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Application of Rodenticides for the Control of Zoonotic Cutaneous Leishmaniasis in Iran: A Systematic Review of the Literature

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ABSTRACT

Introduction: Rodent control programs have a long history of controlling zoonotic cutaneous leishmaniasis (ZCL) in Iran. The present systematic review reports the effect of rodenticides in reducing ZCL in Iran.

Materials and Methods: Various electronic databases were explored for reliable research using appropriate keywords between January 1970 and September 2023. Relevant studies were included based on the inclusion criteria. All articles identified from the systematic search were added into Endnote X9 (Clarivate Analytics) and duplicate articles were removed. This study followed standard procedures for systematic reviews and reported results according to systematic reviews guidelines.

Results: Overall, 637 documents were identified after screening based on the PRISMA checklist, and finally, 13 papers were included in this systematic review. The findings indicated that most of studies used zinc phosphide (2.5%) and Klerat® mixed with wheat grains in rodents control programs in Iran. The results showed that rodent control programs were implemented in five provinces of Iran, including Esfahan, Yazd, Semana, Golestan, Kermanshah, and Fars, with the highest number of studies in Esfahan province. According to results, the incidence rate of ZCL significantly reduced after rodenticide implementation.

Conclusion: This review study provides a better understanding of rodent control programs trends as a promising and practical approach to reducing ZCL incidence in Iran over the past 50 years and can serve as a reference for planning future control and research programs.

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Introduction

Zoonotic cutaneous leishmaniasis (ZCL) is a vector-borne protozoan disease transmitted to humans by the bite of blood-feeding female phlebotomine sand flies [1, 2]. This neglected disease is a growing public health concern in many rural areas of Iran, involving 17 out of 31 provinces [2-4].

In endemic locations, controlling ZCL is more

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challenging. Despite efforts to control this infectious disease, it is still endemic in different countries, including Iran [1.] The incidence of ZCL in Iran in 2019 was 15.8 cases per 100,000 people[5]. One of the effective ways to control ZCL is to eliminate the disease reservoirs in endemic areas [1]. Researchers in Iran have used several approaches to control ZCL, including i. Impregnated bed nets and curtains with pyrethroids, ii. Indoor residual spraying, iii. Application of repellents, iv. A rodent control operation, v. Health education to the community, and vi. Leishmanization in an emergency complex situation [6].

Rodents are the primary reservoir hosts of ZCL in the world, as well as Iran [7]. They are essential vertebrates belonging to the class *Mammalia* and the order *Rodentia*. In addition to being reservoirs, they transmit numerous communicable diseases to humans and livestock [8]. Furthermore, several microorganisms such as bacteria, rickettsia, viruses, protozoa, and helminths are transmitted by rodents to humans and livestock [9].

In Iran, four rodent species are known as the principal animal reservoir of ZCL, including *Rhombomys opimus* (the great gerbil), *Meriones libycus* (the Libyan Jird), *Meriones hurrianae* (the desert gerbil), and *Tatera indica* (the Indian gerbil) [3, 10]. *Rhombomys opimus* has been known as the main rodent reservoir of ZCL in Iran central, north, and northeastern parts [3, 11, 12]. *Tatera indica*, *Nesokia indica,* and *Meriones libycus* are known as the main rodent reservoirs of ZCL in the south, west, and southwestern parts of Iran [11].

Rodenticides have been used to control urban gerbils as effective pesticides [13]. They are anticoagulant pesticides that are widely used in agricultural and urban rodent control. Several rodenticides, including cereal-based baits, pastes, tracking powders, and wax blocks, are commercially available worldwide for controlling rodents [14].

Rodents control programs have been implemented for many years in Iran and are a promising and practical approach to reduce ZCL incidence in Iran. However, there are significant research gaps in this field, and this study aims to fill these gaps. This study systematically evaluated papers that examined the impact of rodenticides on ZCL control in Iran. The study findings were presented with recommendations for policy, identifying critical gaps in the evidence base, and highlighting future needs for rodent control in the field. To the best of the authors' knowledge, no comprehensive systematic review has ever been published on rodent control studies in the field, and the present study is the first systematic review to specifically address the implementation of rodent control operation programs in reducing ZCL in Iran. The collected evidence of this systematic review would serve as a basis to guide priorities in focusing rodent control efforts according to different geographic areas of the world, especially in Iran. Moreover, the results of this review can enable health officers to provide appropriate recommendations for rodent control in fields for workers.

Materials and Methods

Data sources and search strategy

The systematic literature search was performed on September 30, 2023. The search strategy was designed to identify relevant electronic studies published between January 1970 and September 2023. International electronic databases were systematically searched, including Web of Scince, PubMed, Scopus, Google Scholar, and national databases, including Magiran, IranDoc, and Scientific Information Database (SID). The search was performed using medical subject headings (MeSH). Keywords were used to perform the literature search, including (Rodenticides)) OR ((Rodent Control)) AND ((Zoonotic Cutaneous Leishmaniasis)) AND ((Iran)).

Inclusion and exclusion criteria

The inclusion criteria for the current systematic review consisted of i. English and Persian articles (i.e., at least the abstract), ii. Original articles that were conducted in the field, and iii. Articles with available full text or abstract. In this study, all articles identified from the systematic search were added into Endnote X9 (Clarivate Analytics) and duplicate articles were removed. This study

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followed standard procedures for systematic reviews and reported results according to systematic reviews guidelines.

Results

Search results

In total, 637 documents were identified. Duplicated articles (351 articles) were removed and 52 full-text articles were reviewed. Finally, 13 studies that met the eligibility criteria were selected for this systematic review. The flow diagram of the study selection is shown in Figure 1. Articles were published between 1972 and 2017. Eight articles were conducted in Esfahan province, while others were conducted in other provinces in Iran, including Yazd, Semnan, Kermanshah, Golestan, and Fars. The details of the results are shown in Table 1.

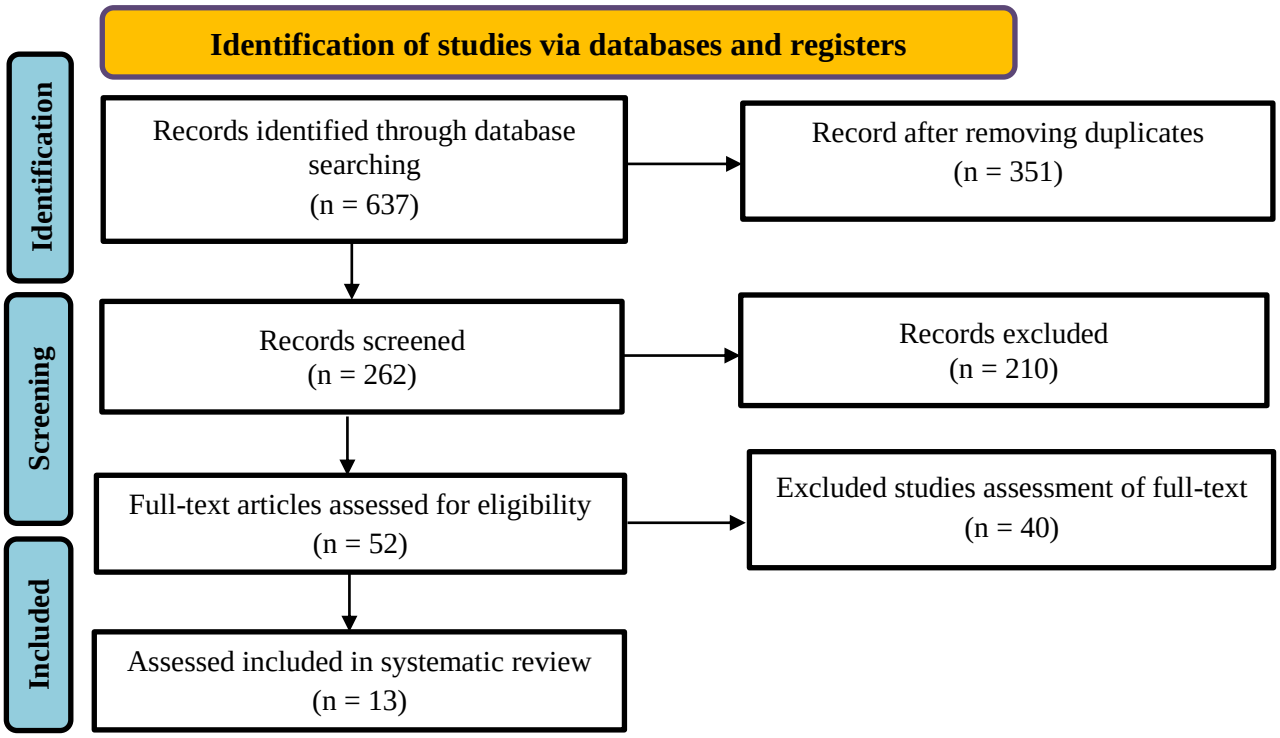


Figure 1: PRISMA flowchart describing the study design process.

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Table 1: Characteristics of studies that focused on rodent control in Iran

No.	Province	Name of village	Year of study	Rodenticide	Destroying of the rodent burrows radius (Meter)	Main findings or suggestions	Ref.
1	Esfahan (Borkhar county)	Colonabad Juzdan Sussart Parvaneh Jaladeran	Between June 1972 to September 1973	Mixture of Wheat with Zinc phosphide (2.5%) and DDT (75%)	300 M	The number of rodent burrows and the incidence rate of ZCL significantly changed.	15
2	Esfahan (Badrood)	Abbasabad Matinabad	Between December 1996 to January 1999	Mixture of Grain with Zinc phosphide (2.5%)	500 M	Rodent burrows reduced by 87.4%, and the incidence rate of ZCL significantly changed.	16
3	Esfahan (Natanz)	Imamzadeh Agha Ali Abbas	1996-1998	Klerat®	2000 M	The incidence rate of ZCL decreased.	17
4	Yazd (Ardakan)	Ahmadabad Torkabad	1999-2000	Klerat®	2000 M	The incidence rate of ZCL decreased.	18
5	Esfahan (Badrood)	Abbasabad Matinabad	1999 to 2002(May and October)	Mixture of Grain with Zinc phosphide (2.5%)	500 M	Rodent burrows changed over time in the intervention and control villages; moreover, the incidence rate of ZCL between the intervention and control villages significantly changed.	19
6	Semnan	Villages of Damghan County	2005-2006	Mixture of Grain with Zinc phosphide	1000-2000 M	The number of rodent burrows and the incidence rate of ZCL significantly changed.	20
7	Esfahan (Natanz)	Imamzadeh Agha Ali Abbas	2006-2009	Zinc phosphide	2000 M	The number of people affected with ZCL decreased.	21
8	Esfahan	Islamabad Gishi Vartoon Parvaneh-Aliabadchi	2011 (April to November)	Phostoxin and Zinc phosphide	500 M	In the village, rodent burrows reduced by 32.68% and 58.14%, treated with phostoxin and Zinc phosphide, respectively. Moreover, the incidence rate of ZCL decreased to 19.23 and 11.40 in areas treated with phostoxin and Zinc phosphide, respectively.	3
9	Esfahan (Esfahan)	Mazraehshoor Gishi Vartoon Parvaneh-Aliabadchi	January 2011 to January 2012	Mixture of Grain with Coumavec® and Zinc phosphide	500 M	Rodent burrows reduced by 48.46% and 58.15% in intervention areas with Coumavec® and Zinc phosphide, respectively. Moreover, the incidence rate of ZCL significantly reduced in the treated areas.	6

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No.	Province	Name of village	Year of study	Rodenticide	Destroying of the rodent burrows radius (Meter)	Main findings or suggestions	Ref.
10	Esfahan	Timyart Gishi Vartoon Parvaneh-Ali abdchi	2011 (April to November)	Klerat® and Zinc phosphide	500 M	Rodent burrows reduced by 62.8% and 58.15% in intervention areas with Klerat® and Zinc phosphide, respectively. Moreover, the incidence rate of ZCL significantly changed.	22
11	Kermanshah (Qasr-e-Shirin)	Villages of Qasr-e-Shirin	2015-2016	Zinc phosphide (2.5%)	500 M	The incidence rate of ZCL decreased.	23
12	Golestan	45 villages of Gonbad Kavous County	2016 (May, July and September)	Mixture of Grain with Zinc phosphide (2.5%)	1000 M	The number of rodent burrows and the incidence rate of ZCL significantly changed.	24
13	Fars (Kharame)	Mehrabad Moezabad Sofla	2016 to 2017	Mixture of Wheat with Fipronil	500 M	The incidence of ZCL reduced by 4.89% in the studied villages.	25

Klerat®: Anticoagulant rodenticide containing 0.005% Brodifacoum.
Coumavec®: A mixture of 0.5% coumatetralyl and 0.5% etofenprox.

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Regional distributions of the studies

Based on the results of this review, rodent control operations have been concentrated in Central and North of Iran, and only one study was conducted in the West of Iran. Based on the results, rodents are more active as reservoirs of ZCL in Central and North of Iran. In total, 13 papers were found in the current review, eight of them were conducted in Esfahan province. The location of provinces in Iran where rodent control operation programs were implemented is illustrated in Figure 2.

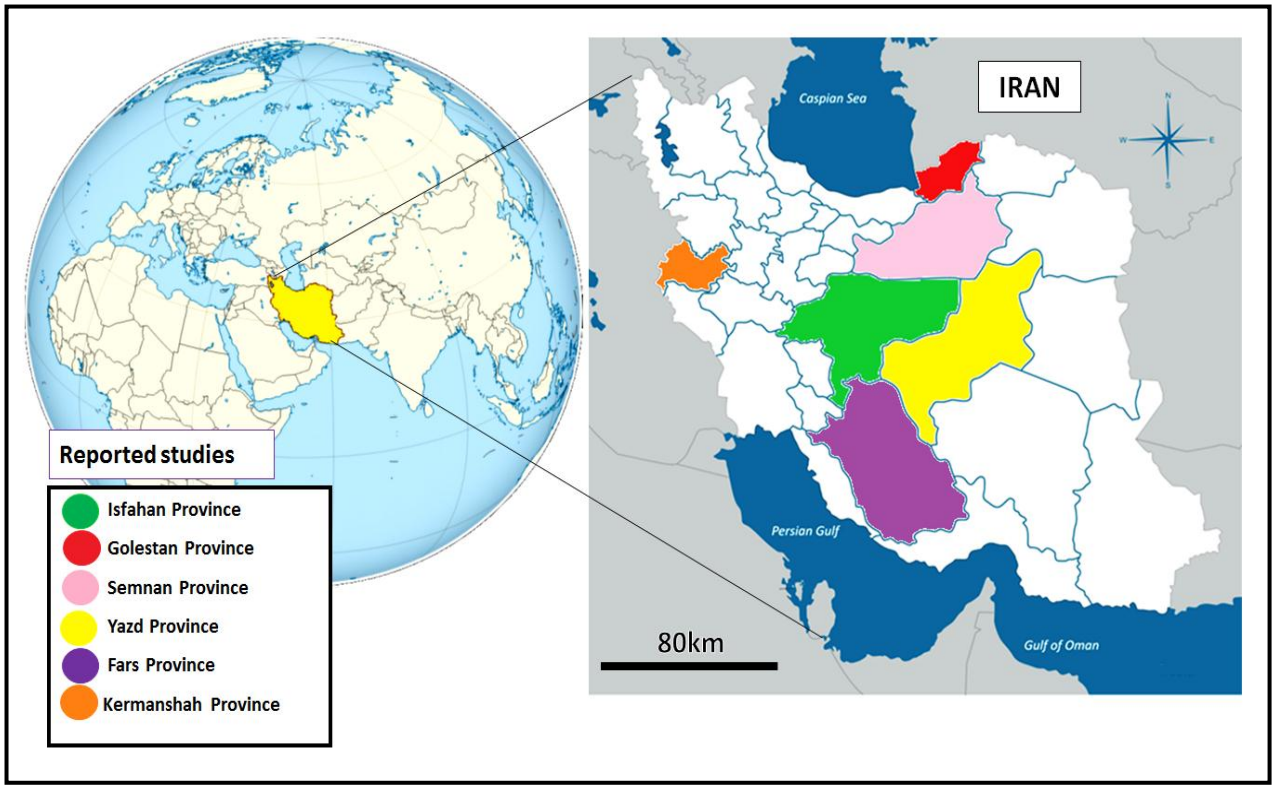


Figure 2: Regional distributions of reported studies on rodenticides use in the reduction of ZCL in Iran.

Forms of rodenticide used

The findings indicated that 10 studies used zinc phosphide (2.5%) mixture with grain of wheat in rodent control programs in Iran. In three studies, Klerat® was used. Rodenticides such as Coumavec®, Fipronil, DDT (75%) and Phostoxin were also used in studies.

Figure 3 shows the rodenticide forms and the number of publications considered in the present systematic review.

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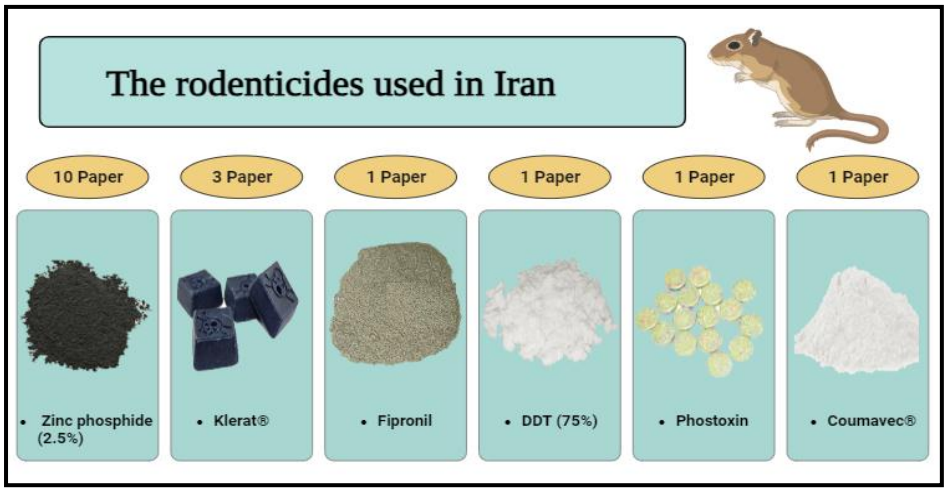


Figure 3: Rodenticides used for each study in the current systematic review.

Rodenticides implementation method

Based on the reviewed articles, the method of applying rodenticides for each study was to destroy the rodent burrows at a distance of 1000 m from houses in the village, and then insert the poisoned baits to a depth of 10 cm in each burrow. A schematic of rodenticide implementation methods for each study in the current systematic review is illustrated in Figure 4.

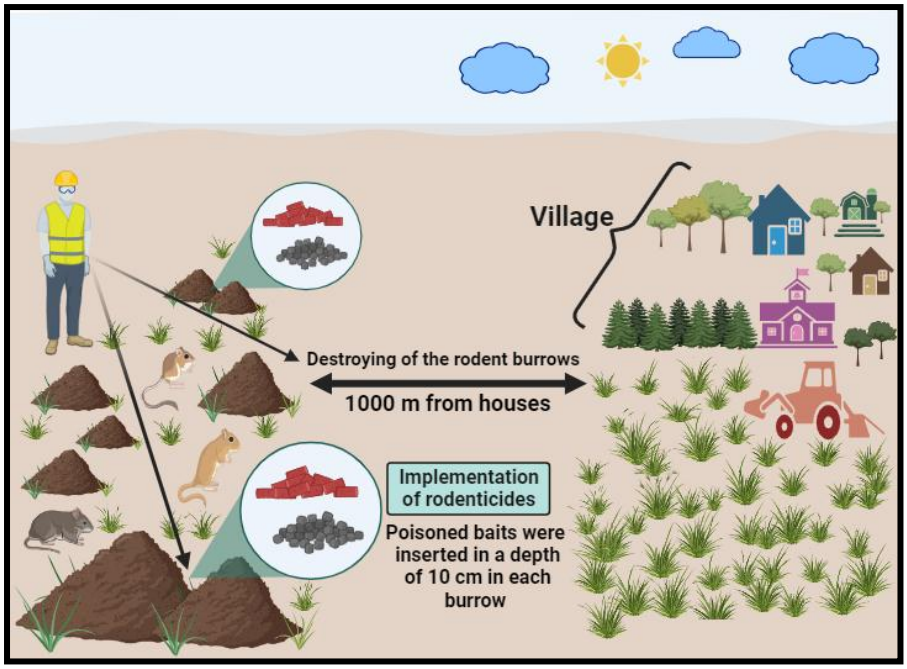


Figure 4: Schematic of rodenticide implementation methods for each study in the current systematic review.

Discussion

Rodents are considered a public health pest, and their health impacts on humans and livestock are an immense issue in many countries. Rodenticides are widely used to manage urban rodents around the world, including in Iran. Based on the results of this study, zinc phosphide mixture with wheat grains and Klerat® have been known as the most common rodenticide in rodent control operations in Iran. In recent years, rodent control programs to

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control leishmaniasis in the field have been conducted by experts in five provinces of Iran, including Esfahan [3, 6, 22], Yazd [18], Semnan [20], Golestan [24], Kermanshah [23] and Fars [25]. Based on the results of this review, rodent control operations have been focused on the Central and North of Iran, and only one study was conducted in the West of Iran. The results show that rodents are more active as reservoirs of ZCL in Central and North of Iran.

According to the results of rodent control operation studies published in Iran (13 papers), the incidence rate of ZCL significantly reduced following the implementation of rodenticides. Furthermore, most of the studies in different provinces of Iran reported that rodent burrows were reduced after rodenticides implementation. In most studies, rodent burrows were removed in a radius of 300 to 500 meters surrounding all communities. Therefore, after 48 hours, reopened holes were counted again in most studies.

In addition, 13 studies were conducted on rodent control programs in Iran for Phostoxin 1 tablet, zinc phosphide 12-15 gr, Klerat® 2 to 4 wax blocks, Coumavec® 12–15 gr, Fipronil 15gr, and DDT (75%). Based on the results, 0.5 gr of poisoned baits were inserted at a depth of 10 cm in each burrow in most studies, and only in one study, the poisoned baits were inserted at a depth of 30 cm in each burrow. There was no difference between the depths of poison baiting in the studies. Pesticides were mixed with grains of wheat, and poisoned baits were finally prepared.

The results of Seyedi-Rashti and Nadim (1974) showed that rodent control using zinc phosphide (2.5%) mixed with wheat and DDT (75%) was very effective [15]. Based on the search results, this study is the first field study conducted in Iran. The results of Yaghoobi Ershadi *et al.* indicated that rodent control with zinc phosphide (2.5%) mixed with grain reduced the rodent burrows, and the incidence rate of ZCL significantly changed [16]. Furthermore, Yaghoobi Ershadi *et al.* reported that rodent burrows changed over time in the intervention and control villages [19].

In another study, Veysi *et al.* reported that both rodenticides used, including Coumavec® and zinc phosphide mixed with grain, were adequate for reducing rodent holes in intervention areas and Coumavec® was less effective than zinc phosphide [6]. Furthermore, t Veysi *et al.* in 2016 found that Klerat® was more effective than zinc phosphide in decreasing the rodent population [22]. Coumavec® and Klerat® are chronic anticoagulant rodenticides that gradually affect rodents within 1–2 weeks. Previous studies did not recommend Coumavec® and Klerat® as alternatives for zinc phosphide to control the reservoir hosts of ZCL in the conventional situation. However, these rodenticides could be a suitable alternative to zinc phosphide under specific conditions such as behavior resistance or occurrence of bait shyness [6, 22].

Similarly, Akhavan *et al.* stated that both rodenticides used in the study, including Phostoxin and zinc phosphide, were effective enough in controlling the rodent population [3]. Kalteh *et al.* in Golestan province also reported a significant relationship between the implementation of rodent control operation and the incidence rate of ZCL in the studied villages [24]. Saki *et al.* [25] found that the incidence rate of ZCL reduced in the studied villages.

Esfahan province is one of the essential foci of ZCL in Iran. Accordingly, , eight studies in this systematic review, including Seyedi-Rashti and Nadim [15], Yaghoobi Ershadi *et al.* [16], Nilforooshzadeh *et al.* [17], Yaghoobi Ershadi *et al.* [19], Nilforoushzadeh *et al.* [21], Veysi *et al.* [6], Veysi *et al.* [22] and Akhavan *et al.* [3] have focused on rodent control operations in this province.

In this systematic review, several studies such as Nilforooshzadeh *et al.* [17], Dehghani Tafti *et al.* [18], Azni *et al.* [20], Nilforoushzadeh *et al.* [21], and Ahmadi *et al.* [23] used a combined control program that included indoor residual spraying, rodent control, and improving the environment to reduce ZCL disease. These combined studies found that rodent control was a very effective method for reducing the incidence rate of ZCL in the studied villages. It appears that rodenticide can be used as a complementary method for reducing ZCL.

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Conclusion

Rodent control programs are a promising and practical approach to reduce ZCL prevalence in Iran. For approximately five decades, the methods used for rodent control to reduce ZCL incidence in Iran have included chemical methods with rodenticides. The results of the present study demonstrated that rodent control programs to reduce ZCL incidence in Iran used rodenticides within 300 or 500 meters of houses. In studies conducted in Iran, 2.5% zinc phosphide mixed with a grain of wheat was the main rodenticide that was used. According to the results of the current study, the incidence rate of ZCL significantly reduced after rodenticide implementation. This systematic review provides a better understanding of rodent control program trends to control ZCL in Iran that have been conducted over the past 50 years and can serve as a reference for future field studies. However, more research is required to better understand the rodent control effect on reducing ZCL incidence.

Recommendations for future studies

Based on the information obtained from this systematic review, which encompassed rodent control research for reducing the incidence rate of ZCL in Iran over the past fifty years and collected information from 13 research articles, we would like to highlight some issues and make some recommendations that may be helpful for future studies on rodent control in the field. Various methods have been used to control rodent populations worldwide. Most research studies in Iran have focused on the use of toxic baits as a chemical method to reduce ZCL. It can be recommended that researchers focus on other methods. Some approaches for rodent control are recommended for future studies, as follows:

- Using new rodenticides with new formulations, such as nano-rodenticides and encapsulated rodenticides.
- Using another chemical method, such as fumigants and repellents.
- Using physical methods such as traps and barriers.
- Using an integrated pest management (IPM) strategy.
- More studies should be conducted in other areas of Iran with ZCL foci to find a suitable practical method for rodent control in Iran.

The methods highlighted above can be expanded with specific experimental designs by researchers to further substantiate the utility of rodent control to reduce ZCL.

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Conflict of interest

The authors declare that there is no conflict of interest.

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Ethical considerations

This study was done without receiving ethical code.

Authors' contributions

All authors equally contributed to the preparation of this article.

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