Chapter 41

Effectiveness of Nanoparticles to Control Ticks and Tick-borne Diseases

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ABSTRACT

Nanotechnology is evolving technology with enormous potential for global revolutionization of animal sector. Ticks are parasitic insects that feed on the blood of vertebrate animals. They are external, and obligate parasites which can cause severe allergic reactions and carry a variety of viruses, bacteria, helminth and protozoans that can affect humans, pets, and livestock. Ticks are ectoparasites that cause skin irritation and injury as well as transmit infections such as tick-borne encephalitis, powassan, borreliosis, lyme, tularemia, ehrlichiosis, anaplasmosis, babesiosis, and theileriosis. The overuse of chemical acaricides (pesticides that kill ticks and mites) is often responsible for the development of fast growing drug resistance in ticks and wide presence of toxic residues in food and ultimately in the environment. Alternatively, plant based acaricides could be used in livestock farming and resistant tick strains, but there are some constraints regarding their commercialization because of quick degradation, less stabilization, and lack of standardization. The availability of vaccines to treat tick-borne diseases is still limited, and the currently available ones showed major limitations in their effectiveness. The metal (copper, zinc, silver, nickel, and gold) nanoparticles synthesized by chemical and biological methods showed broad spectrum of action against ticks parasites and vectors of veterinary importance. Chemically synthesized nanoparticles can be highly toxic to non-target animals due to the presence of hazardous chemicals and their possible side-effects. On the other hand, nanoparticles using plant extracts are easy to prepare, eco-friendly, cost-effective and promising in the control of tick. Nanoparticles effect the immune response of pests, induce oxidative stress, disrupt metabolic processes, and modify proteins or lipids that stop the reproduction and growth of ticks. However nanotechnology-based product against ticks is not available in the market till date.

KEYWORDS		
Nanoparticles, Ticks, Ticks born disease, Control strategies, Photochemical	Received: 30-Jun-2024 Revised: 14-Jul-2024 Accepted: 21-Aug-2024	A Publication of Unique Scientific Publishers

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INTRODUCTION

Nanotechnology is the innovative approach with huge potential for to revolutimize the animal husbandry on the global scale. It offers the same benefits to veterinarians as physicians, including diagnosis and therapy. The nano-applications have the ability to use in animal nutrition, health, reproduction, and yield. It has the ability to solve associated several problems. They are external, and obligate parasites. Ticks have four life stages, egg, larva, nymph and adult. Ticks feed on the blood of vertebrate animals at each stage to survive. Ticks inject saliva into host animals during blood feeding, which contains bioactive substances which includes inflammatory, anti-hemostatic, anti- vasodilator, and immunosuppressive reagents. Mosquitoes considered first while ticks considered as the second most significant vectors of animal diseases globally. Ticks have largest effect on the cattle industry (Estrada-Pena et al., 2008; Peter et al., 2009). Hot and humid environments assist while cold environment hinder the survival of ticks. They are classified into two families,"Ixodidae" and "Argasidae". Because of their capability to spread diseases to humans and animals, ticks had long been studied for their medicinal and to discover viable treatment options. Several examinations on the threats of TBDs have basically focused on a few variables such as precipitation, temperature, and humidity of environment and hygienic condition .It has been reported that certain conditions of precipitation affecting humidity and temperature might impact tick load in animals. Moderate rain and high humidity give conducive micro climatic conditions for mass proliferation of ticks and higher rate of infestation (Khan et al., 2016).

Effect of Ticks on Livestock

Ticks can cause severe allergic reactions and along with various viruses, bacteria, helminth and protozoa that can affect animals badly. Ticks are cause skin irritation, injury and transmit infections such as tick-borne encephalitis, powassan, borreliosis, lyme, tularemia, ehrlichiosis, anaplasmosis, babesiosis, and theileriosis. Being second to mosquitoes, ticks disseminate broader variety of pathogens as compared to any other than blood feeding, insects on a global scale, hence impacting pets, wildlife, livestock, and humans. From the centuries tick bite protection largely relies on the utilization of synthetic insecticides and bio-pesticide. Tick-Borne Diseases (TBDs) impact 80 percent of the world's cattle population, posing a serious threat to worldwide livestock production. However developing countries are suffering from this issue at higher rates because of a long list of associated risk factors of TBDs. Ticks cause enormous economic losses and have several detrimental impacts on the infected animals because anemia, reduced weight gain, and impair the quality of skin (Dantas-Torres et al., 2017). Blood sucking behaviour of ticks may cause transmission of protozoan and helminth parasites.

Control Strategies

To control the ticks, various measures have been adopted as described in fig. 1. Firstly, Chemicals were employed to control the ticks. Chemical, can be divided into groups and have played a significant role in ticks control activities. But repeated and improper exposure of chemicals to infected animals have result into developed of resistance in the tick. Further residues of the chemicals in the milk and meat can pose threats to the human health. These both have serious concerns need to be resolved alternately. Secondly,Plants have been shown to have anti-tick properties in laboratory but plant base acaricides are not available for commercial use (Theron and Magano, 2022). Thirdly, a vaccine against ticks was developed using a recombinant antigen (Willadsen, 2006). Vaccines against numerous tick species may be developed by utilizing antigens that cause immunological cross-reactions with distinct tick species. Vaccines containing a mixutre of essential and different protective antigens may significantly improve effectiveness ofvaccination or immunization (De la Fuente and Kocan, 2006). Lastly, nanobiotechnology is an emerging and unique way of controlling and combating ticks. Iron, nickel, zinc, copper, and silver are key metals nanoparticles have been proposed as anti-tick agents (Norouzi et al., 2019; Underwood and Van Eps, 2012).

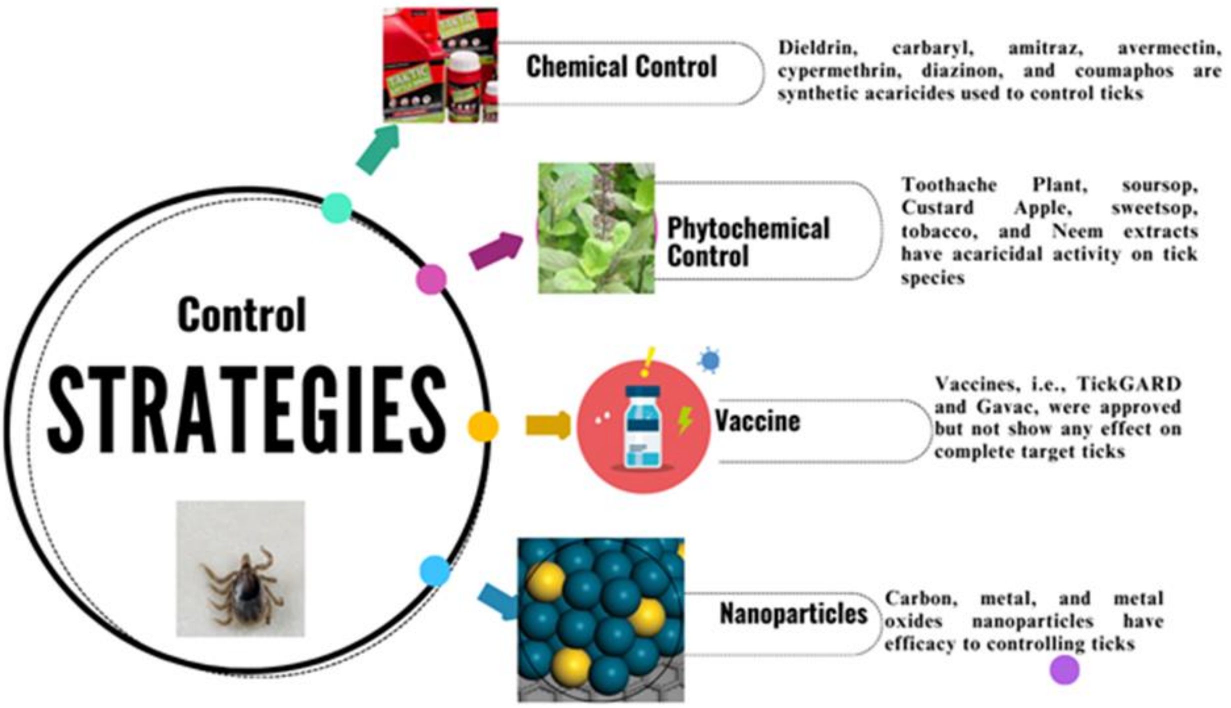

Fig. 1: Control Strategies

Chemical Control

Ticks are causing deterioration of the animal's health and reducing their productivity. Controlling ticks is highly required for the wellbeing of animals and earning the livelihood by cattle rearing communities. The chemical acaricides have been used extensively for their promising results in controlling cattle ticks. But the use of synthetic acaricides have certain side effects including poor and meat quality, and development of resistant in ticks (Reck et al., 2014).
Due to these reason several organochlorine chemicals are banned in various developed countries.

Frequently, lindane and dieldrin, carbaryl, amitraz, avermectin, cypermethrin, diazinon, and coumaphos are synthetic acaricides used to control the ticks. These effect on the nervous system of ticks and cause cell death (Chen et al., 2007; Li et al., 2003).

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Phytochemical Control

Many plants, mostly from the Lamiaceae family, showed acaricidal and repellent effects. Plant base acaricides could be used in organic farming and against resistant tick strains, but there are several constraints toward their commercialization related to their degradation, stabilization, and standardization.Over 200 plant species have tick-repellent and acaricidal properties. Essential oils, extracts, and allelochemicals of plants used to control the ticks. Methods like steam distillation, hydrodistillation, microwave-assisted extraction, maceration, sonication and methanolic extraction are used. Toothache Plant(*Acmella oleracea*), soursop (*Annona muricata*), Custard Apple (*Annona squamosa*), sweetsop (*Annona muricata*), Tobacco (*Nicotiana tabacum*), and Neem(*Azadirachta indica*) extracts have been tested for their acaricidal activity on various tick species and life stages. Medicinal plants demonstrated strong acaricidal effects against several tick species, but their exact mode of action is not fully understood (Quadros et al., 2020).

Vaccine

Vaccination characterizes as a nontoxic alternative method for controlling ticks. This method is environmental friendly and does not leave remains in milk and meat. Vaccine based on Bm86 have demonstrated varying levels of effectiveness in different regions worldwide. Vaccine against ticks have different antigen and pP0 antigen showed high effectiveness. Vaccines i-e TickGARD and Gavac were approved but not showed effect on complete target ticks (Freeman et al., 2010). More research is required to improve an effective vaccine against various tick strains and tick borne diseases (Pereira et al., 2022).

Nanoparticles

A nanopesticide is a product that uses nanoscale technology to enhance performance or effectiveness of pesticides.Nanotechnology is the application of materials with at least one size dimension in the range of 1-100 nm. Nanopesticides have a number of benefits in terms of pesticide use such as pesticide active ingredients to improve their effectiveness (Benelli and Duggan., 2018; Naqqash et al., 2016).NPs have been proposed as novel insecticides that have toxic effects on insect parasites and are important to world’s economy(Amerasan et al., 2016; Benelli et al., 2017). Periplasmic manufacturing of metallic nanoparticles using plants and microbe-borne compounds is a cost-effective, one-step process that eliminates the need for hazardous substances (Lok et al., 2007; Kumar et al., 2015). When produced sustainably, carbon, metal, and metal oxides nanoparticles have demonstrated remarkable efficacy against economically important insect pests (Athanassiou et al., 2018). During the formation of oxides of metal and metal nanoparticles in green synthesis methods, chemicals from microbe processes or plant material could potentially work both as stabilizing and reducing agents (Benelli et al., 2017).There was a global trend to evaluate new agents that are effective, safe, inexpensive, easily available, and ecofriendly. Nanotechnology provides new and important tools expected to significant impact in sciences. The polymer-coated metal NPs have recently appeared active in advanced researches. Metal nanoparticles' stability is a major issue, but nanotechnology can enhance their formulation stability, bioavailability, solubility, slow release, and protect in against premature degradation.

Nanopesticides could have the advantage of having little effect on nontargeted organisms and being environment friendly. They can be made using a variety of processes, including chemical, biological, and green synthesis. Advantages of nanoparticle-based pesticide formulations are improved formulation consistency and improved water solubility of active ingredients. Nanoparticles have the ability to release active substances in a sustainable manner and to enhanced stability of substances to avoid early deterioration. All this occurs because of the reduced particle size. As the particle size is reduced surface area become increased hence mobility and insecticidal ability of the used substance increased that leading to greater and long lasting effect.

Nanoparticles against *Hyalomma spp*. ticks

The *Hyalomma spp* of ticks is hematophagous ectoparasite and responsible for transmission of protozoan, bacterial and viral infection in vertebrate animals and humans.*Hyalomma* genus is one of most prevalent ticks in Asia possessing high ecological plasticity.

The use of nanoparticles is considered as a novel approach for the control of ticks. However the development of a green, non-toxic, and environment friendly method for producing metal nanoparticles involves organisms from higher plants. So that metal reduce metal levels (Jayaseelan and Rahuman, 2012). SiO_2-NPs provide new acaricidal compounds for the effective control of *Hyalomma spp*. (Norouzi et al., 2022). Zinc Oxide nanoparticles (ZnO NPs) prepared from neem (*Azadirachta indica*) and lemon grass (*Cymbopogon citratus*) as effective, safer, and eco-friendly candidatures against *Hyalomma* ticks (Zaheer et al., 2021).

Nanoparticles against *Rhipicephalus Spp* Ticks

Rhipicephalus spp ticks are economically important ticks of bovines, acting as vectors for babesiosis, theileriosis, and anaplasmosis. *Rhipicephalus microplus* is the main cattle tick in the developing countries. The parasitic adaptation in *Rhipicephalus* tick vector has made successful parasites of public health importance. *Rhipicephalus* ticks are known for high genetic diversity, enabling them to thrive in different geographical regions of the world. The study investigated the acaricidal activity of titanium dioxide nanoparticles(TiO_2-NPs) synthesized from plant extract against *Rhipicephalus microplus* demonstrating their high stability (Marimuthu et al., 2013).The study found that the ZnO-NPs coated with cypermethrin led to better tick toxicity relative to the ZnS-NPs coating with cypermethrin, at the laboratory scale. There is statistically significant difference among the NPs treatments given at the egg, larval, and adult stages of the ticks (Zaheer et al.,2023). Neem (*Azadirachta indica*) in the form of green silver nanoparticles have better acaricidal activity against *Rhipicephalus* (Boophilus) *microplus* (Avinash at al., 2017).

Table 1: Metal and Metal Oxide Nanoparticles used to Control the Cattle tick *Rhipicephalus* (Boophilus) *microplus.*

Sr#	Nanoparticles	Mode of synthesis	Material used	References
1	Copper	Chemical synthesis	Copper acetate	Ramyadevi et al., (2011)
2	Nickel	Chemical synthesis	Nickel hydrazine	Rajakumar et al., 2013
3	Silver	Green synthesis	Aqueous leaf extract of *Mimosa pudica*	Marimuthu et al., 2011
		Green synthesis	stem aqueous extract of *Cissus quadrangulari*	Kumar et al., 2012
		Green synthesis	Aqueous leaf extract of *Manilkara zapota*	Rajakumar and Rahuman, 2012
4	Titanium dioxide	Green synthesis	Aqueous leaf extract of *Mangifera indica*	Rajakumar et al., 2015
		Green synthesis	Aqueous flower extract of *Calotropis gigantea*	Marimuthu et al., 2013
5	Zinc oxide (ZnO)	Green synthesis	Aqueous leaf extract of *Lobelia leschenaultiana*	Banumathi et al., 2016
		Chemical synthesis	Zinc nitrate and sodium hydroxide	Kirthi et al., 2011

Table 2: Comparative Study of traditional Chemical Synthesis and Green Synthesis of Nanopesticides

Chemical Synthesis	Green Synthesis
Chemically synthesized nanoparticles is costly and eco-unfriendly.	Green synthesis of nanoparticles is cost-effective and eco-friendly.
• Causes long-term environmental harm.	Easily decomposes and minimizing environmental harm.
The size of these nanoparticles varies between 25 and 450 nanometers.	The size of these nanoparticles varies between few nanometers up to approximately 100 nanometers.
Chemical Nanoparticles small size can lead to inhalation risks.	The primary drawback of green nanoparticle synthesis is its low yield.
	(Deepak et al., 2019)

Major Tick-Borne Diseases (TBDs) and Treatment with Naoparticles

Ticks (Acari: Ixodidae) and Tick-Borne Diseases affect the productivity of bovines in tropical and subtropical regions of the world, leading to significant socioeconomic impacts on the livelihood of farming communities.Globally, four main TBDs, namely theileriosis, anaplasmosis, babesiosis and heartwater/cowdriosis affect the bovines, and cause substantial economic losses to cattle industry(Jabbar et al.,2015). As nano-medications have developed in the last four decades, nano-delivery systems have been applied in treating various diseases. Lipid-based nanoparticles (LNPs) drug delivery system shows the most promising potential to cure diseases.Lipid-based nanoparticles have following advantages;

- High level of biocompatibility
- Less biodegradability
- Loading capability
- Immunogenicity (Lu et al., 2023).

Babesiosis

Ticks of the genera *Hyalomma*, *Rhipicephalus*, and *Amblyomma* serve as natural reservoirs for babesia (Homer et al., 2000). Tick fever (Redwater disease) is caused by *B. bigemina* and *B.bovis*, transmitted by the cattle tick *Rhipicephalus microplus* in many parts of the world. *Babesia* species possess complex life cycles that contain various stages in both the mammalian and the tick host (Elsworth and Duraisingh, 2021). More than 500 million cattle are estimated to be at danger of babesiosis globally (Ozubek et al., 2020). Main symptoms are high fever (over 40°C), hemolytic anemia, forced breathing, loss of appetite and weakness (AbouLaila et al., 2021).Human babesiosis is due to *Babesia microti* (Bloch et al., 2019).With the combination of nanotechnology and mass spectrometry, researchers have developed a method to treat acute *Babesia microti* infection. Using nanoparticle tracking analysis, show that there is a range of Extracellular vesicles (EVs) sizes from 30 to 1,000 nm, emanating from the Babesia-infected RBC. Multiple functional implications of EVs in Babesia-host interactions and support the potential that EVs have as agents in disease pathogenesis (Beri et al., 2022).

Theilerioses

Bovine theilerioses are caused by intracellular parasites of the genus *Theileria* are considered as one of the most economically important diseases of bovines globally. *Theileria annulata* and *Theileria parva* are known to be the most pathogenic species in bovines. Nanoparticles i.e Solid lipid nanoparticles (SLN) represent an attractive nanocarrier system for the hydrophobic drug Buparvaquone (BPQ). High accumulation of BPQ-SLN in the reticuloendotheileial system (RES) organs i.e liver, spleen and lungs, suggests the possibility of improved therapy in theileriosis (Soni et al., 2014).

Anaplasmosis

Anaplasmosis is a vector-borne, infectious and non-contagious disease. . Anaplasmosis has a wide range of host, including pets, livestock, humans, and it is distributed worldwide (Karlsen et al., 2020). The disease is caused by various pathogens of the genus *Anaplasma*. The infectious organism invades and destroys red blood cells, causing anaemia, weakness, and sometimes death of organism. The several species cause different types of anaplasmosis depending on which cells that are infected in the mammalian host.Oxytetracycline-loaded Poly-methyl Methacrylate (PMMA) nanoparticles were found to be an effective oral delivery vehicle and also an alternative pharmaceutical formulation in anaplasmosis treatment (SadguruPrasad et al., 2017).

Mode of Action of Nanoparticles based Pesticides on Ticks

Ticks are affected by nanoparticles based pesticides in various ways. Generally, nanoparticles stimulate the pest's immune system, cause oxidative stress, disrupt metabolisms, and change proteins or lipids that inhibit reproduction and growth of ticks as described in fig. 2.

Following nanoparticles based pesticides that are employed against ticks:

Graphene

By creating reactive oxygen species (ROS) graphene induces oxidative stress and cell death. Graphene also may cause enzyme inhibition and degradation.

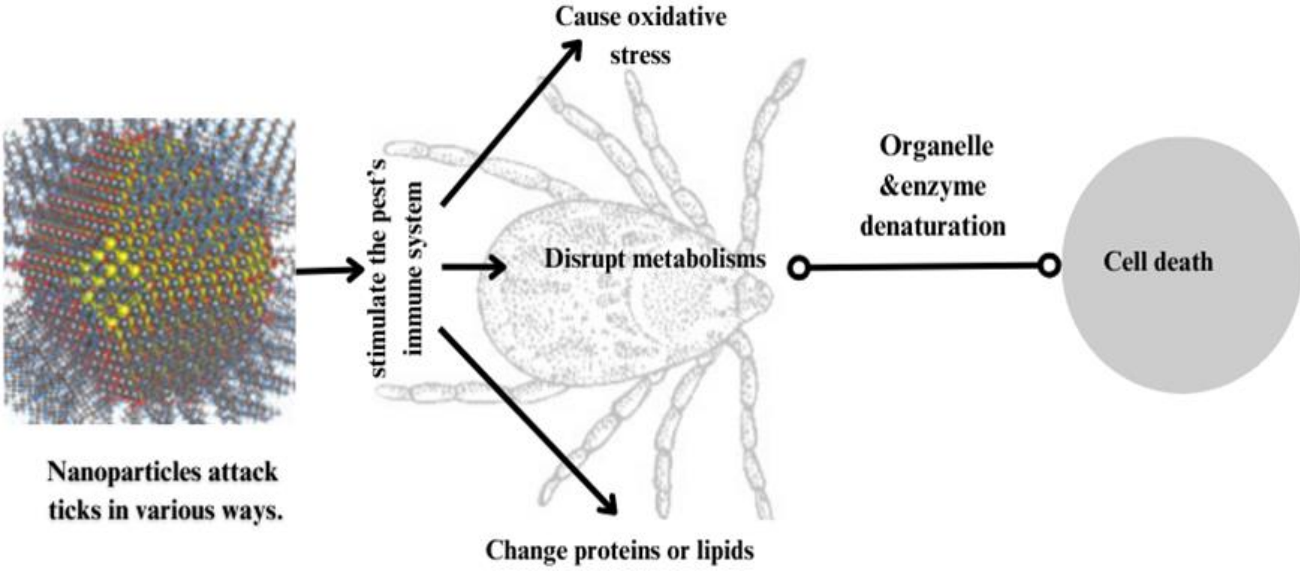

Fig. 2: Mode of Action of Nanoparticles based Pesticides on Ticks

Polystyrene

Polystyrene inhibits the cytochrome P450 isoenzyme through both noncompetitive and competitive mechanisms. Inhibition of enzyme triggers a range of additional processes, the most notable of which is oxidative stress, leading to cellular death.

Silver

Ag-NPs inhibited the activity of acetylcholinesterase. Silver nanoparticles function by binding with proteins and nucleic acids, reducing the permeability of the cell membrane. This is subsequently expanded to enzyme breakdown, which ultimately leads to cellular death. Silver nanoparticles synthesized from aqueous leaf extract of *Manilkara zapota* (Rajakumar andRahuman, 2012) and *Cissus quadrangularis* (Santhosh Kumar et al., 2012) showed the highest mortality rate of ticks.

Gold

Strong bonds are form between the gold nanoparticles and trypsin enzyme leading towards deactivation of malabsorption, poor reproduction and development of tick. Au-NPs can impact growth of ticks by inhibiting enzyme trypsin.

Silicon and Aluminum

Al and Si-NPs bind to tick's cuticle layers, causing the physical uptake of waxes and lipids leading to cell water loss and ultimately cellular death.

Titanium dioxide

Due to smaller size of nanoparticles, easily cross nuclear membrane, effect on the nucleic acids and protein synthesis. Titanium dioxide nanoparticles synthesized from plant impact exoskeleton of ectoparasites and hindering their mobility (Baun et al., 2008). TiO2-NPs synthesized from Crown Flower (*Calotropis gigantea*) showed 100 % mortality of ticks (Rajakumar et al., 2015).

Future Perspectives and Research Challenges

The potential negative effects of nanoparticles on the environment are yet unknown, and determining the dispersion and behavior of nanoparticles both during and after application towards the environment is crucial for understanding their potential influence on the ecosystems. The nanoparticles could be a promising tool against ticks and tick-borne diseases owing to the small and fine particle size causing the oxidative stress and cellular injury in non-mammalian cells only (Benelli, 2018). However as compared to widely used chemical acaricides, the process of nano-based acaricides may be more challenging (Arafa et al., 2019).The acceptability of conventional farmers, costs required to rationalize the dose and routes of administration, and labour expertise for nanomaterial synthesis and study of nano-acaricides. These are among few challenges associated with the usage of NPs to control ticks and tick-borne diseases. However, these factors may not restrict the application of nanomaterial's arised from the pre-existing chemical acaricides. Even though nanotechnology has numerous potential benefits against ticks, there is no nanotechnology-based product available in the market till date.

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