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Recombinant vaccines in the control of tick-borne diseases: a systematic review

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ABSTRACT

Introduction: Ticks are important ectoparasites that eat blood from various animals and sometimes human hosts and this eating causes direct disease or transmission of microorganisms. Investigation and reporting of human bites, vaccines, and treatments can be effective in preventing and promoting human health. Therefore, this study investigated recombinant vaccines for the control of tick-borne diseases.

Materials and Methods: The necessary data for this review were obtained solely from the research articles published by 2022 based on databases including the Iran Research Information System, SID, Magiran, PubMed, Web of Science, Scopus, and Science Direct.

Results: This study showed that the extraction of numerous articles in the regulation of many types of recombinant vaccines, ticks, and tick-borne diseases is important.

Conclusion: Tick-borne diseases are an economic and health problem in the world and have many destructive effects on humans and animals. Recombinant vaccines are available to control a variety of mites and some tick-borne diseases such as Lyme disease, encephalitis, and Crimean-Congo fever. However, new vaccines need to be developed to reduce tick pathogenicity.

Keywords: Recombinant vaccine, Ticks, Antigen, Disease.

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1. Introduction

Ticks belong to the arachnid order and the Acarina suborder and are obligate blood-sucking ectoparasites that are parasites of birds, mammals, reptiles, and amphibians. Ticks are a great danger for humans and livestock and are considered an economic health problem in tropical and subtropical regions of the world. Ticks are divided into four main families: *Ixodidae*, *Argasidae*, *Nuttalliellidae*, and *Laelaptidae* (1-3). Out of a total of 900 types of ticks that have been identified, most of them belong to the two families of *Ixodidae* (hard ticks) and Argasidae (soft ticks) (Figures 1–4). Out of this total, more than 700 species are related to the *Ixodidae* family, and 193 species are related to the *Argasidae* family. The Ixodidae family is divided into seven main genera: *Amblyomma*, *Dermacentor*, *Haemaphysalis*, *Ixodes*, *Hyalomma*, and *Rhipicephalus*, and the *Argasidae* family is divided into two *genera*, *Argas* and *Ornithodoros* (4, 5).

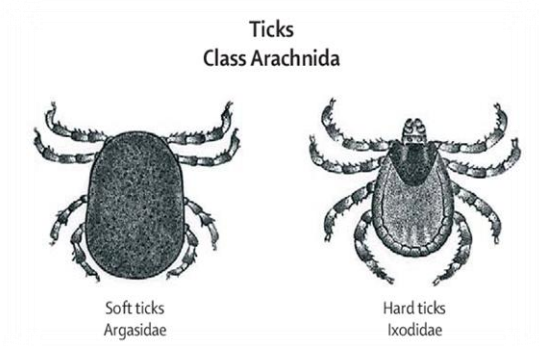


Fig. 1. The two main families of hard and soft ticks (4).

Although ticks are among the most important carriers of bacterial (*rickettsial*), viral (Congo hemorrhagic fever), and parasitic (babesiosis) diseases in humans (3, 5-7), ticks can cause common complications in humans and animals by secreting their saliva and salivary poison. The release of tick saliva in the host body, which is associated with various disorders (Figure 2), and the inhibitory enzymes of saliva are divided into 3 categories, which include: 1-Kunitz, including anti-hemostatic enzymes, which together with several other proteins of coagulation and aggregation Platelets prevent; 2-serpins; and 3-cystatins are two large protein-enzyme families that have a wide role in the anticoagulant and immunological activity of the host. These two families inhibit the innate and acquired immune systems, including inhibition of the complement system and other disorders in the host. On the other hand, today, in extensive research, tick saliva compounds are used for therapeutic and medical purposes due to their anti-immunological and anticoagulant properties (8, 9).

When the tick feeds on blood from the host, enzymes and toxins are released from the tick's saliva to the host, which is sometimes associated with fatal diseases in the host. Tick paralysis disease, or tick poisoning, which is associated with neurological disorders, is an example of these diseases. The first case of this disease was recorded in Australia in 1824. Tick paralysis disease is caused by blood feeding and the secretion of saliva and tick toxins in animals and humans, which are accompanied by symptoms of muscle weakness, acute ataxia, and acute flaccid paralysis. This disease is confused with Guillain-Barre syndrome, botulism, and some other neurological disorders such as transverse myelitis due to the similarity of its clinical manifestations (Table 1). The cause of this disease is more than 40 species of ticks from 10 genera of hard and rarely soft ticks. Most of these ticks are female, and a limited number are male. Unlike hard ticks, soft ticks cause tick paralysis in immature stages (10–12).

The control of ticks and pathogens transmitted by ticks has been of interest to medical and veterinary researchers for a long time; however, the control of the transmission of pathogens transmitted by ticks in humans is due to the large number of tick hosts, the multiple life cycles of ticks, and the use of numerous animal products. (7, 11).

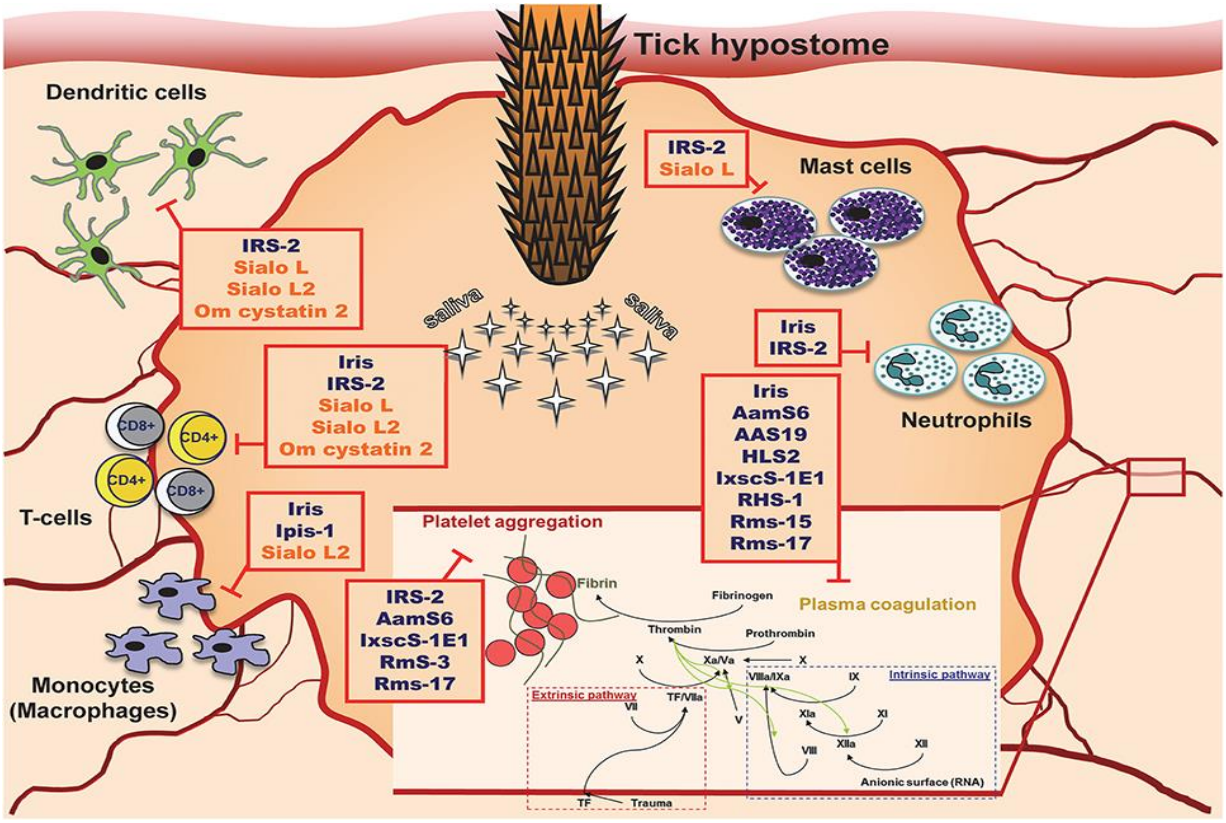


Figure 1. The types of proteins and antigens secreted by ticks, which play a role in controlling and inhibiting different body systems (such as the immune system, complement system, blood coagulation system, and inhibiting different functional enzymes of the body, such as serine protease) (8).

The challenge is fundamental. On the other hand, knowing the ecology of local species of ticks, knowing the types of diseases transmitted by ticks, and isolating suspected and known carriers of diseases transmitted by ticks play an important role in controlling and reducing these diseases. (7, 11).

The use of spraying poison methods plays a part in controlling ticks, but despite ticks' resistance to toxins, ecosystem instability, and side effects in livestock and livestock products, scientists turned their attention to a newer approach: recombinant vaccines. The use of saliva compounds and different tick antigens can be used with the approach of treatment and prevention. This approach is more compatible with the environment. Recombinant vaccines against ticks and tick-borne diseases are prescribed to humans, livestock, and other wild animals and rodents today due to the reduction of tick populations, the reduction of tick-borne diseases, and the few side effects they have (9, 13). The use of vaccines to prevent and control diseases has been one of the greatest achievements in medical history. After the introduction of vaccines against infectious diseases, the World Health Organization (WHO) reported significant reductions in mortality and morbidity due to vaccine stability. In general, vaccines are divided into 3 generations based on the development process, and there are specific characteristics and coverage spectrums in each generation (14).

The first generation of vaccines, which includes live and inactivated vaccines, is used in this generation of vaccines to stimulate the immune system against live and weakened pathogens. second-generation vaccines, which include recombinant, subunit, and conjugate vaccines. The basis of this generation of subunit elements is recombinant or synthetic proteins, which

Table 1: Clinical manifestations of tick-borne diseases examines tick-borne paralysis with diseases such as Guillain-Barre syndrome, cervical spinal cord injury, botulism, and polio from the point of view of clinical manifestations (10, 12).

Symptoms	Tick paralysis	Guillain-Barre syndrome	Cervical spinal cord injury	Botulism	Polio
Ataxia	Has	Does not have	Does not have	Does not have	Does not have
Ophthalmoplegia	Has	This syndrome is observed in Miller's type	Does not have	Often has	Does not have
Fever	Mild or none	Rarely	Does not have	Often has	Has
Cerebrospinal fluid protein levels	Normal	Above 40	Ascending	Normal	Above 40
Exanthema (rash)	May be	Does not have	Does not have	Does not have	Does not have
Plantar reflex	Does not have	Does not have	Has	Does not have	Does not have
Pathway of neuromuscular paralysis	Ascending	Ascending	Ascending	Ascending	Ascending

include different molecules and epitopes from different species and pathogenic strains (14). The potentially immunogenic administration of a plasmid containing an antigen-encoding gene, known as a genetic vaccine, is classified as a third-generation vaccine and is a valuable method that has been the focus of researchers since the early 1990s. Different names have been given to these types of vaccines, such as DNA vaccine, RNA vaccine, and plasmid vaccine. In 1996, the WHO Expert Committee on Vaccination chose nucleic acids containing both DNA and RNA vaccines (14).

According to the Fuente et al. study, the only commercial vaccine against ectoparasites to control cattle tick infestation was produced and registered in the 1990s. These vaccines were made based on BM86/95 recombinant antigens of the Rhipicephalus microplus tick and showed advantages such as cost-effectiveness, environmental friendliness, and the dual effect of reducing tick infestation and tick-borne diseases. This BM86/95 recombinant vaccine antigen controls ticks and some tick-borne diseases, such as the disease caused by the bacterium *Borrelia burgdorferi* and the *protozoan Babesia*, which causes Lyme disease and Babesiosis (15).

Based on another study by Fuente et al. confirming the BM86/95 recombinant vaccine, this study investigated several other recombinant antigens that play a role in controlling different types of ticks and tick-borne diseases, such as the recombinant antigens TROSPA, SUB, RAS, 64P, OSPA/C, and other antigens made as recombinant vaccines. Most of these vaccines were in the laboratory stages, and several types of them entered the clinical stages and mass production. For example, the SUB antigen, which plays a role in the control of ticks of the genus *Ixodidae* and *Rhipicephalus*, and tick-borne diseases such as anaplasmosis, borreliosis, Lyme disease, and babesiosis can be mentioned (16).

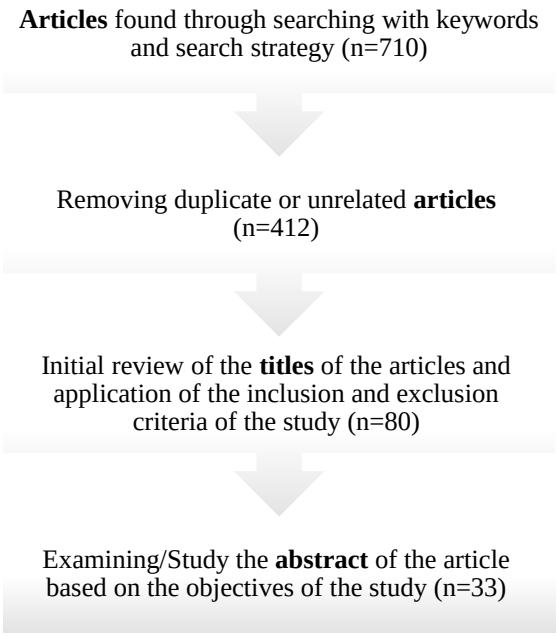
A review study was conducted by Clark et al. in 2008 and investigated the types of vaccines that play a role in the control of communicable diseases. The recombinant OSPA vaccine, which has more than one role in the control of borreliosis disease, can produce antibodies in the host's body. In the endemic areas of this disease, bacteria are transmitted to the host through the tick's saliva by sucking and sucking blood, and the host's body produces antibodies against them and destroys them. On the other hand, the antibodies produced in the host's body

are transferred to the ticks and the bacteria present in the ticks, preventing their transmission to the next host. Several vaccines have been developed in Austria, Germany, and Russia to control the encephalitis virus, which is caused by *flaviviruses*, which play a role in controlling this disease.

The vaccine, which was first developed in Austria in 1976 and entered the clinical stage, was associated with an 86% reduction in cases by 2001, although there were few side effects in children. These vaccines, which had reached mass production in three countries, require three stages (first day, seventh day, and twenty-second day) of injection to produce antibodies in the host's body (17). In addition, other vaccines have been made to control transmitted diseases, which are mostly in the laboratory stages. This study also examines the types of recombinant vaccines used in the control of tick-borne diseases.

2. Material and methods

In this systematic review study, to investigate recombinant vaccines in the control of tick-borne diseases, articles indexed in databases including Iran Medical Articles, Magiran, SID, Web of Science, PubMed, Scopus, and Science Direct were collected. Articles were reviewed using English keywords: tick vaccine, vaccine of tick-borne disease, anti-tick vaccine, prevention of tick, and recombinant vaccine between 2008 and 2022. The inclusion criteria of studies in this study were a written original article and a study on vaccines, and the exclusion criteria of studies, review articles, and inconsistencies with the purpose of the study were determined. Articles related to the category and similar articles in different and unrelated databases were excluded from the study. Then, a checklist of the information in the selected articles, including the name of the researcher and the year of conducting the study, the location of the study, and the type of study, was prepared. At the end of the search, 80 articles were obtained, and after reviewing the abstracts of the articles, finally 36 articles were reviewed.



3. Results

The results of this study have been discussed concerning the investigation of recombinant vaccines for the control of tick-borne diseases. Several studies have investigated recombinant vaccines for the control of ticks and tick-borne diseases. Tick saliva contains various substances and enzyme compounds that play a role in suppressing the immune system and creating immunity in the body.

Using these antigens, researchers made recombinant vaccines to control all kinds of ticks. Inhibiting the attachment of ticks to the host and disrupting their feeding, in addition to reducing the tick population, can be important in controlling the transmission of tick-borne diseases, especially the encephalitis virus. Ticks attach to the host's skin using protein 64P (cementing); this protein was first isolated from the tick *Rhipicephalus appendiculatus* (13).

The recombinant form of this protein in the form of a recombinant vaccine prevents ticks from attaching to the skin surface, and on the other hand, the administration of these vaccines to mice, hamsters, rabbits, and guinea pigs has

reduced the transmission of encephalitis virus disease (13, 18). SUB antigen is a molecule that protects the tick from the host's immune system (innate and acquired) and plays a role in the reproduction and spread of ticks. The vaccine or its recombinant antigen can be effective in controlling all kinds of ticks and diseases, such as Lyme and Babesiosis, *Anaplasmosis*, and *Ehrlichiosis*, but it does not play a role in controlling encephalitis virus disease (Table 2) (16, 18).

The TROSPA protein is a receptor in the tick intestine for the surface protein of the bacterium *Borrelia burgdorferi*, the causative agent of Lyme disease. The TROSPA recombinant vaccine, in addition to reducing the control of *Rhipicephalus* and *Ixodes* ticks, can cause the destruction of bacteria in the host and the intestines of ticks. Other recombinant antigens such as tHRF, TSPI, Salp25D, and TROSPA play a role in controlling Lyme disease, and Silk, RAS, and Sialo L2 play a role in controlling babesiosis and anaplasmosis (13, 16, 18).

Crimean-Congo hemorrhagic fever (CCHF) is a deadly disease with a death rate of over 30% all over the world, the common symptoms of which are severe bleeding and high fever (23, 24). The cause of this disease is a single-stranded RNA virus from the genus of nairoviruses, which is transmitted to the host by the Hyalomma tick carrier (25, 26). For the first time in 1974, an inactive vaccine from the mouse brain was prescribed to control patients, which led to the control and reduction of disease cases. However, another vaccine was made in Bulgaria in 1981 by BulBio-NCIPD Ltd. from the CCHFV V42/81 strain that was isolated from the patient's sample. This vaccine is administered in three doses: on the first day, on the 30th day, and the third day, one year later. The booster dose of this vaccine is prescribed once every 5 years (23, 27, 28). Recently, many recombinant vaccines based on the nuclear proteins and glycoproteins of these viruses, which play the main role in the multiplication of the virus and the host's immune system, have been candidates for the control and reduction of this disease and are in the laboratory and clinical stages (27, 28). Encephalitis, or meningoencephalitis, is caused by the flavivirus, which is characterized by meningitis and flu-like symptoms (29). The carriers of this virus are Ixodes ticks and *Dermacentor*, which cause common disorders in the brain and central nervous system. The first-generation vaccine was made in China. The first-generation vaccine was prepared from strains of the virus isolated from deceased patients, and the virus was grown in the brains of mice to make the vaccine and was isolated from the tissue of mice after inactivation by formalin. A few years later, the vaccine was isolated from chicken embryos. However, due to the side effects of the mouse brain vaccine and the instability of the chicken embryo vaccine, these two vaccines were withdrawn from the market. The second-generation vaccine, which was isolated from primary hamster kidney cells, is available today and works well. However, there is no information about its effectiveness, side effects, or vaccination rate in China (30). A recombinant OSPA/C vaccine is commercially available for the control of Lyme disease. It is derived from the surface protein of the bacterium *Borrelia burgdorferi*, which plays an important role in binding bacteria in the tick's gut. By targeting this bacterium by using the recombinant vaccine for this antigen, this bacterium can be controlled and reduced in the host's body and the intestines of ticks (17).

4. Discussion

Ticks are obligate blood-sucking arthropods that feed on vertebrates and are of medical importance due to the transmission of dangerous and common pathogens.

Table 2: The summary of recombinant vaccines shows the recombinant vaccines that play a role in the control of ticks.

Vaccine antigens	Tick	The host	References
Bm86/bm95	*Rhipicephalus microplus, R. Annulatus, r. Decoloratus, R. Sanguineus, Hyalomma dromedarii*	Cow, camel, dog, deer	(13, 19)
Subolesin/akirin chimeras	*R. Microplus, r. Annulatus, ixodes scapularis, i. Ricinus, hyalomma spp., haemaphysalis spp., amblyomma americanum, d. Variabilis, d. Reticulatus*	Cow, sheep, deer, rabbit, mouse	(16, 18)
Metalloprotease	*R. Microplus*	Cow	
Ribosomal protein p0	*R. Microplus*	Cow	(16, 20)
Microplus ferritin 2	*R. Microplus. R. Annulatus, i. Ricinus*	Cow, rabbit	
Microplus aquaporin	*R. Microplus, i. Ricinus*	Cow, rabbit	
Microplus silk	*R. Microplus*	Cow	
Trospa	*R. Microplus, i. Scapularis*	Cow, mouse	(16, 21)
Serpins (ras)	*R. Appendiculatus*	Cow	(16, 22)
Protein 64p	*R. Appendiculatus, i. Ricinus*	Guinea pig, hamster, rabbit, mouse	(16, 18)
Salivary protein (salp) salp15	*I. Scapularis*	Mouse	(16, 21)
Salp25d	*I. Scapularis*	Mouse	(16, 18)
Tick histamine release factor (thrf)	*I. Scapularis*	Mouse	
Tick salivary lectin pathway inhibitor (tspi)	*I. Scapularis*	Mouse	
Byc, vtdce and gst	*H. Longicornis*	Cow	(13)
Brrm-mp4	*R. Microplus*	Cow	
Omc2	*Ornithodoros moubata*	Mouse	(13, 19)

In particular, ticks are carriers of many types of livestock and human diseases worldwide, which cause many economic and health problems (31, 32). To complete the meal from the host's blood, the ticks must pass the barrier of the host's immune system or suppress the host's immune response. Escape from the host's immune system is mainly done through the salivary secretions of ticks, which are secreted into the cavity of the tick's feeding place in the host's body. Tick salivary secretions are a large multigene protein family containing more than 200 individual members that differ only by a few amino acids. A small number of these proteins have been identified from the point of view of specific function and structure and have been made recombinantly (33).

By using the available antigens in the design of all kinds of recombinant vaccines, many tick vaccine candidates have been made. The

recombinant BM86/BM95 vaccine has reached mass production in the control of ticks and some tick-borne diseases and has a significant effect in reducing the population and reproduction of all types of ticks and reducing pathogenic factors such as Lyme disease and babesiosis (19). SialoL2 antigen is an important tick salivary protein that has a wide role in controlling and inhibiting the host's immune system (inhibition of T cells, dendritic cells, mast cells, monocytes, and macrophages).

The production of the SialoL2 recombinant vaccine and its administration to a guinea pig caused a large production of antibodies against ticks and reduced the population of ticks (33). Serine protease has a wide role in blood coagulation (such as factor nine), the immune system, and body function regulation. Neutrophils, mast cells, natural killer cells, and cytotoxic T cells all produce serine proteases, which are responsible for extracellular matrix regeneration, killing microbes, and cytokine activation. Sometimes the secretion of this substance also carries pathogenic agents. Neutrophil proteases from azurophil granules, namely cathepsin G, elastase, and protease 3, play an important role in the antimicrobial activity of neutrophils and are essential for the clearance of some pathogens. Ticks secrete a large number of serine protease inhibitors (serpins) into the host's body through their saliva, which can inhibit this enzyme and disrupt the functioning of the host's body (8).

A recombinant vaccine based on this antigen reduced the population of ticks and controlled some pathogenic factors in the host (16). The efforts of scientists and researchers in designing vaccines to effectively control all types of pathogens from ticks from the second half of the 20th century to today have not been without results. Many types of vaccines have been designed to control tick-borne diseases and have been entered into laboratory and clinical trials. In the meantime, the Lyme disease recombinant vaccine uses bacterial surface antibodies (17), meningoencephalitis (30), Crimean Congo fever, of which many types have been made over the years (27, 28), and Ehrlichiasis and Babesiosis can be mentioned, which played a role in the control of these diseases from different parts of pathogenic agents or artificially combined in making vaccines (16, 18).

Conclusion

Several vaccines have been designed to control all types of ticks, with the aim of including proteins and tick antigens. In Table 2, there are several available recombinant vaccines, a limited number of which (such as BM86 and BM95) are in the clinical stages of mass production, and a large number of them are in the laboratory stages. However, the recombinant vaccine has been able to control and reduce a wide range of ticks and some tick-borne diseases. Although these vaccines have played a significant role in the control of pathogens in the host, they did not receive the attention of the world due to several reasons (high cost, several booster doses, and sometimes side effects). But today, these vaccines are prescribed to people in high-risk areas, people working in livestock, farmers, and people in endemic areas of that disease. In general, it can be concluded that despite the advancement of technology and the knowledge of numerous pathogenic agents and their genomes, ticks and their harmful effects on health and the global economy are still a problem.

Suggestions

This review study examines recombinant vaccines for the control of ticks and tick-borne pathogens. There are several problems in identifying the salivary and secretion proteins of ticks and tick-borne agents in molecular form. The molecular identification of these antigens facilitates the development and design of new recombinant vaccines.

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