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A Review of Rabies Treatment Methods in Ancient Iran

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Abstract

Rabies is a fatal viral disease affecting warm-blooded mammals (bats, carnivores, and ruminants) and even humans. The virus is usually transmitted between humans or other animals through the bite of infected animals. However, there are unusual ways to share the virus, such as organ transplants. Rabies has been known in the ancient world since about 2300 BC. Dogs were commonly known as the leading carriers of the disease. There were strange methods that were sometimes mixed with superstition and thought to treat or prevent rabies effectively. In ancient Iran, rabies was endemic. Scientists such as Avicenna (Ibn Sina, 980-1037 AD), Rhazes (Abu Bakr Al-Razi, 964-864 AD), Al-Biruni (970-1050 AD), Jorjani (1042-1136 AD), and Akhawyni Bokhari (913-971 AD) have described rabies, transmission, and treatment methods. This study aimed to present the development history of treatment methods against rabies based on ancient Iran's culture, civilization, and knowledge and examine its progress and development of practical skills against rabies.

Keywords: Rabies; History; Ancient; Iran

Abbreviations: PEP: Post-Exposure Prevention, FAO: Food and Agriculture Organization

Introduction

Infectious diseases are caused by bacteria, viruses, fungi, prions, worms, or other parasites. The consequences of infectious disease vary depending on the infectious agent, and its range can be from mild to severe. Although infectious diseases are always found worldwide, the type of infection may vary depending on the weather, health conditions, and other environmental factors. Infectious diseases are emerging at an unprecedented rate and significantly affect the global economy, public health, society, and ecological conditions **[1]**.

Rabies is a fatal viral disease affecting warm-blooded mammals (bats, carnivores, ruminants) and even humans. It can typically spread to other animals or humans by biting infected animals, scratches, and unusual ways such as organ

transplants. The main vectors of the disease are dogs, wolves, jackals, foxes, and bats **[2]**. Rabies is present on all continents except Antarctica, but over95% of all human deaths occur in Asia and Africa, and 40% are children **[3]**. Annually, 59,000 people die from rabies **[4]**, more than double the estimated deaths from the tragic Ebola outbreak in West Africa in 2016-2014 **[5]**.

Rabies is one of the oldest zoonotic diseases. Evidence suggests that the disease has been known in the ancient world since about 2300 BC. In the ancient world, dogs were commonly known as the leading carriers of the disease **[6]**. Rabies is derived from the Latin word Rabere, which means to make furious or tumultuous, and may have its origins in the Sanskrit word rabhas, which means to commit violence. In the ancient Greek language, the word for rabies was lyssa or lytta, which translates into English to "madness" or "being bitten by a dog," respectively **[2]**. In traditional Iranian medicine, it also means madness **[3]**, and in Dehkhoda (Persian) dictionary, rabies has been introduced as a crazy animal, especially a crazy dog **[7]**.

Using collars to restrict the movement of dogs dates back to 3500 BC in ancient Egypt. The first effective measures to control rabies were to limit dogs' exercise and snout and eliminate stray dogs **(Figure 1)**. These methods were the basis of a program that led to the eradication of canine rabies in Britain in 1902 **[8]**.

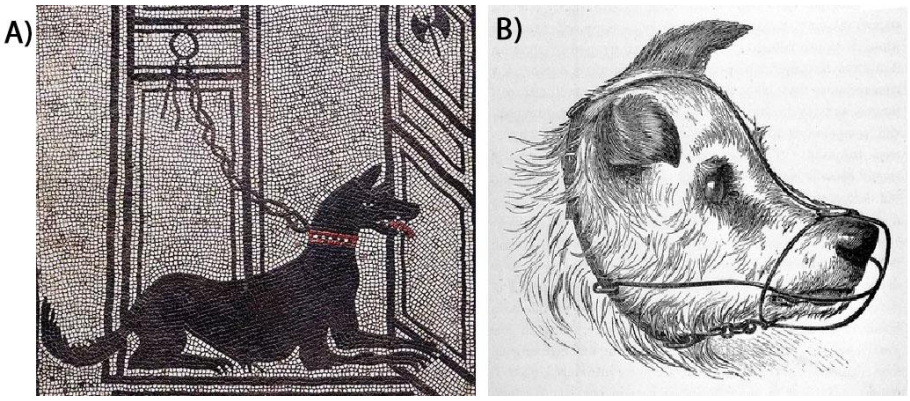

Figure 1: (A) The people of ancient Egypt in 3500 BC used collars to restrict the movement of dogs (B) Using the snout for the dog was one of the first measures for controlling rabies in the nineteenth century **[9]**.

In the ancient world, unorthodox methods were sometimes mixed with superstition and were thought to treat or prevent rabies effectively. This study aims to present the history of the development of treatment methods against rabies based on ancient Iran's culture, civilization, and knowledge and examine its progress and development of practical skills against rabies.

Study Method

This study used books and articles found by Google Scholar and referred to libraries about the history of rabies in the ancient world and ancient Iran. The keywords used in the search for this study were: rabies, rabies history, ancient Iran, Asia, ancient world, Jorjani, Avicenna, Rhazes, and Akhawyni.

Based on available written texts, we tried to find the history of our current understanding of rabies in dogs and humans and its prevention and treatment in the pre-Renaissance period. Articles and books obtained from this search showed that many studies had been conducted on the history of rabies in the world; however, recent studies on the history of rabies in ancient Iran are few. In addition to studying the books of Iranian scholars such as the book of Canon in medicine belonging to Avicenna, Hidayat al-Muta'allemin Fi al-Tibb (Akhawyni, 11 century A.D.), Alhavi (Rhazes, 11 century A.D.), and The Natural History of Rabies (George Baer, 1975 A.D.), 12 articles were obtained. The history of rabies or its treatment methods was long gone, and four articles had more repetitive content or sources.

Rabies in the ancient world

In ancient texts from the Mediterranean to India, human rabies has been related to infecting dogs. Ancient Greek mythology, Roman history, Avestan teachings, Zoroastrian literature, and Pre-Islamic Arab poetry all mention a rabid

dog or wolf, its bite, and the disease produced by rabid animals, particularly dogs **[10]**. From two cuneiform tablets describing Sumerian legislation unearthed in Tal Abu Harmal, Baghdad Province, Iraq, in 1945 and 1947, it can be deduced that there was a cause-and-effect relationship between rabid animal bites and human death about 4,000 years ago. It was well known for its rabies effect **[11]**. However, rabies was attributed to other animals such as cats and dogs in ancient Greece and China **[11]**.

Homer (Greek poet) also describes rabid canines in the eighth hymn of the Iliad. Aristotle, a Greek philosopher and physician (384-322 BC) described rabies as a fatal disease and transmission from dogs to other animals. Apollonius (an ancient Roman author) mentions rabies in the Golden Donkey story of a rabid dog. In addition, Philomenus (the Greek physician in the third century A.D.) explained rabies in dogs **[12]**.

The Greek philosopher Celsus, 25 years before Christ, made the term hydrophobia a symptom of rabies and stated that the saliva of a rabid animal contained toxic substances **[13]**.

Jahangir Shah, King of India, in 1613 AD, first reported rabies on an elephant caused by rabid dog bites in Jahangirnameh **[12]**. In the 16th century, an Italian physician Girolamo Fracastro considered dog bites the primary rabies method **[13]**.

Despite the long history of rabies, in 1769, John Morgagni (father of pathology and anatomy) hypothesized that the rabies virus travels along nerve fibers rather than in arteries **[13]**. In traditional Indian medicine, 12th-century thinker Susruta Samhita says that rabies is neurological and refers to its hydrophobicity **[14]**.

By the end of the nineteenth century, there was a sharp rise in rabies in dogs across Europe. In England's second half of the nineteenth century, 1122 people died of rabies. In St. Petersburg, 47 people died of rabies between 1863 and 1847, and in 1878, only 500 dog rabies and 24 human deaths from rabies were recorded in Paris alone **[8]**.

Rabies in ancient Iran

The history of Iran is divided into two parts: pre-Islamic and post-Islamic. In pre-Islamic Iran, rabies was known by farmers and shepherds **[7]**. In verses 38-35 of Chapter 13 of Vendidad (part of the book of Avesta in Zoroastrianism, 200-400 AD), rabid dogs are mentioned as crazy dogs and ordered to treat crazy dogs like crazy humans. If treatment is impossible, tying its neck with a rope does not bother people. In paragraphs 29-34, the same chapter mentions the surprised dog and gives the order to close and discipline it. Overall, the book's authors were vaguely aware of the transmission of dog disease to humans and animals, but the issue is not mentioned clearly **[12]**.

One occupation that pre-Islamic Iranians engaged in from the beginning was animal husbandry. The Aryans brought horses to Iran and established animal and human care centers. In ancient Iran, horses were essential for their use in wars. The person who was treating humans was also treating animals. It can be said that the brilliant period of veterinary medicine and animal care in Iran began during the Sassanian era (224–651 B.C.). Not much information is available about that time's scientific advances and treatments. In the early Islamic period, the ancient Iranians called the animal treater person "pecheshk sotour". Then, this person was called Beitar with the introduction of Arabic words. In 1937, the Persian term "dampezeshk" was coined **[15]**.

In the post-Islamic and medieval period, Iranian historians said about the existence of rabies, and scholars such as Ibn Sina, Rhazes (Abu Bakr Al-Razi, 964-864 AD), Biruni, Jorjani, and Akhawyni described rabies, its transmission method and the development of rabies treatment methods. The Middle East was full of stray dogs, despite religious opposition to dogs considered unclean and recommendations for restraint.

Abu Ja'far Muhammad ibn Musa Al-Khwarizmi (Persian philosopher and scientist, 850-780 AD) says about a rabid dog: "If a dog bites a human, the person becomes seriously ill and becomes afraid of the water until he dies of thirst."

Rhazes, a post-Islamic Iranian physician and philosopher (964-864 A.D.), in his book (Al-Hawi), says: "The rabid dog does not know its owner and attacks whatever it finds. Its mouth is open, and its tongue is out, its eyes are red, and other dogs run away from him" **[15]**.

Abu Bakr Rabee ibn Ahmad Al-Akhawyni Bokhari (famous as the Mad Doctor because he studied the nerves) (981-921 AD) in his book "Hidayat Al-Muta'allemin fi Al-Tibb", the first post-Islamic Persian medical book, describes the dura-

-tion of rabies 15 days. He mentioned the duration of rabies and described the symptoms of rabies in dogs as the tongue sticking out, saliva constantly coming out of the dog's mouth, and fear of water. In addition, he said that the dog does not know anyone and attacks everyone and dies (Hedayat Al-Mutalimin, Akhwini Bukharaee) **[15]**.

Baha-Ol-Dole, the Persian physician (970-1013 A.D.), seems to have been the first to explicitly consider rabies in dogs to result from another rabid dog's bite. He mentioned rabies in wolves, donkeys, foxes, and other animals and said for the first time that some wild animals develop the disease without being bitten by another animal **[15]**.

According to Avicenna (Ibn Sina, 980-1037 A.D.), an Iranian physician and scientist (980-1037 A.D.), in the book on description of a rabid dog, wolf, and jackal and on Conditions Arising from the bite of a rabid dog, rabies caused by an imbalance in 4 behavioral senses in the body in a rabid dog. He described the manifestations of rabies in dogs, noting the fear of water, excessive salivation, and aggressive behavior. Ibn Sina also explains transmitting rabies through rabies to humans and other animals. According to Ibn Sina, a patient with rabies in the last stage of the disease (after the appearance of hydrophobicity) will no longer be saved and is sentenced to death.

He believed that bleeding from the bite site increased the chances of survival **[13]**. Today, it has been revealed that the saliva of rabid animals is full of virus particles. Avicenna, almost eight centuries before Francois Magendie (French physiologist) and George Gottfried Zinke (German scientist), mentioned the possibility of transmitting rabies from the saliva of a rabid animal to humans **[13]**.

Al-Jurjani (Iranian physician and philosopher) (1140-1040 A.D.) believed that the bite of a healthy dog differed from a rabid dog, and rabies could be transmitted from other animals such as wolves and jackals, foxes, and even humans. The disease's incubation period is one week to 6 months and describes the disease's symptoms **[15]**.

Sheikh Mahmoud Shabestari (Iranian poet) (1328-1288 A.D.) writes a poem in "Saadatnameh" about the hydrophobicity of the crazy rabid dog.

In the late 15th century, Muhammad ibn Yusuf al-Harawi (Iranian physician) (1518-1492 A.D.), in his book (Yousefi Medicine) described the symptoms of rabies such as red eyes, salivation, severe movement of the head and neck, holding the animal's tail between the legs. He explained that the dog could not walk easily and dragged its feet. Dogs attack everything and everyone. A person whom a rabid dog usually has bitten shows symptoms similar to insanity after one week. This person escapes from light and water **[15]**.

Methods of treating rabies in medieval Iran

In the Middle Ages, because of the widespread prevalence of rabies in Europe and the Mediterranean, various treatments for rabies were developed by scientists and physicians. Strange methods were sometimes mixed with superstition and were thought to effectively treat or prevent rabies, including removing part of the dog's tongue before rabies and feeding the dog chickenpox or wild roseroot. Putting a dog's tongue in shoes under the toe was said to prevent rabies in humans, or a piece of hyena skin wrapped in cloth was vital prevention. If these methods failed, the rabid patient with hydrophobia had thrown into a pond to drink enough water **[8]**. Besides mentioning the signs of rabies in the third century AD, Philoumenos named the best treatment for burning a sting wound. Because he considers fire more potent than anything that destroys rabies venom, he also said that the injury caused by the bite should be kept open for 40 days to remove the poison **[12]**.

In ancient Iran, rabid dog liver was sometimes grilled and eaten by a rabid person. There is a similar method in the Jewish "Talmud". The Bedouin of Nguyen killed the rabid dog, grilled its liver, and ate the bitten person for 3 to 5 days, depending on the size and number of bite wounds.

Akhawyni emphasized that the bite wound should be left open and recommended substances to cure the wound, and disease, including opium, permanent milk, almond oil, pistachio, pomegranate juice, and Plantago psyllium glaze, sour apple juice, and camphor tablets **[15]**.

Abu Rihan Biruni (1050-973) and Aghili Khorasani, a famous Iranian physician in the 12th century A.D., also recommend using "Abkameh". Abkameh is a mixture of dry bread made from wheat or barley soaked in water, put to evaporate in the sun, and celery seeds, cinnamon, and Dianthus Barbatus are added. They also fed the patient the seeds and whole plant of Allusen (probably fennel) and

placed the whole plant on the bite wound. Heracleum persicum and Asafoetida were also used for treatment. In popular culture, the water of some springs helped heal the rabid. During a trip to Khuzestan in 1882, Najm al-Mulk mentioned the severe rabies outbreaks in dogs and humans and said that a physician used an insect extract called Cantharis in humans and animals as a medicine. Abu Rihan al-Biruni also quotes Ali ibn Abbas Arjani as saying, "The dried liver of a mad dog, benefits the bite of a mad dog" **[12,16]**.

Four Iranian and Islamic encyclopedias of traditional medicine were written in Iran for about three centuries. Abu Bakr al-Razi (Rhazes) (925-854 A.D.), the author of the first Iranian and Islamic encyclopedia of traditional medicine, Alhavi in Medicine, has various views on rabies treatment. In this book, he described the signs and symptoms of this disease. In the book Alhavi, quoting the Greek physician, pharmacist, and botanist Dioscorides (40-90 A.D.), he said that to cure a mad dog bite, a bitten person burned the crab and ate three ounces of it with 1.5 ounces of cinnamon. Mix and eat with wine for three days. He also described crab consumption with cinnamon and frankincense to treat rabid dog bites as impressive.

Razi has recommended that if a few days have passed since the dog was bitten, the amount of burnt crab ash should be doubled. Elsewhere in this book, Razi, referring to the usefulness of the pomegranate plant, describes its consumption of gum, very sour vinegar, and olive oil as the definitive cure for rabies in bites. Razi believed that sardine extraction or pickle would effectively treat mad dog bites if consumed as a poultice. Razi also mentions the treatment of mad dog bites with clay, wine, and water or honey alone (Alhavi, Rhazes). In his book "Man la yazharo al-Tabib," Razi mentions substances as a poultice for wounds, including onions, garlic, and ginger. He also suggested that a combination of camel urine, licorice, frankincense, and Cuscuta can be used before the onset of symptoms. Epithymum has been used to treat bite wounds, and it is recommended to inflate the wound caused by rabid dog bites to remove blood from it **[15]**.

Ahvazi or Haly Abbas (994-930 AD), in the second encyclopedia of Iranian and Islamic traditional medicine, Kamel-al Sanaeh uses Razi's ideas to explain the clinical symptoms of rabies **[3]**.

According to Ibn Sina, who cited Avicenna's Canon of Medicine in the Third Encyclopedia of Iranian and Islamic Medicine, to prevent rabies, a rabid person should keep his wound open immediately after the bite for up to 40 days, and the blood at the bite site must be taken out. He recommends ointments to keep the wound open and placing rabid dog liver on the bite wound as a treatment. It is now known that rabies antibodies are present in the blood of rabid dogs. Anti-rabies immunoglobulin, systemic use in humans, and used for local injection at the edge of the bite wound. It leads to inactivated immunization and reduced post-exposure mortality **[13]**.

Jorjani, in the fourth encyclopedia of Iranian and Islamic traditional medicine, Zakhireye khwarazmshahi has mentioned the words of his predecessors, which are given in three encyclopedias **[3]**.

In the Zoroastrian Bible, the Avesta (200-400 AD), rabies prevention is also mentioned **[14]**.

Discussion

Humans have lived with animals and become acquainted with animal diseases for at least 14000 years (even about 32000 years). By examining the tablets leftover from the Sumerian civilization, which is one of the existing civilizations in ancient Iran, the familiarity of the people of that time (4000 years ago) with the disease transmitted from animal to human (rabies) has been determined [**11,17]**.

The results showed that rabies in Iran and the ancient and medieval world had a similar situation. Iranian scientists' general ideas and theories and the treatments they invented were similar. Based on some superstitions, people consider rabies as the existence of a devil in a rabid animal. However, it was believed that the bite of a rabid dog caused human rabies. As noted, scientists then developed most rabies treatments based on herbs, rabid liver, burning of the bite wound, keeping the bite wound open, and bleeding from the wound site. About eight centuries ago, Ibn Sina pointed out that rabies could be transmitted through the saliva of a rabid animal. The findings of Francois Magendie (1783-1855) and Georg Gottfried Zinke (1771-1813 AD) in the nineteenth century confirmed the Avicenna hypothesis. Ibn Sina also

discusses passive immunization, which has led to advances in medieval medicine.

During the three centuries in which four encyclopedias of traditional medicine were written in ancient Iran, progress in medicine was slow; no significant difference was found in the opinions of the four scientists. In non-sources of traditional medicine, among Iranian scientists cannot find any document that related the disease to superstitions. In addition, there has always been an external cause for its occurrence. However, since human knowledge was insufficient, rabies was considered the toxic saliva of rabid animals and transmitted to humans and animals. Besides the ancient wisdom and attitude about rabies in the sources of traditional Iranian medicine, Iran has played a significant role in new scientific developments related to rabies.

Table 1: A summary of rabies treatment methods in ancient Iran

Inventor of therapeutic methods	**Treatment method**
Rhazes (9th century A.D.) and Avicenna (10th century A.D.)	Leaving the sting open and pulling blood out of it
Abu Rihan al-Biruni (10th century A.D.) - Aghili Khorasani (18th century A.D.)	Abkameh mixture ،Heracleum persicum & Asafoetida
Quoted from Najm al-Mulk (19th century A.D.)	Insect extract of Cantharis
Bedouins in ancient Iran	Eating grilled liver bites rabid dogs
Quoted from Ali Ibn Abbas Arjani (10th century A.D.)	Use rabid dog dried liver
Avicenna (10th and 11th centuries A.D.)	Put rabid dog liver on a bite wound
Rhazes (9th century A.D.)	Dressing of onion, garlic, ginger and using a combination of licorice, camel urine, Frankincense, Eftimone on the bite wound before the onset of symptom. Burnt crab ash and cinnamon with wine or frankincense Pomegranate gum with sour vinegar and olive oil A mixture of clay, wine, and water Honey
Jorjani (10th century A.D.)	Opium, milk, almonds, pistachios, pomegranate juice, spearmint glaze, sour apple juice, camphor tablets

On November 14, 1881, after establishing the Pasteur Institute by Louis Pasteur (1822-1895) as an anti-rabies center in Paris, the Iranian government met in October 1919 with Professor Emile Roux, the director of the Pasteur Institute in Paris. About three years after the meeting on January 20, 1921, René Legro signed an agreement with the Iranian Foreign Minister for technical cooperation between the two countries on behalf of the Pasteur Institute in Paris. Therefore, the Pasteur Institute of Iran, headed by Joseph Menar, provided public health services for preventing and treating infectious diseases. Since then, the official activity of the Pasteur Institute of Iran has begun **[7]**. Two years after establishing the Pasteur Institute of Iran, the National Center for Reference and Research on Rabies Reference of the Pasteur Institute of Iran was established under Dr. Mehdi Ghodsi as needed to control and treat this disease in Iran. In 1955, Dr. Ghodsi, Dr. Baltazar, and Dr. Bahmaniar could change the rabies vaccination process globally. The rabies Department of Pasteur Institute of Iran was selected in 1956 in cooperation with the World Health Organization. Since 2014, according to standard certificate 15189 by the Health Reference Laboratory as a rabies reference laboratory of the Ministry of Health, Treatment and Medical Education and Veterinary Organization **[2]**.

Carrying out a detailed study to identify rabies reservoirs in Iran's nature is one of the first steps of the National Center for Reference and Research on rabies in collaboration with the Veterinary Organization and the Environment Organization.

Currently, rabies is a health-economic problem in Iran, and almost all provinces are more or less affected by this disease. Most cases of this disease are observed along the Caspian Sea in the northeast and southwest of the country. According to statistics from rabies pre-death data from the National Center for Reference and Research on rabies of the Pasteur Institute of Iran, 5 to 11 people die annually from rabies in Iran. Due to the prevalence of this disease throughout the country, preventive measures should be taken in all provinces **[7]**. Given the high prevalence of rabies in the wild, it is undoubtedly a practical step in controlling rabies **[2]**.

Our understanding of rabies's mechanisms of primary and secondary prevention in animals and humans has changed profoundly since introducing Sumerian law, one of the first known civilizations. However, tools and concepts such as the first attenuated vaccine and the first post-exposure prevention regimen (PEP) were developed to control rabies in the late nineteenth century; there has been no progress in treating etiology. Rabies has not been developed and has disabled veterinarians and physicians caring for animals or patients with symptomatic rabies as much as their counterparts in Mesopotamia 40 centuries ago. Today, vaccination of dogs and timely and effective prevention after exposure to rabies are effective ways to control rabies proposed by the WHO. The World Organization for Animal Health, WHO, and the Food and Agriculture Organization of the United Nations (FAO) are currently working to eradicate rabies transmitted by dogs worldwide by 2030. In Iran, in addition to trying to vaccinate all dogs, an urgent effort is needed to produce a WHO-approved vaccine (and immunoglobulin) that is geographically and financially suitable for the rural population most vulnerable to rabies.

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