Review Article

A Comprehensive Review of the Situation of Visceral Leishmaniasis Vectors in Iran

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Abstract

Background: This study's major aim is to investigate the situation of visceral leishmaniasis vectors, with a focus on their distribution and relationships to the disease in Iran and some other old-world nations.

Methods: The terms Iran and the Old World, along with the keywords sand flies, vectors, visceral leishmaniasis, distribution, and *Phlebotomus*, were searched in electronic databases from 1930 to 2018, including Pub-Med, Web of Science, Google Scholar, and MEDLINE.

Results: According to the findings, *Phlebotomus tobbi* was a mountain species, but it was also found in the plains, rodent nests, and rock crevices. This species was considered to be one of the vectors of visceral leishmaniasis in Iran. *Phlebotomus kandelakii* has been caught in Afghanistan, Iran, Lebanon, Turkey and Georgia. In Iran, the first infection of *Phlebotomus kandelakii* and *Ph. perfiliewi transcaucasicus* with *Leishmania infantum* were reported in northwest of Iran. *Phlebotomus major* was one of the complex sand flies, and its members include *Ph. major* (India, Nepal, and Pakistan), *Ph. neglectus* (Southern Europe, Crimea and Iran), *Ph. syriacus* (Southwest Asia, Caucasus), *Ph. notus* (Afghanistan and Iran), *Ph. wenyoni* (Iran and Iraq), and *Ph. wui* (China). The first natural infection of *Ph. alexandri* with *Leishmania infantum* was reported in 2006 in endemic foci of visceral leishmaniasis in Fars Province, southern Iran.

Conclusion: The findings of this project suggest that sand fly species of the subgenus *Larrousisus* play a key role in the transmission of all types of visceral leishmaniasis in Iran.

Keywords: Sand flies; Vectors; Visceral leishmaniasis; Old world; Iran

Introduction

Visceral leishmaniasis (VL), also known as kala-azar, is a protozoan disease that kills millions of people worldwide, ranking second only to malaria in terms of fatalities. (1). An estimated 50,000 to 90,000 new cases of VL are reported annually, with the majority of infections occurring in East Africa, South Asia, South America and the Mediterranean region. The countries of Brazil, Ethiopia, India, Kenya, Somalia, South Sudan and Sudan account for over 90% of all recorded cases of VL (2). The World Health Organization (WHO) designated VL as a neglected tropical disease (NTD) in 2015 as a result of the disease's high mortality rates (more than 20,000 in 2015) and extensive distribution in underdeveloped areas of the world (3, 4). Visceral leishmaniasis is one of the most prevalent human diseases, with over 20 species of *Leishmania* reported worldwide (5). The symptoms of VL often occur internally, unlike those of other prevalent types of leishmaniasis such cutaneous leishmaniasis (CL), mucocutaneous leishmaniasis (ML), and post-kala-azar dermal leishmaniasis (PKDL), which makes it more challenging to detect and treat than other leishmaniases (1). Visceral leishmaniasis can be classified as either anthroponotic (AVL) or zoonotic (ZVL)

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depending on the different vulnerable species involved. In East Africa and the Middle East, particularly Sudan, Somalia, Yemen and Saudi Arabia, *L. donovani* is the main cause of AVL, which is spread by vectors among people (3). Only early diagnosis and treatment or the use of long-term insecticide nets are necessary for AVL prevention because the majority of human VL vaccines are either under study or are only slightly effective (6). However, ZVL is transmitted between humans and other animals, for example dogs. With varying concentrations in East Africa, South America, the Mediterranean basin and South Asia, *L. donovani*, *L. infantum* and *L. archibaldi* will contribute to ZVL (6). Dog pulling, dog vaccinations and the use of pesticide collars are ZVL control measures that are more widely used than any AVL control strategies due to the fact that dogs are the most common mammal carriers of ZVL (7–10).

Between 1998 and 2012, there were 2632 cases of VL documented in Iran, with the northern and southern regions of the country having the majority of cases (11).

Visceral leishmaniasis has been sporadically recorded in Iran, in contrast to cutaneous leishmaniasis, which accounts for around 20,000 new cases annually (11). However, the disease is common in Iran's northwestern and southern regions (12–13), where 100–300 new cases of VL are reported yearly. Based on epidemiological, parasitological and molecular research performed in Iran's endemic VL regions over the past two decades, *Ph. kandelakii* (14, 15), *Ph. perfiliewi transcaucasicus* (16–19) and *Ph. tobbi* (20) in northwestern Iran, *Ph. major* s.l. (21, 22), *Ph. keshishiani* (23) and *Ph. alexandri* (24) in southern parts of Iran are known as probable or confirmed VL vectors. The primary objective of this study is to carry out a comprehensive assessment of visceral leishmaniasis vectors' distribution and relationships to the disease in Iran and some other Old World nations.

As there is no systematic and comprehensive review of the status of visceral leishmaniasis vectors in Iran and other countries of the old world (distribution and disease relationship), this research is thus the first step in this regard and is entirely new.

Materials and Methods

The following steps were used to access the data.

1. The literature search were conducted to identify all published studies reporting the parasites, proven and probable vectors of visceral leishmaniasis, its relation to disease and distribution of visceral leishmaniasis in old worlds as well as in Iran. The search was conducted in electronic databases of Pub-Med, Web of Science, Google Scholar and MEDLINE, and Science Direct from 1930 to 2018.

2. The specific search medical subject headings (MeSH) terms include “Visceral leishmaniasis in old world and Iran", "Distribution of visceral leishmaniasis in old world and Iran", "Probable and proven vectors of visceral leishmaniasis in old world and Iran", "Relation between vectors and disease", "Phlebotomine sand flies in old world and Iran " were used.

3. Initially all the titles of the article were inserted into a database for the information manager, including the End Note. They were assorted for additional screening until the duplicate cases had been removed. These titles to the article were checked in the first stage. Subsequently, all publications unrelated to the study's goals were excluded from the primary database.

4. Next, we scrutinized the titles and abstracts; and the articles that were selected and finalized for subsequent analysis based on individual provinces, endemic and non-endemic areas, as well as proven and probable vectors.

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Table 1. Proven or Probable vectors of visceral leishmaniasis by geographical zones in Iran (1992–2018)

Geographical zone	Province/District	*Phlebotomus* Sp.	*Leishmania*
North-west	Ardabil/Meshkin-shahr	*Ph.*(*Lar.*) *kandelakii*	*L. infantum*
North-west	Ardabil/Meshkin-shahr	*Ph.*(*Lar.*) *kandelakii*	*L. infantum*
North-east	North Khorassan/Shirvan	*Ph.*(*Lar.*) *kandelakii*	*L. infantum*
North-west	Ardabil/Germi	*Ph.*(*Lar.*) *perfiliewi transcaucasicus*	*L. infantum*
North-west	Ardabil/Germi	*Ph.*(*Lar.*) *perfiliewi transcaucasicus*	*L. infantum*
North-west	Ardabil/Bilesavar	*Ph.*(*Lar.*) *perfiliewi transcaucasicus*	*L. infantum*
North-west	Ardabil/Germi	*Ph.*(*Lar.*) *perfiliewi transcaucasicus*	*L. infantum/donovani*
North-west	East Azerbaijan/Kalibar	*Ph.*(*Lar.*) *perfiliewi transcaucasicus*	*L. infantum*
North-west	East Azerbaijan/Azar-Shahr	*Ph.*(*Lar.*) *tobbi*	*L. infantum*
North-west	Ardabil/Bilesavar	*Ph.*(*Lar.*) *tobbi*	*L. infantum*
North	Alborz/Savodjbolagh	*Ph.*(*Lar.*) *tobbi*	*L. infantum*
North-west	Ardabil/Bilesavar	*Ph.*(*Lar.*) *perfiliewi transcaucasicus*	*L. infantum*
South	Fars/Ghir-Karzin	*Ph.*(*Lar.*) *keshishiani*	*L. infantum*
South	Fars/Ghir-Karzin	*Ph.*(*Lar.*) *major*	*L. infantum*
South	Fars/Ghir-Karzin	*Ph.*(*Lar.*) *major*	*L. infantum*
South	Fars/Ghir-Karzin	*Ph.*(*para.*) *alexandri*	*L. infantum*

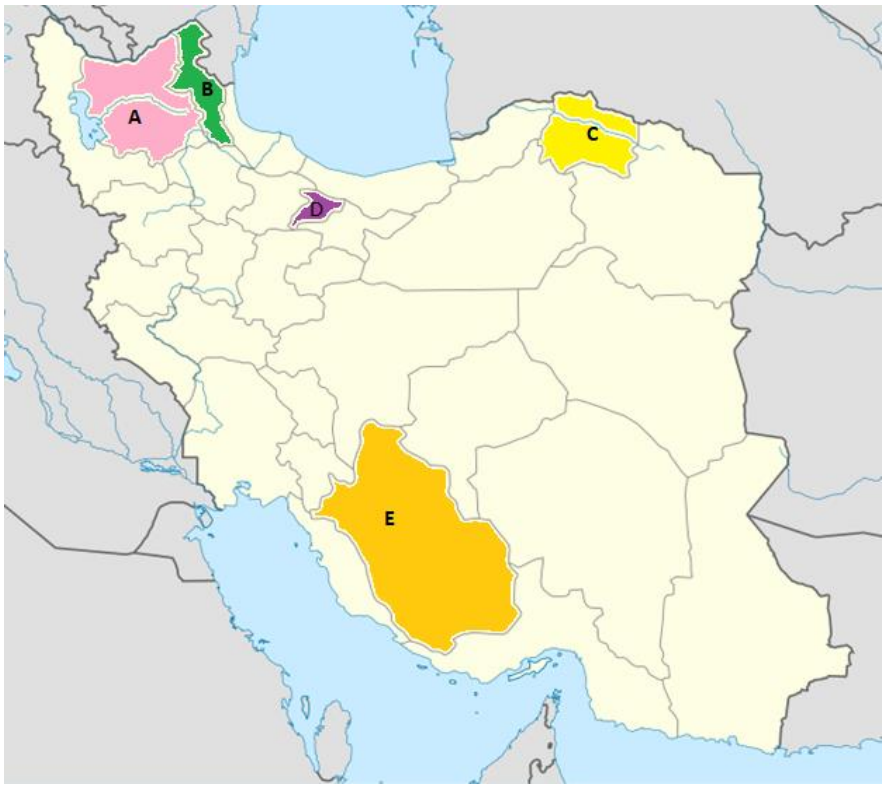

Fig. 1. Distribution of visceral leishmaniasis vectors in the main foci of the disease with natural infection with *Leishmania infantum* and *L. donovani* in Iran

A: East Azerbaijan Province. *Phlebotomus* (*Larroussius*) *perfiliewi transcaucasicus*, *Ph.* (*Lar.*) *tobbi*
B: Ardabil Province. *Ph.* (*Lar.*) *perfiliewi transcaucasicus*, *Ph.* (*Lar.*) *tobbi*, *Ph.* (*Lar.*) *kandelakii*
C: North Khorassan Province. *Ph.* (*Lar.*) *kandelakii*
D: Alborz Province. *Ph.* (*Lar.*) *tobbi*
E: Fars Province. *Ph.* (*Lar.*) *keshishiani*, *Ph.* (*Lar.*) *major*, *Ph.* (*par.*) *alexandri*

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Results

Phlebotomus (*Larroussius*) *tobbi* Adler and Theodor, 1930

Phlebotomus perniciosus var. *tobbi* Adler, Theodor and Lourie, 1930 and *Phlebotomus pirumovi* Burakova and Mirzayan, 1934 were two synonyms for this species (24). Its type localities are in Iran and Israel, and the Natural History Museum of London has 17 male and 10 female specimens of this species (25). North Africa, Europe, and countries in the Eastern Mediterranean have all received reports of this species and Albania, Greece, Israel, Iran, Iraq, Lebanon, Turkey, Yugoslavia, and Sicily Island were among the places where *Ph. tobbi* was collected (25).

The primary vector of visceral leishmaniasis in the western areas of Turkey has been identified as *Ph. tobbi*, which has been reported to be infected with the *L. infantum* parasite (25). The same study found that *Ph. tobbi* showed a strong tendency to consume both human and canine blood (26). This species is a vector of the cutaneous leishmaniasis in southern Anatolia, Turkey. The cycle of anthroponotic transmission has been identified due to the high proportion of infected human cases and the low number of infected dog cases (27).

Leishmania infantum and *L. donovani* parasites were previously found naturally infected with *Ph.tobbi* in Cyprus and Syria (28, 29). *Phlebotomus tobbi* is considered one of the most significant vectors in the transmission of cutaneous and visceral leishmaniasis in the Eastern Mediterranean Region and the Middle East due to its sensitivity to all types of *Leishmania* parasites, including *L. major*, *L. donovani* and *L. infantum*. (27, 29, 30). This species' capacity to transmit various *Leishmania* parasite species has previously been documented in Italy, Greece, Cyprus, Turkey and Syria (31).

Leishmania infantum parasite infection of the *Ph. tobbi* species was first detected in Iran in 2017, with an infective rate of 6.25%, in Bilesavar district in Ardabil Province (32). In 2009 and 2011, respectively, two cases of *L. infantum* infection in this species were recorded from rural areas of the districts of Azarshahr in East Azarbaijan Province and Savoojbolagh in Alborz Province as part of a research on the visceral leishmaniasis vectors of the country (20, 33). This species is thought to be one of the important vectors of visceral leishmaniasis in Iran, according to several reports of infection with *L. infantum* in different disease foci of Iran.

Phlebotomus (*Larroussius*) *kandelakii* Shurenkova, 1929

This species has been referred to as *Phlebotomus kandelakii kandelakii* Shchurenkova, 1929, and *Phlebotomus burneyi* Lewis, 1967 (25). Both plain and mountainous regions are ideal locations to get this species. It has been caught in environments up to 1400 meters above sea level (25). Afghanistan, Iran, Lebanon, Turkey, and Georgia are among the Central Asian nations where *Ph. kandelakii* has been recorded (25). *Phlebotomus kandelakii* infection with the *Leishmania* parasite was recorded in the Georgia city of Tbilisi in 2014, with a 5.7% infection rate (34). Although the type of parasite in this sand fly has not been identified, it is thought to be the primary vector of visceral leishmaniasis in this nation due to the relatively high prevalence of *L. infantum* among humans (14.5%), stray and domestic dogs (16% and 7.7%), as well as the fact that *Leishmania* infection was only seen in this dominant species in the region (34). The first case of *Ph. kandelakii* infection with *Leishmania* parasite was reported in 1992 with a rate of 0.3% without identifying the parasite in the north west of Iran (35). Rassi et al. (36) also reported the first case of *Ph. kandelaki* infection with *L. infantum*, with an infection rate of 1.1%, in the same region. The dominant species in the area was *Ph. kandelakii*, which had an average propensity to consume

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human and dog bloods of 32.8% and 21.2%, respectively (36). These results identified the *Ph. kandelaki* species from Ardabil Province as the primary vector of visceral leishmaniasis (Table 1, Fig. 1) in the rural areas of Meshkinshahr district due to its relatively high abundance (40%) in the area, excellent tendency to feed on blood from humans and dogs (the main reservoir of the disease agent), and the only species infected with *L. infantum* (36). In North Khorasan Province, which is in the northeast of Iran, the second occurrence of *Ph. kandelakii* infection with *L. infantum* was detected and infection rate was calculated 3.4 %. (37). *Phlebotomus kandelakii* species has the potential to be a vector in this region as well, given that it was the only species infected with the *L. infantum* in this area and that it was amounted up about 10% of the captured sand flies.

Phlebotomus perfiliewi transcaucasicus Perfiliev, 1937

Phlebotomus (*Larroussius*) *perfiliewi* taxonomic position was not quite clear. It has been classified into three species or subspecies, including *Ph. perfiliewi perfiliewi*, *Ph. perfiliewi galilaeus* and *Ph. perfiliewi transcaucasicus*. The Transcaucasian subspecies was semi-domestic, anthropophile, and had a positive tendency toward yellow light (photophile), which is caught from human places, rodent nests, and rock crevices. Its type location was in the Azerbaijani cities of Nakhchivan and Baku, and the male type is kept at the Zoological Institute of St. Petersburg (Leningrad) in Russia (38). Their actual distribution has been reviewed (24, 25), and as a result *Ph. perfiliewi* s.st had a widespread distribution in the area from North Africa to the Crimea, including the northern Mediterranean basin, while *Ph. perfiliewi galilaeus* has only been discovered in Israel/Palestine and Cyprus. *Ph. perfiliewi transcaucasicus* has also been reported in the Caucasus (39), Central Asia, and primarily in Iran. Turkey has recently been the source of reports for all three subspecies (40). *Phlebotomus perfiliewi* species have generally been reported from the following countries: Albania, Bosnia and Herzegovina, Croatia, Cyprus, Georgia, Greece, Hungary, Italy, Montenegro, Romania, Serbia, Southeast France, Republic of Macedonia, Turkey, Ukraine, Israel, Balkan Peninsula, Malta, North West Africa, former Soviet Union (Crimea), Algeria, Morocco, Tunisia, Sardinia Island, Turkey, Yugoslavia, Iran and Iraq (41). *Phlebotomus perfiliewi* s. s. has been reported as a suspected or proven vector of *L. infantum* in Algeria and Tunisia in North Africa (42, 43), as well as in Greece (44), Poland (45), Italy (46), Romania, Serbia and former Yugoslavia (47) in Europe.

The first *Ph. perfiliewi transcaucasicus* infection of *L. infantum* in Iran was observed in 2004 in the rural areas of Germi district, in the Ardabil Province (Table 1, Fig. 1), in Northwestern Iran (18). This species was introduced as the primary vector of visceral leishmaniasis due to the wide abundance of the species in the area, its high anthropophlic index, and the fact that it was the only species infected with *L. infantum* in the research region (18). In the course of these observations, the first infection of this species with *L. donovani* parasite in addition to *L. infantum* was noted in Germi district, northeastern Iran (16). It should be mentioned that *L. donovani* (LON 50) was previously reported from *Meriones persicus* in northwest Iran (48).

Phlebotomus (*Larroussius*) *major* s. l.

According to the most recent information, the members of *Phlebotomus major*, which was one of the complex species, were *Ph. major* (India, Nepal, and Pakistan), *Ph. neglectus* (Southern Europe, Crimea and Iran), *Ph. syriacus* (Southwest Asia, Caucasus), *Ph. notus* (Afghanistan and Iran), *Ph. wenyoni* (Iran, and Iraq), and *Ph. wui* (China). Most of these species were previously referred to as *Ph. major* (49). *Phlebotomus major* was first recognized in the Himalayas in India and has been listed

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for a long time as an exclusive species with a wide distribution and the potential to transmit the *L. infantum* in the nations of India, Southeast Asia, Dalmatia, Italy and Crete (50). However, supplementary and comprehensive studies carried out by various researchers on its mature specimens based on morphological characteristics in different biogeographical regions have shown that *Ph. major* was a complex species (25, 39, 51, 52).

According to Theodore (1958), *Ph. major* only exists in India, whereas its two subspecies, *Ph. major syriacus* and *Ph. major neglectus*, can be found in Southern Europe and Southwest Asia, respectively. It appears that both species of *Ph. syriacus* and *Ph. neglectus* were widespread in the Middle East, despite the fact that the majority of members of the *Ph. major* complex had an allopatric distribution (53). According to research done by Léger and Depaquit in 2002, *Ph. neglectus* was widespread in western Mediterranean nations such as Albania, Italy, Greece, former Yugoslavia, Montenegro, Poland, Dalmatia, Israel, and Palestine (54). *Phlebotomus major* was reported in Iran for the first time in the northern regions of the country, particularly in the eastern Caspian Sea regions (55). Absavaran et al. conducted the initial investigation to assess the systematic status of *Ph. major* in Iran in 2009 (56). The *Ph. major* complex population was phylogenetically analyzed using molecular techniques and the cytochrome b (Cyt b) gene in Ardabil Province, northwest Iran, one of the major foci of visceral leishmaniasis. It was the first scientific report of the second species in Iran when this investigation revealed the presence of two species of *Ph. major* and *Ph. neglectus* in this region (56).

Leger et al. (57) reported the first case of naturally occurring *L. infantum* parasite infection of *Ph. major* in 1988. Ivovi et al. (58) reported a natural promastigote infection of this species in Montenegro, however they did not identify the parasite. The mentioned species was a vector for visceral leishmaniasis in Cyprus, according to reports by Leger and Depaquit in 2008.

This species was introduced to Albania in 2017 by Velo et al. (59) as the primary vector of *L. infantum*.

In Qir and Karzin district of Fars Province in Iran, the first report of naturally occurring *Ph. major* infection with *L. infantum* was reported in 2008 (22). The results of that study demonstrated that the *L. infantum* parasite was naturally present in 6.65% of the examined *Ph. major* samples (Table 1, Fig. 1). It appears to be a vector of visceral leishmaniasis in the area of southern Iran where the disease is endemic due to this species' natural infection with the *L. infantum* and its relative frequency (11.2%) in the research area (22).

***Phlebotomus* (*Larroussius*) *keshishiani* Shurenkova, 1936**

Another species of the subgenus *Larroussius*, *Ph. keshishiani*, has been found in the former Soviet Union, Afghanistan, Iran, and Pakistan. Although the mentioned species has been observed in Afghanistan's plainer regions, it is often found in mountain places. Both its locality type and syntype can be found in the Tajik districts of Pamir and Dushanbe (25). Only one report of *Ph. keshishiani* infection in the promastigote form of the *Leishmania* parasite has been made, and it was in the southern Iranian province of Fars, where visceral leishmaniasis was endemic in the district of Qir and Karzin in Fars Province (Table 1, Fig. 1), south of Iran (23). The above species has been identified as a potential vector of visceral leishmaniasis in the area due to its relatively high frequency, infection with the promastigote form of the parasite, positivity of the susceptible animal after injection, tendency to feed on human and dog's blood, and compatibility of its distribution range with the spread of the disease (23). According to a review of the publications, there was no records of this species being infected with the *Leishmania* parasite in any other regions of the world.

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***Phlebotomus* (*Paraphlebotomus*) *alexandri* Sinton, 1928**

Phlebotomus sergenti var. Newstead, 1920; *Phlebotomus sergenti* var. *alexandri* Sinton, 1928; and *Phlebotomus* (*Paraphlebotomus*) *marismortui* Theodor, 1947 were synonyms of this species (26). Its syntype locality was unknown (25). Paralectotypes of them (also known as Paranéotypes) are held in the Natural History Museum of London (25). In addition to Africa and the Mediterranean regions, *Ph. alexandri* has also been found in Algeria, Afghanistan, China, Cyprus, Djibouti, Ethiopia, Greece, Iran, Pakistan, Israel, Romania, Saudi Arabia, Spain, Tunisia, Turkey, United Arab Emirates and Yemen (43).

In the old world, the *Ph. alexandri* species is widely distributed. This sand fly has been identified as an *L. donovani* parasite vector in China (60) and has been introduced in China, Iraq, Oman, Turkey, and Mongolia as a vector of both *L. infantum* and *L. donovani* (61). In Fars Province, one of the major endemic foci for visceral leishmaniasis, there was first reported case of *Ph. alexandri* infection with *L. infantum* parasite in 2006 (Table 1, Fig. 1). This was also the first occurrence of this species infection with *L. infantum* parasite worldwide (24). Recent research has shown that the B, C, and D morphotypes *Ph. alexandri* are infected with the *L. infantum* parasite. Furthermore, the morphotype D was found to be infected with *L. donovani* parasite for the first time in Iran. *Leishmania* infection has not been observed in the A or E morphotypes because they were cryptic (62).

Conclusion

Up till 2018, this study is the first thorough analysis of the distribution and role of visceral leishmaniasis vectors in Iran and some other Old World nations. According to the findings, *Ph.kandlakii*, *Ph. perfiliewi transcaucasicus*, and *Ph. tobbi* were key players in disease transmission in the endemic foci of visceral leishmaniasis in northwestern Iran (Ardabil and East Azerbaijan Provinces), Alborz Province, and Shirvan in North Khorasan Province. Because *L. donovani* is anthropontic and primarily causes the visceral form of the disease, while *L. infantum* is an anthropozoonotic parasite with canine reservoirs, it is crucial to observe *L. donovani* in *Ph. perfiliewi transcaucasicus* in order to understand the ecology and epidemiology of visceral leishmaniasis in Iran. The vectorial competency of *Ph. major* in relation to visceral leishmaniasis was not entirely evident because of the complexity of this species' population, which was previously discussed in this respect. The research done in Iran suggests that *Ph. alexandri* was certainly a complex species, but more research is needed to determine all of its potential members. In this situation, its members may be restricted, intermediate or even permissive in terms of leishmaniasis transmission. The findings of this study update researchers' understanding of diseases distributed by sand flies, particularly leishmaniasis, and, in line with the objectives of their research work, they offer very valuable information about the status and distribution of sand flies as well as their relationship to and role in visceral leishmaniasis. The findings of this study are particularly helpful for the national health policy makers in this regard and influence how they decide to take on the challenge of controlling the vectors that transmit visceral leishmaniasis.

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Ethical consideration

Research ethics approval ID: IR.NIMAD.REC.1399.171.

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Conflict of interest statement

The authors declare there is no conflict of interests.

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