, but the improvement was better in group 1 than in group 2. Hair growth and complete skin recovery were observed on the 28th day of treatment (Fig. 2) in both groups with a general improvement in body condition. Examination of a skin scraping on day 0 revealed that rabbits were infested with *S. scabiei*, which was identified by its size, shape, and morphology following up the identification key of (Soulsby, 1968), (Fig. 3). Examination of a skin scraping on the 14th and 28th day of treatment revealed the absence of *S. scabiei* in all rabbits under treatments.

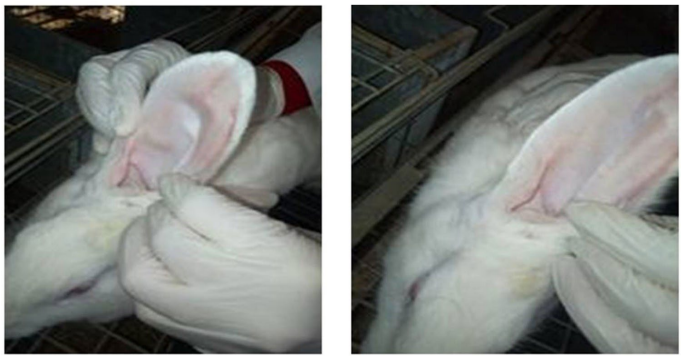

Fig. 2. The skin of treated rabbits appeared to heal and improve with disappearance of crusts and scabs.

Molecular identification

In the present study, the mite specimens were identified based on ITS2 PCR products as *S. scabiei* and the DNA sequence was submitted to the GeneBank (Accession No. MZ541991). The results of the phylogenetic analysis based on the ITS2 were performed using MEGA X10.1 software and the tree was constructed using the UPGMA method (Fig. 4) and the estimates of

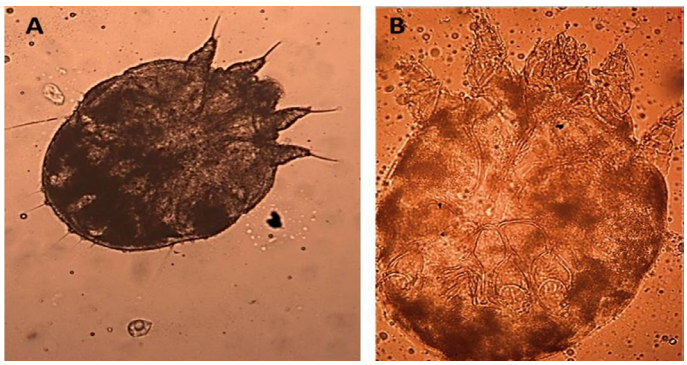

Fig. 3. Light microscopy (LM) of fresh specimens *Sarcoptes scabiei* adult (A): dorsal view (B): ventral view.

evolutionary divergence (Fig. 5), showing that although there is higher variation between our sequence sample and some other *S. scabiei* sequences from Egypt and different geographic areas, they are clustered together and sharing the same original ancestor. However, there is a low variation between other Egyptian *S. scabiei* sequences, from the gene bank and they have the same branch.

Assessment of redox and inflammatory state

Table 1 showed the effects of various treatments on redox state and interleukin-6 in mange infected groups. On zero day, the infested groups had significantly higher MDA and IL-6 levels and significantly lower TAC levels than the control group. However, following treatment, the infected groups improved gradually. MDA and IL-6 levels decreased after two weeks, while TAC levels increased in groups 1 and 2 in comparison with the values obtained on the zero day. At four weeks post treatment, the levels of the measured parameters had approached those of normal rabbits.

Prevalence of skin infestations and cost analysis

The trend of infestations as shown in Table 2 was unsteady through the study period. In Ismailia, mange cases generally rep-

Table 1. The effect of mange treatments on redox state and interleukin-6 in different groups

Parameters	Zero time			2 weeks			4 weeks		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
MDA (µM/ml)	3.23±0.02^{a}	3.22±0.02^{a}	1.81±0.01^{b}	2.55±0.07^{a}	2.57±0.03^{a}	1.79±0.02^{b}	1.90±0.02^{a}	1.91±0.01^{a}	1.82±0.01^{b}
TAC (mmol/L)	1.43±0.03^{b}	1.46±0.02^{b}	2.21±0.04^{a}	1.73±0.04^{b}	1.77±0.04^{b}	2.23±0.04^{a}	2.06±0.04^{b}	2.09±0.05^{b}	2.29±0.00^{a}
IL-6 (pg/ml)	358.55±2.07^{a}	358.55±2.04^{a}	244.75±0.47^{b}	291.23±3.56^{a}	288.55±2.19^{a}	243.33±2.2^{b}	254.53±1.77^{a}	253.54±2.65^{a}	246.75±0.32^{b}

Data were expressed as Mean ± Standard Error. Mean values within the same row having different superscript letters are significant at ($p<0.05$). MDA: malondialdehyde; TAC: total antioxidative capacity; IL-6: Interleukin 6.

resented more than 85% of the admitted cases; except in 2017. The figures through Egypt varied where the number of treated cases ranged from 16.52 to 25.72%. Despite the low infestation rate compared to Ismailia, a 25% infestation rate will cause economic losses. Concerning the cost analysis, results in Table 3 showed that the TC of treatment of group 1 is more than that of group 2 (11.94 and 2.44 LE/head, respectively).

DISCUSSION

Sarcoptic mange is a highly contagious persistent disease and an important non-seasonal zoonotic pruritic skin disease of rabbits (Kumar, A. *et al*., 2018). From the parasitological examination, it was found that rabbits were infested with *S. scabiei* and the identification was confirmed by the molecular examination, which is an accurate and objective method of mite diagnosis because it revealed that there is higher variation between the present sequences sample and other *S. scabiei* sequences from Egypt and different geographic areas and low sequence variation between other species sequences, these variations may be attributed to the difference between the host species and the geographic area variations (Abo-Elhassan, 2020).

The skin of infested rabbits had thickened and raised crusts, dry scabs, and fur loss in some parts; similarly, different lesions

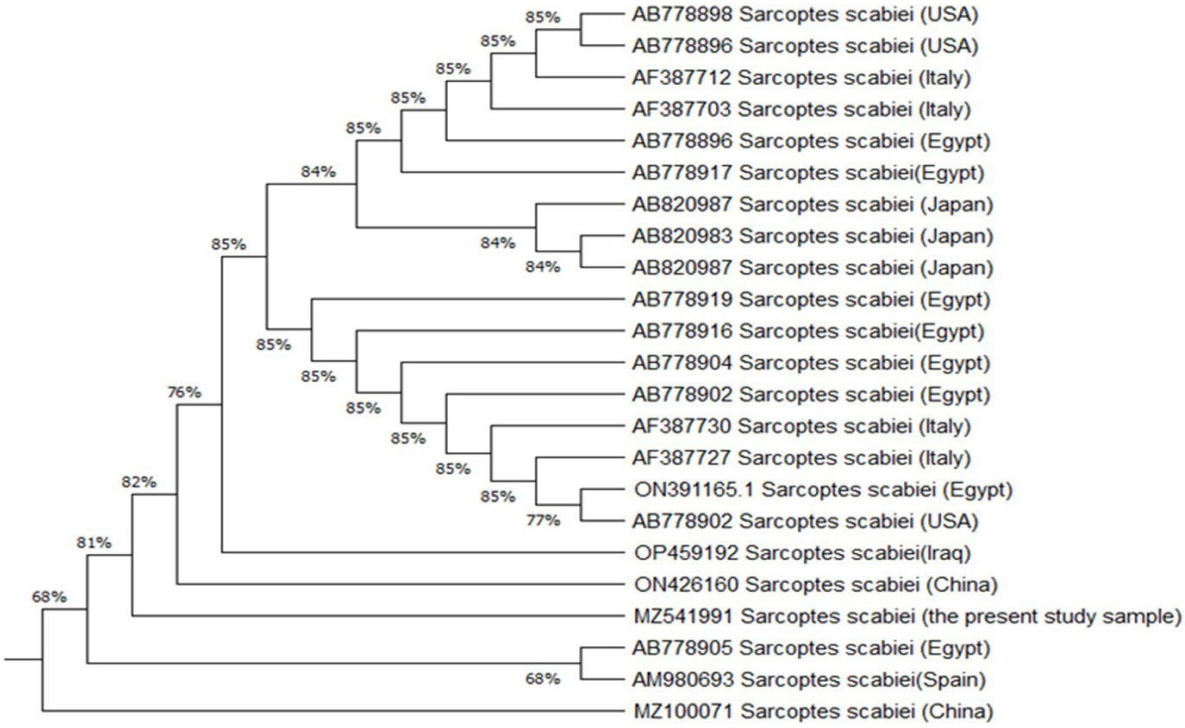

Fig. 4. Phylogenetic relationships of *Sarcoptes scabiei* sequences from the Genbank from Egypt and different geographic regions and our sequence sample are included based on ITS2 sequences.

		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
1	AB778919_Sarcoptes_scabiei_(Egypt)																						
2	AB778917_Sarcoptes_scabiei(Egypt)	0																					
3	AB778916_Sarcoptes_scabiei(Egypt)	0	0																				
4	AB778905_Sarcoptes_scabiei_(Egypt)	2.2	2.12	2.16																			
5	AB778904_Sarcoptes_scabiei_(Egypt)	0	0	0	2.2																		
6	AB778902_Sarcoptes_scabiei_(Egypt)	0	0	0	2.2	0																	
7	AB778896_Sarcoptes_scabiei_(Egypt)	0	0	0	2.1	0	0																
8	AF387730_Sarcoptes_scabiei_(Italy)	0	0	0	2.2	0	0	0															
9	AF387727_Sarcoptes_scabiei_(Italy)	0	0	0	2.2	0	0	0	0														
10	AF387703_Sarcoptes_scabiei_(Italy)	0	0	0	2.1	0	0	0	0	0													
11	AF387712_Sarcoptes_scabiei_(Italy)	0	0	0	2.1	0	0	0	0	0	0												
12	AB820987_Sarcoptes_scabiei_(Japan)	0	0	0.01	2.1	0.01	0.01	0	0	0	0	0											
13	AB820983_Sarcoptes_scabiei_(Japan)	0	0	0.01	2.1	0.01	0.01	0	0	0	0	0	0										
14	MZ100071_Sarcoptes_scabiei_(China)	3.7	3.72	3.66	3	3.66	3.66	3.72	3.7	3.7	3.72	3.7	3.8	3.77									
15	ON391165.1_Sarcoptes_scabiei_(Egypt)	0	0	0	2.3	0	0	0	0	0	0	0	0	0.01	3.6								
16	OP459192_Sarcoptes_scabiei(Iraq)	0	0.03	0.03	2.2	0.03	0.03	0.03	0	0	0.03	0	0	0.04	2.9	0.03							
17	ON426160_Sarcoptes_scabiei_(China)	0.1	0.09	0.08	2.5	0.08	0.08	0.09	0.1	0.1	0.09	0.1	0.1	0.09	4	0	0.2						
18	MZ541991_ (the_present_study_sample	2.2	2.17	2.21	2.9	2.21	2.21	2.17	2.2	2.2	2.17	2.2	2.2	2.2	3	1.99	2.19	2.2					
19	AB778902_Sarcoptes_scabiei_(USA)	0	0	0	2.2	0	0	0	0	0	0	0	0	0.01	3.7	0	0.03	0.1	2.2				
20	AB778898_Sarcoptes_scabiei_(USA)	0	0	0	2.1	0	0	0	0	0	0	0	0	0	3.7	0	0.03	0.1	2.2	0			
21	AB778896_Sarcoptes_scabiei_(USA)	0	0	0	2.1	0	0	0	0	0	0	0	0	0	3.7	0	0.03	0.1	2.2	0	0		
22	AB820987_Sarcoptes_scabiei_(Japan)	0	0	0.01	2.1	0.01	0.01	0	0	0	0	0	0	0	3.8	0.01	0.04	0.1	2.2	0.01	0	0	
23	AM980693_Sarcoptes_scabiei(Spain)	2.1	2.11	2.15	0	2.15	2.15	2.11	2.1	2.1	2.11	2.1	2.1	2.09	3.1	2.25	2.24	2.5	2.9	2.15	2.11	2.1	2.1

Fig. 5. Estimates of Evolutionary Divergence between the present study *Sarcoptes scabiei* sequence, and sequences of *Sarcoptes scabiei* from the Genbank (ITS2).

Table 2. Number and percentage of cases in Ismailia and Egypt.

Year	Ismailia			Egypt		
	Skin	Total	%[a]	Skin	Total	%[a]
2015	4587	5328	86.09	329609	1599414	20.61
2016	8062	8872	90.87	309233	1871621	16.52
2017	5613	11029	50.89	372045	1713576	21.71
2018	19015	21712	87.58	563810	2192195	25.72
2019	14152	14452	97.92	161747	723644	22.35

*Original data were obtained from (CAPMAS, 2015-2019), other problems were malnutrition, metabolic diseases, viral diseases, and internal parasites.
[a]Computed by the authors. CAPMAS (Central Agency for Public Mobilization and Statistics) (2015-2019): Annual bulletin of animal and poultry diseases statistics). Several issues.

Table 3. Cost breakdown, total cost, and percentage.

Medication	Group 1		Group 2	
	Treatment cost (LE)	%	Treatment cost (LE)	%
Ivermectin	0.5	4.19	1	40.98
Vitamin supplements	1.44	12.06	1.44	59.04
Disinfection	7	58.63	0	0
Topical treatment	3	25.12	0	0
Total cost	11.94	100	2.44	100

were recorded in the rabbits infested with sarcoptic (Kaplaywar *et al*., 2017). These lesions were distributed over the ears, nose, face, and toes of the legs, similar distribution was also detected by Arul Prakash *et al*. (2017) and Sharun *et al*. (2019), sarcoptic lesions occur frequently on the slightly haired parts of the body (Aiello and Mays, 1998). Among the different rabbit ages, there were heavy infestations in both males and females over 6 months of age while infestation in rabbits under 3 months of age was not recorded also, Sharun *et al*. (2019) mentioned that adult rabbits were more severely infested than growers, while suckling kids have no scabies infection. In this study, rabbits infested with mites had a significant increase in the MDA level, which is an oxidative stress marker linked to cell deterioration, the progress of skin lesions, and the clinical manifestation of mange (Kanbur *et al*., 2008). However, after 2 and 4 weeks, the MDA level in the treated groups gradually decreased when compared to the control group. This could be due to the curing of the infested rabbits following ivermectin treatment (Mohamed *et al*., 2017). Our study also found a significant decrease in TAC level in the infested group when compared to the control group. Overproduction of free radicals by inflammatory cells is recruited to combat the parasites, resulting in the exhaustion of the infested rabbits' antioxidant system (Shang *et al*., 2014).

When infested rabbits were compared to the control group, IL-6 levels were increased significantly. This may be due to the severe allergic inflammation caused by mange, which contributes to parasite pathology (Majewska *et al*., 2016). However, as inflammation was reduced, IL-6 levels gradually decreased in the infested group compared to the control.

For control of sarcoptic mange infestation in rabbits, the skin of rabbits in group 2 on the 14th day after subcutaneously treatment with 1% ivermectin revealed marked clinical improvement in the affected part, subcutaneous administration of ivermectin is very effective against rabbit scabies mite infection (Panigrahi *et al*., 2016). Ivermectin in the mite's nervous system binds to gamma- aminobutyric acid gated and chloride channels glutamate-gated, followed by cellular hyperpolarization leading to paralysis and death of the mite (Hillyer and Quesenberry, 1997; Aulakh *et al*., 2003). However, the improvement was better in group 1 treated once subcutaneously with 1% ivermectin with topical application of sulfur ointment 10% after dipping of affected part in 1% deltamethrin compared to group 2. Sulphur ointment 10% is low-priced, rapid, and highly effective chemical preparation used well for control of rabbit's mange in Egypt (Abdelaziz *et al*., 2020). Along with deltamethrin provided a high level of mange control as permethrin had the ability to kill mites and its eggs (Pourhasan *et al*., 2013). On day 28th of treatment in this study hair growth and complete skin recovery were detected in both treated groups since ivermectin regime for control sarcoptic mange requires multiple dosing as mite eggs are resistant to acaricidal products so two doses of ivermectin separated by two weeks interval provide adequate levels of the drug in the circulation and presence of active principle at hatching time (Arends *et al*., 1999; Gokbulut *et al*., 2010). Supplementing vitamins with acaricides can enhance the clinical and parasitological recovery of rabbits infected with sarcoptic (Kumar, S. *et al*., 2018), In addition to treatment cleaning, disinfecting the rabbit cage and surrounding environment, help in effective controls of the problem (Darzi *et al*., 2007).

Concerning the skin infestation problem in Ismailia, cases generally represented more than 85% of the treated cases; except in 2017. The figures through Egypt varied, where the number of treated cases ranged from 16.52 to 25.72%. Despite the low infestation rate compared to Ismailia, a 25% infestation rate will cause economic losses. It can be concluded that bad hygienic practices are common and prevailing for many rabbit breeders (Elshahawy *et al*., 2016). Despite the fact that a single dose treatment is cheaper, the total cost of treatment per head for group 1 was more than that of group 2, this might be because of the treatment scheme provided for this group. It was also noticed that supplementation and disinfection constituted more than 60% of the total treatment costs which indicates the importance of prophylaxis in mite control.

CONCLUSION

Molecular technique is considered a sensitive and rapid diagnosis method, more genetic studies involving larger samples are needed. In the current study the single dose of ivermectin with topical application of sulfur ointment 10% after immersing the affected area in 1% deltamethrin reduce the stress associated with multiple injections of ivermectin but it is more costly. It is highly recommended for the veterinary authorities in Ismailia to develop extension campaigns for rabbit breeders about good hygienic practices for rabbit production, as proper management strategy will be reflected on sustainable production and consequently cheaper protein for the domestic population. Further studies are encouraged for the cost effect of mange on body weight, delayed mating and overall farm profitability.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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