

Eco-Epidemiology of Cutaneous Leishmaniasis in Golestan Province, Northeastern Iran: A Systematic Review

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Abstract

Background and objective: zoonotic cutaneous leishmaniasis (ZCL) is one of the most important health problems in Golestan Province, northeastern Iran. Several studies have investigated various aspects of the disease in this province. Herein, we provide a detailed review of the results of all studies related to leishmaniasis to give a reliable insight into the state of the disease in this province.

Methods: The search for articles was performed in PubMed, Scopus, and Web of Science without language restriction until the beginning of 2019. Articles in Persian were retrieved from the Magiran, Scientific Information Database, and IranMedex. Overall, 41 articles were subjected to content analysis under the different themes.

Results: Counties of Gonbad-e-Kavus and Maraveh Tappeh are endemic areas of ZCL with an incidence rate 99.4-379.1 in 100000 population and has mesoendemic situation in these counties. *Leishmania major* is the dominant (99.1%) agent of leishmaniasis. Among 18 sandflies species detected in the province, *Phlebotomus papatasi* was the main vector of the disease with a mean infection rate of 9.2%. Peak of sandflies activity was recorded in the mid-July and mid-September. *Rhombomys opimus* and *Meriones libycus* were the main reservoirs of this disease with a mean infection rate of 25.3 and 31.8%. The density of sandflies and wild rodents were highest in the endemic areas for ZCL.

Conclusion: In Golestan Province, ZCL has been in a hypoendemic situation and in some areas in a mesoendemic situation and has increased significantly in recent years, so it is recommended to investigate the reasons for this increase.

Keywords: cutaneous leishmaniasis, sand fly, wild rodents, Golestan

Introduction

Cutaneous leishmaniasis (CL) is an important vector-borne disease that is transmitted to humans and animals by the bite of infected female sandflies, this disease causes skin lesions, mainly ulcers, on exposed parts of the body such as face, legs and hands and treated with current anti-leishmanial drugs such as sodium stibogluconate (Pentostam), meglumine antimoniate (Glucantime), miltefosine, pentamidine isethionate, amphotericin B, and heat therapy or cryotherapy (1, 2). The disease usually occurs in two main forms: zoonotic cutaneous leishmaniasis (ZCL) and anthroponotic cutaneous leishmaniasis (ACL). More than one million new cases of CL are reported annually in worldwide but the real figures are 6 to 10-folds. About 90% of all cases of CL occur in Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia, and Syria (3-6). ZCL and ACL are the most common forms of cutaneous leishmaniasis in Iran. Each year, more than 22,000 new cases of cutaneous leishmaniasis are reported in Iran, that 80% of which are ZCL (7). ZCL is endemic in rural areas of 17 out of 31 provinces of Iran (8). In these areas, *Leishmania major* is the causative agent, while *Phlebotomus papatasi* and wild rodents such as *Rhombomys opimus* and *Meriones libycus* are known as the vector and reservoir hosts, respectively (8).

Golestan Province is one of the most important hotspots of leishmaniasis in Iran. ZCL is endemic in this province, especially in its northeastern areas. Therefore, many studies have been conducted on various aspects of the disease in this province. Collecting the results of these studies could help clarify the features of this disease and contribute to decision-making for prevention, diagnosis, control, and treatment of

leishmaniasis in this area. Therefore, we aimed to provide a detailed review of the results of all studies related to leishmaniasis to give a reliable insight into the state of the disease in this province.

Materials and Methods

Study area

The Golestan Province (53°57'- 56°23' E, 36°30'- 38°08' N) is located in the northeast of Iran, bordering the Caspian Sea and Turkmenistan. The province has a dry and semi-arid climate in the north and northeastern parts, a temperate climate in the central parts and a mountainous and cold climate in the southern parts. The province has an area of 20437.74 Km² and comprises 14 counties.

Search strategy

This review includes results of all published studies until the beginning of 2019 that have been conducted on Cutaneous Leishmaniasis in the Golestan Province.

First, the following search terms were used for finding relevant articles in the Golestan Province: Golestan, Gonbad-e Kavus, Maraveh Tappeh, Turkmen Sahra, Leishmaniasis, Leishmania and sand fly. Since some of the words may have different spelling, the following search syntax was used: (*Leishmania* OR Sand*fl*) AND (Golestan OR Turkemen* OR Gonbad* or Maraveh*).

The search was performed in PubMed, Scopus, and Web of Science without any language restriction until the beginning of 2019. Articles in Persian were retrieved from the Magiran, Scientific Information Database, and IranMedex. In addition, the "Iranian Journal of Parasitology" was investigated as a

key journal. Reference lists of the retrieved articles were also hand-searched. Finally, we contacted local experts and active researchers in the field of leishmaniasis to avoid missing any relevant articles.

Selection of articles

Articles on *Leishmania* type, prevalence (in humans), vectors, and reservoirs in the Golestan Province were included in the study. Studies that have been conducted in the whole country or in several provinces were included only if they had reported data related to the Golestan Province separately and clearly. After removing excluding duplicate articles by EndNote software and those that did not

meet the inclusion criteria, 41 articles were subjected to content analysis under the following themes: 1. Epidemiology of leishmaniasis (distribution, incidence in counties of the province, prevalence of acute ulcer and scar in different age groups, and status of endemicity); 2. Ecology of vectors (fauna, monthly activity and its correlation with climate and geographical conditions); 3. Ecology of reservoirs (fauna, distribution and effect of climate and geographical conditions on distribution of rodents); 4. Relationship between the distribution of disease and distribution of sand flies and wild rodents; 5. Treatment of the disease (Fig. 1).

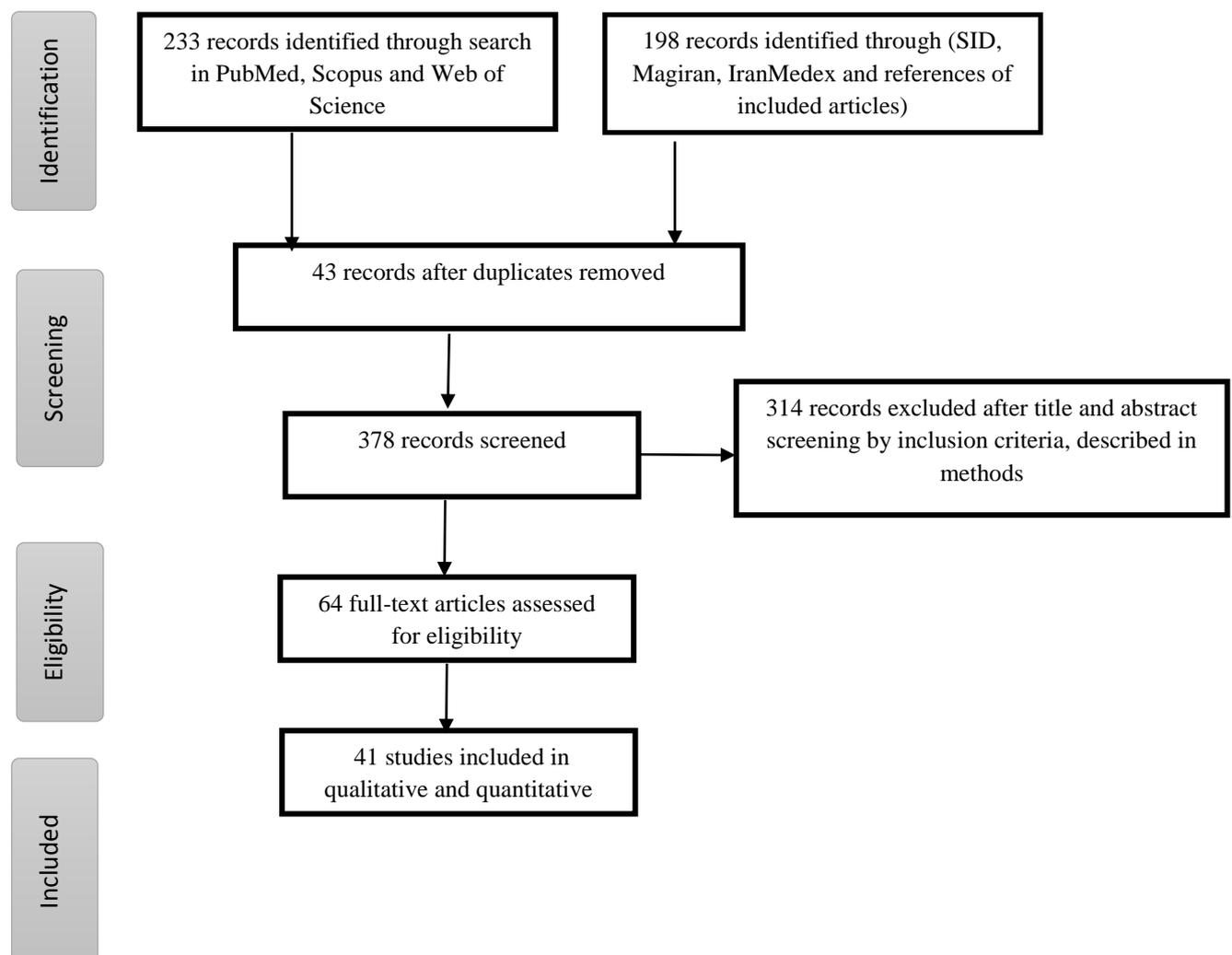


Fig 1. Flowchart describing the study design process

Data extraction

Two researcher (A.S. and H.R.SH) extracted the Ecological characteristics of sand flies, Number of positive case. Author name and reviewed year. They evaluated the selected articles independently by reading titles, abstracts, and if necessary full texts. Any disagreements between the 2 researchers were solved by consultation of another reviewer.

Plotting maps: Using results of the published articles about Golestan Province, as well as unpublished information available in Golestan Province health center, the maps of cutaneous leishmaniasis distribution and incidence, distribution of sand flies and villages where have undergone rodenticide operations to reduce cutaneous leishmaniasis cases, have been drawn.

Results

The selected studies

After a comprehensive search, 233 records identified through search in PubMed, Scopus and Web of Science and 198 records identified through SID, Magiran, IranMedex and references of included articles, 43 duplicates were removed. The relevance of the remaining 378 studies was evaluated based on the titles/abstracts alone; of them, 64 studies were subjected to full-text review, which eliminated another 23 studies according to the inclusion and exclusion criteria. Finally, 41 studies were included in the present systematic review (Fig. 1).

Epidemiology of leishmaniasis

Leishmania species circulating in the Golestan Province

L. major was the predominant (99.1%) species circulating in the province, and is endemic to this region; *L. tropica* was the least prevalent (0.7%) species. Patients infected with *L. tropica* had a history of traveling to ACL endemic areas (9-18). One study also found *L. turanica* in 0.2% of patients (16).

Incidence, prevalence, and distribution of leishmaniasis

In the province, the most common form of leishmaniasis is ZCL with an annual incidence 31.7 per 100000 population. The disease is not uniformly distributed throughout the province; most cases were reported from counties of Gonbad-e Kavus and Maraveh Tappeh. The incidence rate in these endemic areas was 99.4 to 379.1 per 100,000 people between 2010 and 2016. The most important hotspots with the highest incidence rates were the districted of Karand and Atrak from the Gonbad-e Kavus County and the central districts from the Maraveh Tappeh County. In other counties, the incidence of leishmaniasis was between 3.8 and 28.7 per 100,000 people in 2016, and most of the affected individuals in these counties had a history of traveling to endemic areas in the province or neighboring provinces. According to studies, about 68.4% of the affected population had cutaneous leishmaniasis scars. However, cutaneous leishmaniasis scars were present in all affected individuals in some villages (Tab. 1 and Fig. 2,3) (9-16, 19-20)

Tab 1: incidence of cutaneous leishmaniasis in different counties of Golestan Province, 2006-2016.

Author(s)	Published year	Reviewed year	Counties	Num. Positive cases	Incidence (1/100000)	Mean of Incidence (1/100000)
Cherabin et al.	2012	2006	Maraveh Tapeh	1	1.8	117
		2007		17	32	
		2008		14	26	
		2009		104	196	
		2010		161	303	
Sofizadeh et al.	2015	2012		75	138.4	
Sofizadeh et al.	2016	2013		69	121/5	
Sofizadeh et al.	2013	2007	Gonbad-e Kavus	-	37.3	153
		2008		-	48.9	
		2009		-	199.9	
		2010		-	379.11	
Sofizadeh et al.	2016	2013		334	99/4	
Sofizadeh et al.	2016	2013	Aghghala	37	28/7	28/7
			Ramiyan	24	27/3	27/3
			Gamishan	9	14	14
			Aliabad-e katool	18	12/8	12/8
			Azadshahr	10	10/1	10/1
			Gorgan	39	8/7	8/7
			Kalaleh	10	8/5	8/5
			Kordkooy	5	6/9	6/9
			Bandar-e Gaz	2	3/8	3/8
Sofizadeh et al.	2016	2013	Golestan Province	573	31/7	31/7

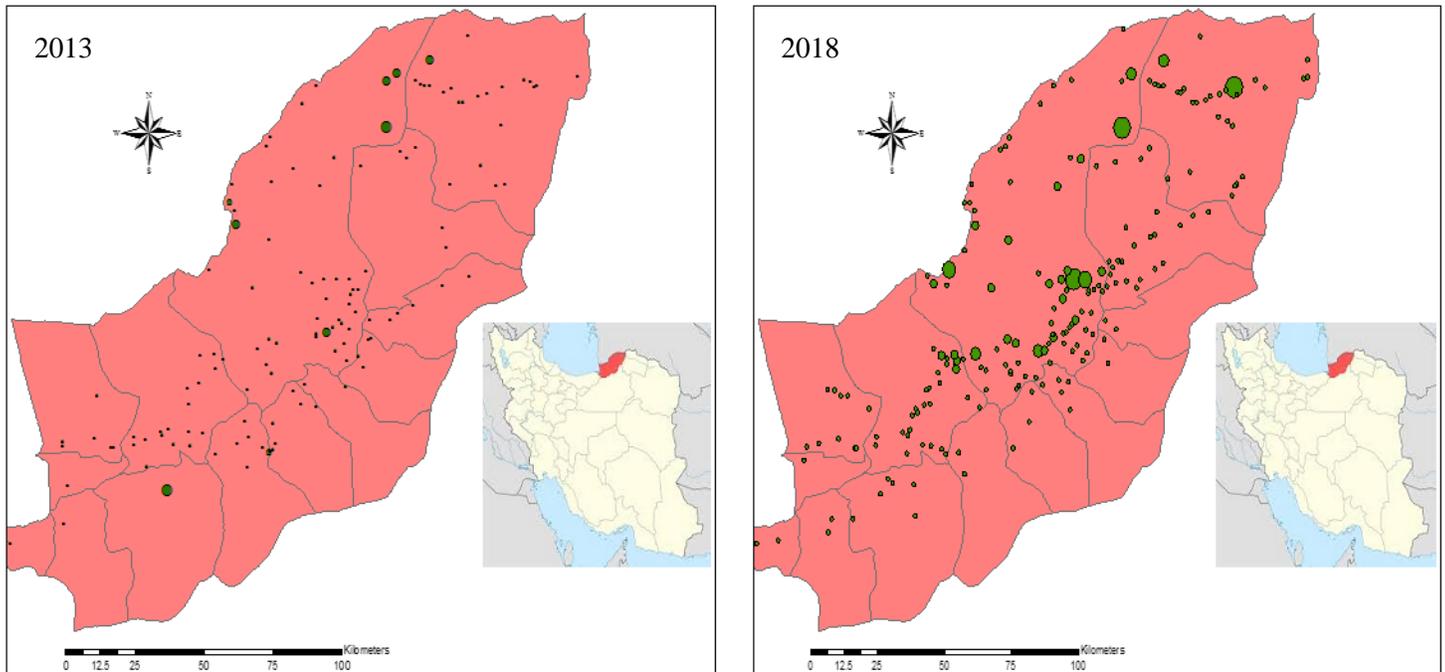


Fig 2: Number of cutaneous leishmaniasis cases in different villages of Golestan Province during 2013-2018. Each green circle represents a village, and the larger circles show the greater number of cutaneous leishmaniasis cases.

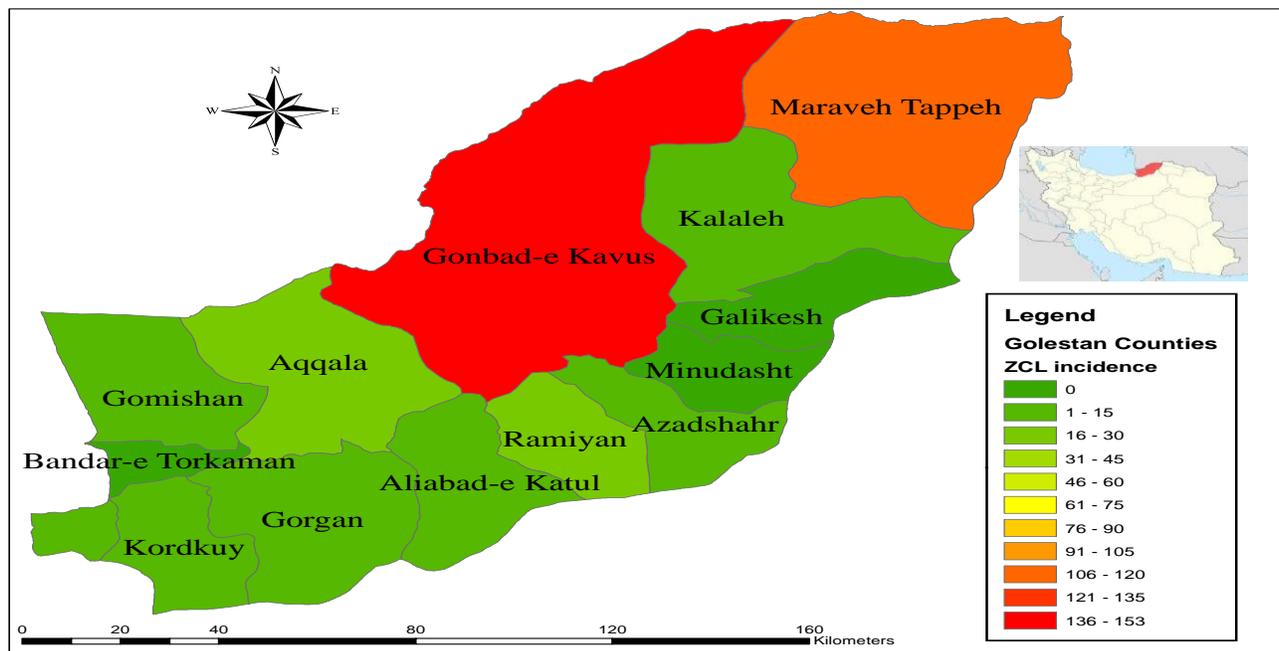


Fig. 3: mean incidence of cutaneous leishmaniasis reported in different counties of Golestan Province, 2006-2019

Temporal incidence of the disease

Various studies in the province have shown that the incidence of leishmaniasis is more likely during November and December. This could indicate that the affected individuals might have been bitten during summer (the peak of sand flies activity) and later show clinical symptoms of illness after the incubation period (9, 21, 22).

Endemicity of ZCL in Golestan Province

In five studies conducted in the province, approximately 55.5% of the examined population with acute ulcers was above 14 years of age. Thus, it can be inferred that the disease is hypo endemic in the province, but in some villages, majority of the affected individuals were under the age of 5 years, whilst the percentage of people under 14 years of age with acute ulcer had increased. Therefore, it can be stated that the disease is mesoendemic in some areas of the province (9, 19, 21-23).

Ecology of vectors

Fauna and monthly activity of sand flies

Of 18 sand fly species identified in the province, 10 species were from *Phlebotomus* genus and eight were from *Sergentomyia* (Tab. 2) (20, 24-28).

The monthly activity of sand flies differed between arid/semi-arid areas and the southern foothill areas of the province. In the northern areas, especially in counties of Gonbad-e Kavus and Maraveh Tappeh, sand flies activity began in April and lasted until October. In these areas, the peak activity was recorded in mid-July and mid-September (20-21, 26-27). In the southern areas, sand fly activity is shorter and lasts from June to October, and reaches its peak during September (Fig. 4 and Tab. 3) (20, 28). Sand flies are inactive during the day and become active from sunset until sunrise, but the peak activity is at 19-20 pm (26).

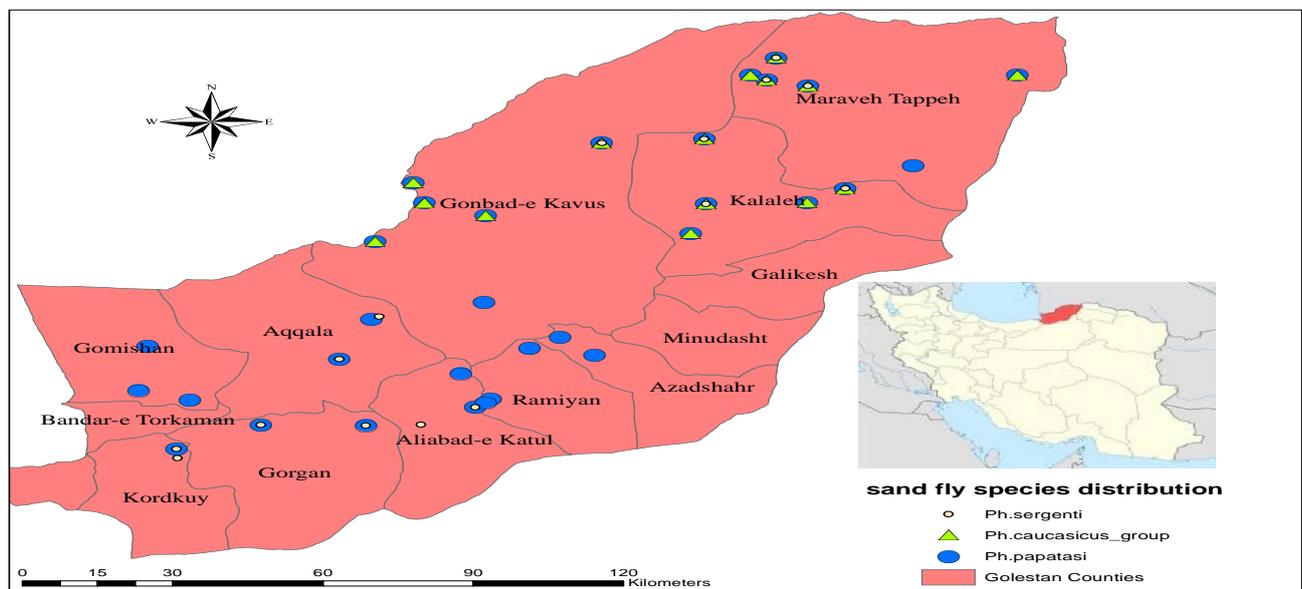


Fig 4. Distribution of important species of sand flies in different counties of Golestan Province

Density of sand flies

Sand flies are more abundant in the northeastern areas of the province, which has an arid/semi-arid climate; however, they are less abundant in the western and southern areas of the province (20). The distribution of sand flies is directly correlated with endemic areas of cutaneous leishmaniasis, so that in north and northeast of the province that leishmaniasis is more prevalent, the frequency of sand flies also is more than other areas (20, 29). The sand flies were commonly found in rodent's burrows and birds' nests, outdoor places, and livestock barns and rarely found in human settlements (24).

Ph. papatasi and *Sergentomyia sintoni* are the predominant species in the Golestan Province (20, 24-29). *Ph. papatasi* is the main vector of cutaneous leishmaniasis in the province, the rate of *L. major* infection in this species was ranging between 0.3 and 13.5% (average 9.2%). In addition, *Ph. papatasi* infection with *L. turanica* and *Leishmania closed gerbili* was reported in some studies (16, 25, 30-32).

Phlebotomus caucasicus and *phlebotomus mongolensis* as well as the female form of these species (known as the *Ph. caucasicus* group) have been reported in most studies in the Golestan Province. They are more abundant in the northeastern and eastern areas of the province (20). Infection of these species with *L. major*, *L. turanica* and *L. closed gerbili* has been reported, and the highest infection rates were related to *L.*

major (18.4%) and *L. closed gerbili* (25%), which is of great importance (17, 31, 32). In Iran, these species are known as the zoonotic cycle vectors of *L. major* among rodents and the secondary vectors to humans. Therefore, the role of these species in the spread of cutaneous leishmaniasis and stability of parasites in this region is irrefutable (7-8, 33).

Although *Phlebotomus sergenti* is regarded as a vector for ACL in Iran (8), there has been no report of *Ph. sergenti* infection with *L. tropica* in the Golestan Province. This sand fly is a mountainous species and has a high prevalence in the province. It is found in arid and semi-arid parts of the province, such as Gonbad-e Kavus and Maraveh Tappeh, as well as in temperate foothill areas, such as Aliabad-e-Katul. Nevertheless, it is more abundant in the eastern and northeastern areas of the province, especially in the foothills of the aforementioned cities and less abundant in low-altitude areas (20- 21, 26-28).

Phlebotomus alexandri and *Phlebotomus adlerius* (sp) have also been reported in the province. These species are known as probable and primary vectors of *Leishmania infantum* in different parts of the world (34, 35). These two species had a limited distribution in the Golestan Province but were more prevalent in the foothill areas of Maraveh Tappeh, which is endemic for visceral leishmaniasis (20). In the city of Gonbad-e Kavus, *L. (Sauroleishmani) gymnodactyli* has been detected in *S. sintoni*, a known vector of lizard *Sauroleishmania* (36).

Tab 2: distribution of different species of sandflies in Golestan Province.

Author(s)	Year of publication	Counties	<i>Ph. papatasi</i>	<i>Ph. caucasicus</i>	<i>Ph. caucasicus group</i>	<i>Ph. mongolensis</i>	<i>Ph. andrejivi</i>	<i>Ph. alexandri</i>	<i>Ph. sergenti</i>	<i>Ph. adlerus (sp)</i>	<i>Ph. brevis</i>	<i>Ph. kazerini</i>	<i>Ph. wenyoni</i>	<i>S. sintoni</i>	<i>S. sogdiana</i>	<i>S. dentata</i>	<i>S. hodgsoni</i>	<i>S. grekovi</i>	<i>S. chydai</i>	<i>S. antenata</i>	<i>S. tiberiadis</i>
Parvizi et al.	1998	Gonbad-e Kavus	*	-	-	*	-	-	-	-	-	-	-	*	-	-	-	-	-	-	-
Rassi et al.	2008	Maraveh Tapeh	*	*	*	*	*	-	*	*	*	*	-	*	*	-	-	-	*	-	-
Sofizadeh et al.	2009	Maraveh Tapeh	*	*	*	*	*	-	*	*	*	*	-	*	*	-	-	-	*	-	-
Sofizadeh et al.	2014	Aliabad-e Katul	*	-	-	-	-	-	*	*	*	-	-	*	-	*	-	-	-	-	-
Sofizadeh et al.	2015	Maraveh Tapeh	*	*	*	*	-	-	-	-	-	-	-	*	-	-	-	-	*	-	-
Agh-Atabay et al.	2016	Gonbad-e Kavus	*	*	*	*	-	-	*	-	*	*	-	*	-	-	*	*	*	*	-
Sofizadeh et al.	2018	Gonbad-e Kavus	*	*	*	*	-	-	*	-	*	*	-	*	-	-	*	*	*	*	*
		Kalaleh	*	*	*	*	*	-	*	-	*	*	-	*	-	-	*	*	*	*	*
		Maraveh Tapeh	*	*	*	*	*	*	*	*	*	*	-	*	*	-	-	-	*	-	-
		Aq Qala	*	-	-	-	-	-	*	*	-	-	-	*	-	-	-	-	*	-	-
		Gomishan	*	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-	-	-
		Kordkuy	*	-	-	-	-	-	*	-	-	-	-	*	-	-	*	-	-	-	-
		Bandar-e Gaz	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Gorgan	*	-	-	-	-	-	*	-	*	-	-	*	-	-	-	-	-	-	-
		Aliabad-e Katul	*	-	-	-	-	-	*	*	*	-	-	*	-	*	*	-	-	-	-
		Ramian	*	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-	-	-
		Azad Shahr	*	-	-	-	-	-	-	-	-	-	-	*	-	-	-	-	-	-	-

Tab 3: Ecological characteristics of sandflies in Golestan Province

Author(s)	year	region	Dominant species		Monthly activity	Peak of activity	highlights
			indoor	outdoor			
Parvizi et al.	1999	Gonbad-e Kavus	-	-	May - October	August	-
Sofizadeh et al.	2009	Maraveh Tapeh	<i>Ph. papatasi</i>	<i>S. sintoni</i>	early May - mid October	Mid June and September	-
Sofizadeh et al.	2014	Aliabad-e Katul	<i>Ph. papatasi</i>	<i>S. sintoni</i>	mid May - early October	early August	-
Sofizadeh et al.	2015	Maraveh Tapeh	<i>Ph. papatasi</i>	<i>S. sintoni</i>	-	-	-
Agh-Atabay et al.	2016	Gonbad-e Kavus	<i>S. sintoni</i> <i>Ph. papatasi</i>	<i>S. sintoni</i> <i>Ph. papatasi</i>	early May to mid-October	early July and mid-September	The peak of hourly activity of sandflies occurred at night (1900–2000 hrs.). Population dynamics of <i>P. papatasi</i> was completely in agreement with calculate accumulated degree days required for the various stages of their growth
Sofizadeh et al.	2018	Golestan	-	-	May-November	-	The frequency of sand flies in the villages located in northeast of the Golestan Province (the plateau area, Lower altitude, arid and semi-arid climates, and lower vegetation cover density) were more than other villages in this province. There was a significant correlation between the number of collected <i>Ph. papatasi</i> and incidence of the ZCL ($r=0.837$, $P=0.019$).

Ecology of reservoirs

According to studies, *L. major* is frequently found in *R. opimus* (25.3%) and *M. libycus* (31.8%) and less commonly found in *Meriones persicus* and *Hemiechinus auritus* (17, 25, 37-39). Regarding to the distribution of rodents in Golestan Province, it is necessary to pay attention to a few points:

First, the predominant species is *R. opimus* (25, 26, 37-38, 40) and reported as the main reservoir of the disease, but infection rate of *M. libycus* is higher than *R. opimus*.

Second: Although these rodents exist in most counties of the province, unfortunately, all studies on cutaneous leishmaniasis reservoirs have been concentrated in the counties of Gonbad-e-Kavos and Maraveh Tappeh, but in other parts of the counties, especially in the Kalaleh, Aq Qala and Gomishan Counties, which each year significant reports of leishmaniasis, a study has not been done.

Third: *L. turanica* has been isolated only from *R. opimus* (17, 40-41) and *L. closed to gerbili* has not been found in reservoirs of the province.

Relationship between the spread of disease and distribution of sand flies and wild rodents

Recent studies in the province using geographical information systems (GIS) have shown that hotspot areas of cutaneous leishmaniasis and distribution of *R. opimus* completely overlaps with each other particularly in the north and northeastern parts of the province, where in this areas, the presence probability of *Ph. papatasi* is more high (42-43). Findings also suggest that the incidence of cutaneous leishmaniasis may be significantly correlated with the number of

rodents' active burrows and frequency of *Ph. papatasi* (19-20, 29, 43).

In the Golestan Province, the incidence of ZCL seems to be correlated with high temperature, high evaporation rate, low relative humidity, low rainfall rate, low altitude, low normalized difference vegetation index, and low socioeconomic status. Meanwhile, the Max temperature of warmest month (°C), mean temperature of warmest and driest quarter (°C), altitude from the sea level (m) have highest percent contribution distribution of *L. major* in the Golestan Province (20, 42, 44-47).

Altitude from the sea level, slope, normalized difference vegetation index, mean annual temperature, mean temperature of wettest quarter, and geographic distribution of *R. opimus* are the most important factors affecting the distribution of *Ph. papatasi* species in the province (43, 45-47). Also the most important factors affecting with distribution of *R. opimus* are including: Mean temperature of driest quarter (°C), Mean temperature of warmest quarter (°C), Max temperature of warmest month (°C), Altitude from the sea level (m), Normalized difference vegetation index (NDVI) and type of soil.

Treatment

The efficacy of oral miltefosine for the treatment of cutaneous leishmaniasis caused by *L. major* was identical to that of meglumine antimoniate (Glucantime) (49). The first case of acute urticaria in an infant following systemic glucantime injection to mother was reported from the city of Gonbad-e Kavus (50).

Control of ZCL

Unfortunately, not much research has been conducted on the prevention and control of cutaneous leishmaniasis in this province

In this regard, only one study has been published which reported that proper and extensive control of rodents could

significantly reduce the incidence of cutaneous leishmaniasis (Fig. 5) (51).

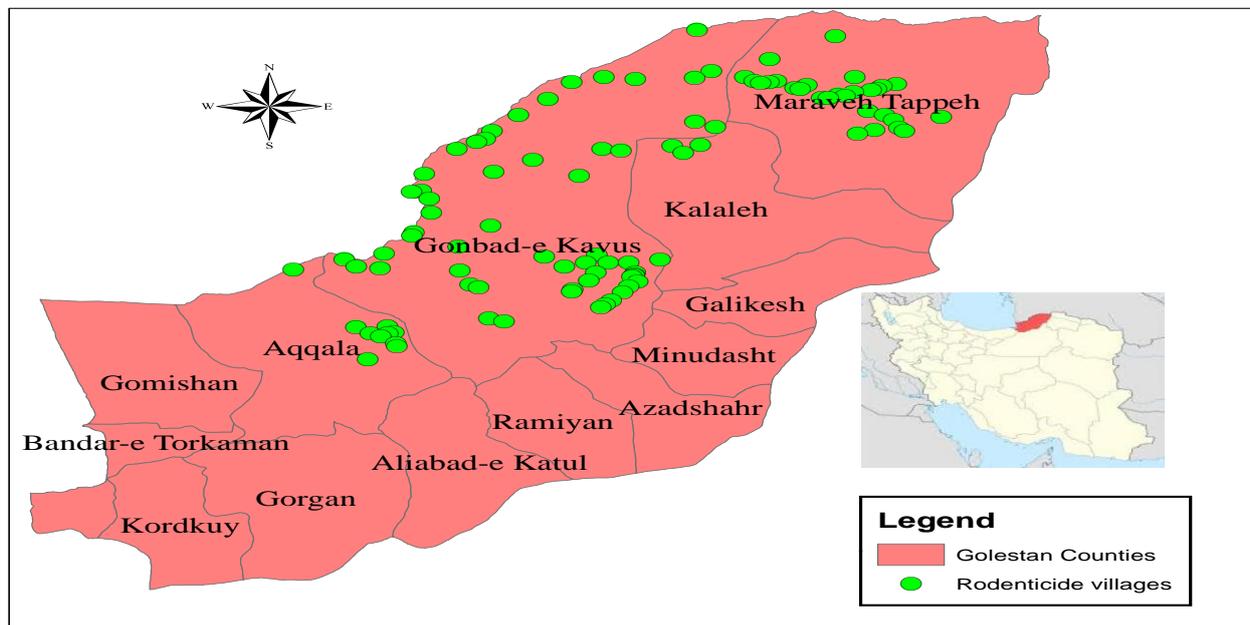


Fig. 5: Villages that have undergone at least one rodenticide operation to decrease the incidence of disease in the past 10 years due to the presence of wild rodents in the village.

Discussion

The results of various studies in Golestan Province show that the highest number of new cases of cutaneous leishmaniasis and incidence of disease have been reported in Gonbad-e-kavus and Maraveh Tappeh in northeast of Golestan Province and villages in northeast of Gonbad-e-kavus and east of Maraveh Tappeh have been recognized as endemic foci of disease. Therefore, in recent years, control of wild rodents (as cutaneous leishmaniasis reservoir host) has been carried out in these villages to control of cutaneous leishmaniasis (51). Comparison of reported cases of disease over 2013-2018 shows that in 2018 the number of infected cases has increased significantly, and disease were distributed to the central areas of Gonbad-e-Kavus, Kalaleh and Aq Qala Counties, where have been identified as disease non-endemic areas in recent years. These endemic foci are

the habitat of wild rodents due to favorable geographical conditions and soil type, and spreading the disease to non-endemic areas can due to the spread of rodents in these areas or because of infection in endemic areas while traveling endemic areas of the disease. Like other endemic areas of zoonotic cutaneous leishmaniasis, rodents have been also known as the disease reservoir in this province, and *R. opimus* and *M. libycus* are known as the primary and the secondary reservoir, respectively. The similar results are reported in central and northeastern foci of Iran (40, 52-59).

In terms of the distribution of sand flies in Golestan Province, like other parts of the country, *Ph. papatasi* and *S. sintoni* are dominant species of sandflies in this province and, *Ph. papatasi* has been known as a proven vector of cutaneous leishmaniasis in the province like other endemic areas of zoonotic

cutaneous leishmaniasis (56-59). Regarding the monthly activity of sand flies, there are two states in this province:

1. In the semi-arid regions of the north and northeast of the province, the sand flies have two peaks of activity in July and at the end of August or early September that these results are similar to the results of studies carried out in most parts of the country and Libya (7,60,61,62,63), also in some areas of Iran, sand flies have two peaks of activity in May and October (64) and in Yazd Province, they have two peaks of activity in the end of April and mid-September (65).

2. the colder and south regions of the Golestan Province, sand flies have one peak of activity in August that is similar to the seasonal activity of the sand flies in the northwest areas of the country (66). Like most studies conducted in Iran, the abundance of sand flies in Golestan Province in places such as rodents' active burrows and outdoor areas was higher than indoor, which could be due to the favorable temperature and humidity for living the sand flies inside the rodents' active burrows. In addition, with starting night and decreasing temperature, they will start their activity but their peak activity is during 19-20 hours, as similar to other studies in Iran and other countries (67-69). The results of studies conducted in Golestan Province showed that there is a direct relationship between distribution of *Ph. papatasi* and *R. opimus* with the distribution of cutaneous leishmaniasis, so that in the north and northeast of Golestan Province where the incidence of the disease is more, distribution of sand flies and wild rodents was also more and their maps are completely matched and similar results have been reported in other studies in Iran (42), these areas are areas with geographic conditions of lowland, low altitude, and semi-arid climate

that are conducive to the distribution of sand flies and wild rodents and accordingly, to the distribution of cutaneous leishmaniasis.

Conclusion

Given the high rate of *L. major* infection in rodents and the considerable abundance of *Ph. papatasi* in the northeast areas, the Golestan Province can be considered an endemic area for zoonotic cutaneous leishmaniasis. Nevertheless, prevention and control of the disease are not sufficiently investigated in this province. Only one article has been published on the impact of rodent control on the incidence of leishmaniasis. Therefore, it is recommended to carry out more studies on the prevention and control of this disease in the Golestan Province, Iran. In addition, as the number of new cases of the disease has increased in recent years and the disease has spread to non-endemic areas, research on the causes of this increase is suggested.

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Ethics approvals and consent to participate

This study was approved by the ethical committee of Golestan University of Medical Sciences.

Conflict of interest

There are no conflicts to declare

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