Role of essential oils and other alternatives to control ticks (*Hyalomma* species) the Major Cause of CCHF (a threat for humans and livestock)

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SUMMARY

Ticks being hematophagous parasites can transmit a number of diseases of human and veterinary importance. For example, Hyalomma ticks are responsible for the transmission of the Crimean Congo hemorrhagic fever (CCHF) Virus originated in Africa, but cases have also been reported in Europe. This background has generated effective tick control methods which include industrially synthesized chemical acaricides. However, due to the acaricidal resistance alternate control methods such as essential oils, vaccines, plant extracts, entomopathogenic fungi, and nanoparticles have been implemented. Continued strategies are also required to generate and devise new and innovative methods of tick control. This chapter highlights different control methods for ticks.

INTRODUCTION

Parasitic diseases are a serious threat to the growth and development of animals around the globe (Baker et al., 2022). Parasitic diseases are caused by endoparasites (parasites which live inside of the host body) and ectoparasites (parasites which live outside the body of the host). Endoparasites include almost all protozoans, nematodes, cestodes, and helminths while ectoparasites include ticks, mosquitoes, mites, midges, lice, flies, fleas, and midges. Among all ectoparasites, ticks are hematophagous parasites of mammals and birds (Ogrzewalska & Pinter 2016). Ticks have medical and veterinary importance because they are responsible for transmitting several bacterial, viral, and protozoal diseases (Brites-Neto et al., 2015). Ticks belong to phylum, Arthropoda, order Acarina, and class Acari. Ticks are divided into categories such as hard-bodied ticks (*Ixodidae*) and soft-bodied ticks (*Argasidae*).

Ticks are widely distributed globally, and they are more comfortable to live in warm and humid environments (Dantas-Torres, 2015). These conditions are very important for the metamorphosis of ticks. On the other hand, low temperature hinders eggs' hatchability and larval development. Ticks also have a diverse spectrum of potential hosts because they are involved in infesting amphibians, reptiles, birds, and mammals (Jongejan & Uilenberg 2004). Heavy tick infestations in livestock cause considerable loss by transmitting pathogens, anemia due to blood loss, and damage to their hides and wool (Hurtad & Giraldo-Ríos 2018; Shifera, 2018; Yadav & Upadhyay 2021).

STRUCTURE AND ANATOMY OF HARD TICKS

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The external anatomy of hard ticks includes 3 major parts: the capitulum, the idiosoma, and the legs (Sonenshine, 2013). The capitulum contains the basis capituli, the chelicerae, the hypostome, and the leg-like palps. The body of the tick is divided into anterior and posterior regions. The anterior region, also known as podosoma bears four pairs of legs for walking and a genital pore while the posterior region, the opisthosoma includes spiracular plates and an anal portion (Madder et al., 2014). The legs articulate with the body via the coxae and contain 6 segments (Dunlop & Alberti 2008). The segment of 1st leg contains a sensory organ called Heller's organ for the detection of odors, temperature, cold, and other external factors. Hard ticks are called so because of the presence of a hard, sclerotized plate on the dorsal surface (Sonenshine, 2005). Scutum covers the whole of the dorsal surface in male ticks but half of the anterior region in adult females, nymphs, and larvae (Anderson & Magnarelli 2008). Male ticks have a smaller size than female ticks because of the dorsal plate, which prevents growth in males.

The digestive system, trachea, salivary glands, malpighian tubules, and reproductive organs of hard ticks are their most crucial internal organs. Sinuses of ticks contain hemolymph which bathes organs (Sonenshine, 2005). Hemolymph also contains hemocytes and a bundle of proteins (nutrients). Hemolymph helps in the removal of waste and provides nutrition to different parts of the tick (Wyatt, 1961). The midgut is the largest part of the body but most important are the salivary glands present on the anterolateral side of the body. Salivary glands are multilobed structures and secrete saliva, anti-homeostatic factors, and enzymes that promote and facilitate bleeding at the puncture site. In adults, the reproductive organs fill most of the space instead of the midgut (Sonenshine & Šimo 2021). Fully-fed females cover most of their body parts with brown ovaries.

HEMATOPHAGOUS BEHAVIOR AND TICK HOST INTERACTIONS

Ticks are hematophagous ectoparasites and feed blood to fulfill their nutritional requirements (Schwarz et al., 2012). Ticks attach to their host at the thinner side of the skin such as the ear of the mammal, groin region, and external genitalia (Apanaskevich et al., 2014). To get blood they tightly grasp the skin of the host, insert a hypostome into it, and secrete saliva. Tick saliva contains 1500 to 3000 types of protein including evasins which have anti-inflammatory properties that allow ticks to feed for almost seven to ten days despite being noticed by the host (Páleníková, 2016). Ticks along with blood ingest proteins, iron, salt, carbohydrates, lipids, and vitamins. Ticks not only feed blood but also produce some anticoagulants which leave the wound open leading to anemia (Trüeb et al., 2023). Ticks find their host by their breath, odors, moisture, body heat, and vibration. Ticks are unable to fly, and they show unique behavior called questing to attach to their host (Estrada-Peña & Fuente 2014). Ticks cling to ferns, leaves, and grasses with the help of 3rd and 4th pair of legs while holding 1st pair of legs outstretched, they grasp their passing host (Walker, 2003). Hard ticks remain at the same place on the host skin until they are fully engorged, and their size is increased by three to four times as compared to their unfed size (Samish et al., 2000).

TICK-BORNE DISEASES IN HUMANS AND ANIMALS

Various species of ticks are responsible for the transmission of several diseases transmitted by viruses, bacteria, and protozoa (Rochlin & Toledo 2020) A single tick may contain two different pathogens and create difficulty in the diagnosis of disease. Bacterial diseases that are transmitted through the bite of ticks include typhus, rocky mounted spotted fever, boutonneuse fever, rickettsiae pox, Flinders Island spotted fever, and African tick bite fever (Eldin & Parola 2018). Other diseases include Q fever (Körner et al., 2021), Lyme disease (Caimano et al., 2016), Colorado tick fever (Yendell et al., 2015), Queensland tick typhus (Stewart et al., 2017), tularemia (Zellner & Huntley 2019).), Crimean Congo hemorrhagic fever (Gargili et al., 2017), tick-borne relapsing fever (Jakab et al., 2022), tick-borne meningoencephalitis (Stefanoff et al., 2013), babesiosis (Hong et al., 2019), anaplasmosis (Matei et al., 2019), and ehrlichiosis (André et al., 2022). More than two types of pathogens can be transmitted by a single tick. Some species do not transmit infection, but they produce toxins that are responsible for tick paralysis. One thing to be kept in mind is that all the ticks do not contain disease-causing agents and toxins. Migratory birds are the source of infection from one region to another because they carry ticks which are the important vectors of the above-mentioned diseases (Nasirian, 2022).

CHEMICAL ACARICIDES TO CONTROL TICKS

Synthetic acaricides are chemical agents that can kill the ticks when applied. Different synthetic chemical acaricides such as arsenicals, chlorinated hydrocarbons, organophosphates, carbamates, pyrethroids, formamidines, macrocyclic lactones, phenylpyrazoles, and isoxazolines have been used over the years to control ticks and are much effective (Selles et al., 2021). Among all, pyrethroids are the most effective and reliable pesticides for tick control and are now widely used against ticks (Bardosh et al., 2013).

Different methods and techniques have been used over the years to control ticks, but the most important and efficient method of tick control is the dipping or bathing of livestock with water mixed with chemical acaricides (Moyo & Masika 2009). However, it has the drawback of allowing ticks that have been hidden in toes, ears, and under the tail to survive and repopulate the tick population. Other methods include spraying (mist formation) manually or with the help of high-pressurized sprayers, pour-ons or spot-ons (topical application on hair coat), plastic collars, and ear tags (George, 2000; Rajput et al., 2006; Rahman et al., 2022. The ear tag method is also very effective because it involves the slow release of chemical acaricide (flumethrin) to kill ticks.

Similarly, **Systemic acaricides** have long-lasting effects. In this instance, toxicants like ivermectin are injected into the host blood to kill the blood-feeding ticks, but it has the drawback of being toxic to host animals due to the abundance of poisonous metabolites.

Acaricidal resistance

The continuous and prolonged usage of chemical acaricides has led to the development of resistance in various species of ticks (Abbas et al., 2014). Different species of ticks have developed resistance against arsenicals, chlorinated hydrocarbons, pyrethroids, and formamide (Vudriko et al., 2016; Agwunobi et al., 2021). Research studies revealed that some strains of tick species in Australia are completely resistant to all kinds of chemical acaricides including amitraz and pyrethroids (Githaka et al., 2022). Similarly, complete resistance to chemical acaricides has been reported in different countries including the USA and Mexico (Rodriguez-Vivas et al., 2018). The inappropriate application of chemical acaricides also causes residues to build up in the tissues and muscles of the animals, which reduces the availability of beef and meat for human consumption and poses health risks to people. To combat resistance and other drawbacks to currently used chemical acaricides, more attention is required to discover and establish new acaricidal products. Genetic indicators are being sought, and monitoring assays will help to discover resistant ticks (Sungirai et al., 2018). Scientists are moving to enhance other control strategies to overcome above mentioned drawbacks.

ESSENTIAL OILS

Essential oils (secondary metabolites) are complex and natural compounds that are volatile and fatty in nature, insoluble in water but soluble in organic solvents like absolute alcohol, acetone, benzene, methanol, etc. (Ríos, 2016). These essential oils can be extracted from different parts of the plants such as buds, twigs, flowers, fruits, leaves, stems, bark, roots, seeds, etc. (Schmidt, 2020). Different extraction methods have been utilized over the years to extract essential oils (Reyes-Jurado et al., 2015) but the most frequently used methods by Arabs were steam and hydro distillation (Memarzadeh et al., 2015). In modern days, these two methods are used for the extraction of essential oils with little modifications. Known for, their viricidal, bactericidal, fungicidal, therapeutic, and pharmacological properties, they are being used for the preservation of food, and as anti-inflammatory, antimicrobial, antiviral, antifungal, anti-parasitic, spasmolytic, anesthetic, analgesic, and sedative (Mehdizadeh & Moghaddam 2018; Baptista-Silva et al., 2020). These characteristics are due to the presence of chemical ingredients in essential oils (De-Groot & Schmidt 2016). These chemicals are detected by gas chromatography-mass spectrometry (GC-MS) and gas chromatography flame ionization detection (GC-FID) methods (Maqbul et al., 2019). The ratio and types of chemicals in essential oils of the same plant may vary due to the extraction technique utilized for extraction (Figueiredo et al., 2008). About 3000 essential oils have been found of which nearly 300 are commercially synthesized because of their pharmacological, therapeutic, cosmetic, perfume, dentistry, food additives, flavor additives, and sanitary values (Singh et al., 2022). Some essential oils have been used to cure systemic diseases and organ dysfunctions because of their medicinal properties (Bakkali et al., 2008). Owing to their medicinal properties, these essential oils are used in livestock to inhibit or kill ectoparasites i.e., ticks. But first, it is better to know their mode of action against *Hyalomma* ticks.

Mode of action of essential oils against ticks

The most prevalent class of naturally occurring compounds with tick-controlling properties are essential oils (Selles et al., 2021). Essential oils impede ticks by sucking blood, blocking chitin synthesis, slowing down growth and development, and reducing the reproduction of engorged female ticks (Pereira et al., 2023). Numerous research studies have been conducted to identify the diverse effects of essential oils and their mechanisms of action, although the cytotoxic, neurotoxic, and mechanical impacts are the most prevalent effects. Additionally, several studies have been conducted to examine the repellent properties of essential oils, and they are summarized below.

Neurotoxic effect

The action of chemical ingredients of essential oils on the nervous system of ticks is known as a neurotoxic effect. This neurotoxic effect of essential oils is due to the inhibition of acetylcholinesterase (AChE), its effect on octopamine receptors, and its action on gamma-aminobutyric acid or GABA (Alimi et al., 2022). Some authors are not satisfied with the insecticidal action of essential oil due to GABA neurotransmitters. They concluded that this action is due to the closure of chloride ion channels due to GABA or an increase in chloride ion voltage due to GABA neurotransmitters (Ozoe, 2013).

Inhibition of acetylcholinesterase activity

Tab 1. Acaricidal effect of various essential oils against *Hyalomma* ticks.

Essential oils	**Family**	**Chemical components**	**Dose**	**Tick species**	**References**
Caniibis sativa	Cannabaceae	E- caryophyllene and α-humulene	40 µL/L	*Hyalomma domedarri*	Tabari et al., 2020
Chenopodium ambrosioides	Amaranthaceae	p- cymene, linalool	0.918 µL/mL	*Hyalomma aegyptium*	Abbad et al., 2023
Citrus sinensis	Rutaceae	Limonene, linalool	40% with absolute alcohol	*Hyalomma dromedarri*	Salwa et al., 2007
Cupressus sempervirens	*Cupressus sempervirens*	α-pinene and δ-3-Carene	20 mg/mL	*Hyalomma scupense*	*Alimi et al., 2022*
Elettaria cardamom	Zingiberaceae	1,8- cineole, α-pinene	40 µL/L	*Hyalomma anatolicum*	Alanazi et al., 2022
Eucalyptus camaldulensis	Myrtaceae	p-cymene, spathulenol, farnesol, α-pinene, cuminic aldehyde, 1-phellandrene, sabinene, carvacrol, and p-cymene-7-ol	6.2 µl/mL	*Hyalomma scupense*	Djebir et al., 2019
Eucalyptus globulus	Myrtaceae	1,8-cineole, α-pinene, viridiflorol, camphen, d-pinocarvone, aromadendrene	6.2 µl/mL	*Hyalomma scupense*	Djebir et al., 2019
Juniperus thurifera	Cupressaceae	Terpinene, myrcene	0.0118 mL/cm^2	*Hyalomma aegyptium*	El-Mustapha et al., 2021
Laurus nobilis	Lauraceae	1.8-cineole, α-terpinenyl acetate, sabinene, α-pinene, linalool, methyleugenoland β-pinene.	100 mg/mL	*Hyalomma scupense*	Alimi et al., 2021
Lavandula pedunculata	Lamiaceae	Linalool, β-pinene, 1,8-cineole	0.0110 mL/cm^2	*Hyalomma aegyptium*	Laghzaoui et al., 2018
Lavandula stoechas	Lamiaceae	α-thujone, camphor, camphene, D-fenchyl alcohol, l-bornyl, dl -limonene, α-pinene, and linalool	3.12µl/mL	*Hyalomma scupense*	Djebir et al., 2019
Lavendula angustifolia	Lamiaceae	Linalool, 1,8-cineole	20 µL/L	*Hyalomma marginatum rufipes*	Mkolo & Magano 2007
Lippia javanica	Verbernaceae	myrcene 1,8-cineole, dyhydrotagetone, ipsenone, bicyclo heptanes-2-one, 2-butanone		*Hyalomma marginatum rufipes*	Magano et al., 2011
Mentha suaveolens	Lamiaceae	α-thujene, terpineole	1.465 µL/mL	*Hyalomma aegyptium*	El-Mustapha et al., 2021
Origanum floribundum	Lamiaceae	carvacrol, p-cymene, γ-terpinene, β-myrcene, o-cymene, thymol, trans-caryophyllene, α-pinene, and α-terpinene	3.12µl/mL	*Hyalomma scupense*	Djebir et al., 2019
Rosmarinus officinalis	Lamiaceae	1,8-cineole, l-camphor, α-pinene, borneol L, camphene, α-terpineol, β-pinene, trans-caryophyllene, l-bornyl acetate, β-myrcene, and γ-terpinene	0.781 µl /mL	*Hyalomma scupense*	Martinez-Velazquez et al., 2011
Satureja calamintha	Labiatae	Sibenene, limonene	1.347 µL/mL	*Hyalomma aegyptium*	
Satureja thymbra	Lamiaceae	Carvacro, γ-terpinene	40 µL/L	*Hyalomma marginatum*	Çetin et al., 2010
Tagetes minuta	Asteraceae	Ihydrotagetone, E-ocimene, tagetone	20 µL/L	*Hyalomma rufipes*	Nchu et al., 2012
Thymus capitatus	Lamiaceae	carvacrol, p-cymene, and γ-terpinene, transcaryophyllene, m-thymol, β-myrcene, α-terpinene.	1.56µl/mL	*Hyalomma scupense*	Djebir et al., 2019
Mentha pulegium	Labiatae	Pulegone and cis-Menthone for M. pulegium.	20 mg/mL	*Hyalomma scupense*	*Alimi et al., 2022*
Eucalyptus cammadelulensis	Myrtaceae	p-cymene, eucalyptol, 1,8-cineole, α-pinene and α-terpinol	0.04 and 0.08%	*Hyalomma anatolicum*	Hatem et al., 2020

Acetylcholinesterase is a specific enzyme of neuronal and neuromuscular junction, that can control the excitatory neurotransmitter acetylcholine (ACh) at the synapse, and it is the most important neurotransmitter of the central and peripheral nervous system of arthropods (Thapa et al., 2017). Research data revealed that the terpenoid compounds present in various essential oils have Acetylcholinesterase activity (Borah et al., 2020). Various chemical components extracted from essential oils such as carvacrol, limonene, menthol, menthone, 1,8-cineole, α-pinene, β-pinene, and linalool can block the neurotransmitter acetylcholine at the pre and pro synaptic membrane (Wojtunik-Kulesza et al., 2021). Research on a monoterpenoid (Terpinen-4-ol) obtained from tea tree oil at a high concentration can inhibit tick acetylcholinesterase at the synapse (de-Sena Filho et al., 2022). The research study also revealed that various characteristics of a particular essential oil are due to differences in the structure of chemical constituents. For example, carvacrol has a 10 times greater ability to inhibit AchE as compared to the thymol isomer because of the presence of a hydroxyl group in the carvacrol structure (Rodríguez et al., 2022).

Octopamine receptors

Octopamine is an organic substance that can act as a neurotransmitter or as a hormone in invertebrates, particularly arthropods (Farooqui, 2012). It is closely related to the hormone nor-adrenaline (Bauknecht & Jékely 2017). Octopamine is produced by tyramine in the presence of tyramine β-hydroxylase enzyme (Schützler et al., 2019). Three different types of octopamine receptors are present in ticks (Koh-Tan et al., 2016). The α and β-adrenergic factors are the most important receptors that are involved in the mobility of the insects to perform functions. These receptors are also involved in the instincts and learning behaviors of insects such as flying, egg-laying, and jumping (Devineni & Scaplen 2022). When essential oils are applied to control insects particularly ticks the chemical constituents present in the essential oils such as eugenol, terpineol, and cinnamaldehyde bind with the tyramine and octopamine receptors in such a way that they completely block the neurotransmitters, hence hindering ticks' movement which lead to the paralysis of the ticks (Chaudhari et al., 2021). These chemical ingredients release more Ca^{+2} ions inside the cell and, cause the activation of kinases and phosphorylation of enzymes, receptors, and ion channels.

Mechanical effects

The hydrophobic nature of essential oils is responsible for this effect (Ellse & Wall 2014). All essential oils have heterogeneous groups of compounds and are hydrophobic in nature. When ticks are treated with essential oils, they face water stress and suffocation that lead to the destruction of the exoskeleton and blocked respiratory spiracles (Salman et al., 2020). Furthermore, essential oils are also recognized for their antihistamine effect (Lillehei & Halcon 2014). Essential oils increase the production of interleukin-10, hence reducing inflammation (Zhao et al., 2021).

Repellent effects

Undoubtedly, synthetic acaricides work well as repellents, but there are issues with the safety, effectiveness, and environmental impact of their compounds (Wieren, 2016). So scientist are diverting their attention toward the use of natural and plant-derived products against different species of ticks because these are less toxic, biodegradable, and eco-friendly.

Tick repellents are those chemicals that act in such a way that they prevent the ticks from landing and biting. Some researchers defined these repellents as chemical substances which enable ticks to move away from their source. There are various types of repulsion, but the most important repulsion is the strict sense and sensu lato repulsion (Omolo et al., 2021). In a strict sense, repulsion ticks face an irritant effect when they come in direct contact with the repellent substance and ticks also drop off before they attach to the host body. In sensu lato repulsion, the repellant substances inhibit the ticks from attaching to the host body or they detach the already attached ticks from the host body (Halos et al., 2012). The exact mechanism of action of essential oil as a repellent agent against ticks is unknown but researchers believe that the production of vapor barriers that keep ticks from making direct contact with the host and its skin is the mechanism through which essential oils work as repellents.

Different essential oils have been reported that have shown repellent effects against adults and larvae of the ticks (Martinez-Velazquez et al., 2011; Rey-Valeirón et al., 2018; Salman et al., 2020; Selles et al., 2021). For example, *Cupress funebris* and *Juniperus communis* have shown repellent activity against nymphs of *Amblyomma americanum* when used in different concentrations. *Cupress funebris* has also shown repellent activity against Ixodes scapularis adults (Carroll et al., 2011). Another research study was conducted to compare the repellent effect between *Tagetes minuta* and *Tithonia diversifolia* essential oil and concluded that Tagetes minuta essential oil has far better repellent activity against adult and larvae of *Rhipicephalus appendiculatus* (Wanzala et al., 2014). Similarly Mkolo et al., (2007) found out the repellent effect of *Lavendula augustifolia* against larvae and adults of ticks. More study is needed to find the exact mechanism of repellent action at all stages of *Hyalomma* ticks.

OTHER CONTROL METHODS

Vaccines

Various methods have been adopted to immunize the bovines against ticks. Scientists are working to produce vaccines against tick- and tick-borne diseases and somehow, they are successful too (Mazanik, 2023). Vaccine development and production against ticks and tick-borne diseases is very important because major economic losses to the milk and meat industry are due to Babesiosis, Theileriosis, Anaplasmosis, and Cowdriosis (Lew-Tabor et al., 2016). FAO has started and implemented various coordinated programs for the development, production, and delivery of the tick vaccine. Muguga and Boleni vaccines were developed against various strains of *Theileria parva* and are currently being used (Latif & Hove 2011). Then a race starts to produce vaccines at the molecular level around the globe. These vaccines are expensive and have low coverage and high levels of side effects. However, the researchers worked on Bm86 commercial recombinant vaccines against ticks and this discovery brought a revolution in the livestock industry because this vaccine was very helpful in controlling the *Boophilus microplus* in several experiments and it showed much better results when it was given with commercial acaricides in a unified manner (Mears, 2022). Another research trial has observed the oviposition reduction of *Boophilus microplus* in sheep immunized with the vitelline vaccine (Tellam et al., 2002; Abbas et al., 2023). He also used GP80 protein against the cattle tick *Rhipicephalus microplus* and tested it in Brazil on different sheep farms in association with FAO. Jenkins, (2002) used live parasites to prepare subunit vaccines against Babesiosis and Theileriosis by considering some disadvantages which include short shelf life, side reactions, and inversion of attenuation. Antigenic variation and strain diversity also make subunit vaccine development very complicated. The effectiveness of a vaccine to generate immunity depends upon how quickly the vaccine is delivered and the age of the animal (Ogra et al., 2001). Scientist were trying their best to produce accurate vaccines, but identification of protective tick antigens is a big challenge in the development of anti-tick vaccines. In 2000, scientists were successful in isolating the Bm95 gene from the cattle tick *R. microplus* and reported that Bm95 antigen was very effective against Bm86-resistant and Bm86-sensitive tick infestation (García-García et al., 2000). He also concluded that Bm95 is a universal antigen that can be used against infestations produced by *R. microplus* strains around the globe (Parizi et al., 2012). Then similar research was conducted to identify the protective antigens against *Ixodes scapularis* infestation using cDNA expression library immunization.

Plant extracts

Plant extracts have been used over the years to control parasites because they are environmentally friendly, less expensive, and with less negative results for the treated animal (Reverter et al., 2014). These plant extracts have been collected by special techniques such as hydrodistillation or steam distillation methods. Extracts from more than 55 plant species have already been evaluated against the tick genus *Rhicephalus* (Rodriguez-Vivas et al., 2018). Similarly, various plant extracts have been tested on *Hyalomma* species as well (Singh et al., 2017). The anti-tick properties of medicinal plants are due to the presence of several chemical components present in them (Kemal et al., 2020). These chemical compounds act in such a way that they counteract the growth regulatory hormones, decrease reproduction by reducing oviposition, interruption in mating, and inhibit exoskeleton development. Pereira and Famadas, (2004) checked the effect of ethanolic extract of *Dahlstedtia pentaphylla* (Leguminosae) roots against tick species. When 20% concentration was used it showed 100% efficiency against engorged females and larvae. Another research trial evaluated the acaricidal effect of different concentrations of ethyl acetate and ethanolic extract of *Piper aduncum*. They evaluated the larval mortality and checked the reproductive parameters. At higher concentrations, the mortality factor of tick larvae was also very high, but the reproductive parameter was not more than 62% (Silva et al., 2009). Much work has been done to determine the exact ratio of the chemicals and their repellent and acaricidal effects against ticks, but certain limitations have been pointed out such as lack of proper extraction techniques, negligence of a researcher, different climatic conditions, the effect of photooxidation, temperature, pH when used *in vivo* (Nardella et al., 2022). Furthermore, these limitations are also due to the lack of pharmacokinetic studies on the time course of drug absorption, dispersal, metabolism, assimilation, and excretion. One of the biggest advantages of the use of plant extracts is that resistance may develop slowly because of the presence of several heterogeneous active agents with their own mechanism of action (Regnault-Roger et al., 2008). Most researchers ended their research by making natural products in the laboratory, but they should go *in vivo* for better results. However, the major difficulty in producing commercial products is that the active compounds should be safer for human health, should be cost-effective, and eco-friendly.

Use of entomopathogenic fungi to control ticks

Entomopathogenic fungi have been reported to control ticks and tick-borne pathogens but their specific mechanism of action has not been described so far. The general physio-pathological mechanisms include the adhesion of fungal spores to the tick cuticle where they germinate and penetrate the cuticle by physiological changes and enzymatic breakdown (Alonso-Díaz et al., 2021). Once fungal spores reach the hemocoel of the host, they produce toxic metabolites (destruxins) in the hemocoel which are helpful in killing the arthropod hosts, especially ticks (Fernandes & Bittencourt, 2008). These spores (conidia) during their reproduction will remain on the cuticle of the dead tick host which may disperse to surroundings and target other arthropods (ticks). Adhesion, germination, and toxic metabolite production are very crucial and important steps, but the latter varies considerably among fungal isolates (Kurtti & Keyhani 2008). The later study indicated that the quantity of toxic metabolite may not be important for pathogenicity to arthropods, including ticks. To check the effect of toxic metabolite (destruxin A), different concentrations of destruxin A were prepared and inoculation was done into engorged female *R. microplus* but it did not cause any physical damage to the host, no change in reproduction parameter, and did not cause any mortality (Sullivan et al., 2020). On the other hand, when trials were conducted on the larvae of *Galleria mellonella* (insect), high mortality of larvae was observed, and concluded that they are very sensitive to destruxin. However, research studies also demonstrated that this toxic metabolite is not always a main pathogenic factor for ticks.

To check the immune response in ticks against fungus, different ticks were infected with *M. anisopliae* and found a reduced number of hemocytes and degranulated cells in the hemolymph of ticks. These both things represent a severe and immediate cellular response and lead to the activation of prophenoloxidase (Angelo et al., 2010). This activation helps arthropods to activate their defense mechanism for the removal of infective agents. However, these infections may also lead to esterified cholesterol, phosphatidic acid/phosphatidylethanolamine in ticks. On the other hand, several immune reactions take place in hemolymph which leads to the coagulation of proteins in the hemolymph and to the paralysis of ticks (Angelo et al., 2010)

Our knowledge of the interactions between ticks and their entomopathogenic fungus infection, particularly in the immunological responses of ticks, is rather incomplete. However, more knowledge in this area would help in choosing fungal isolates and their formulation for application in tick biological control.

Nanoparticles to control ticks

Nanoparticles nowadays are used in Bio-nanotechnology and are widely used in medicine, food, biotechnology, biomedical, medicine, environment, agriculture, etc. such as for wastewater treatment, as food additives, and as antimicrobial agents (Husain et al., 2023; Nasibova, 2023). Due to the presence of different properties of nanoparticles such as biocompatibility, anti-inflammatory and antibacterial activity, effective drug delivery, bioactivity, and bioavailability nanoparticles are being used in applied microbiology and biotechnological fields. Recently they have been used for gene delivery, diagnosis of diseases, tissue engineering, artificial implants, and as novel pesticides that are lethal to insects and pests. (Ifijen et al., 2023; Mitra et al., 2023). The laboratory synthesis of metal nanoparticles by using physical and chemical methods from botanicals is a cheaper way to produce nanoparticles and does not require much energy, temperature, and high pressure (Kumar et al., 2015). Mostly nanoparticles are generated through green synthesis methodology which includes bioactive agents from plant materials, microbes, vegetable wastes, fruit weel waste, agricultural waste, and algae (Kumari et al., 2021). Nanoparticles obtained from plant extracts or microbes can work as reducing and stabilizing agents. This green synthesis method of nanoparticle production has advantages in such a way because it is very straightforward, affordable, highly stable, less time-consuming, less toxic, and production of large quantities.

Recent studies revealed the toxic effects of green synthesized nanoparticles on tick species of public health significance, particularly *Hyalomma* (Zaheer et al., 2022) and *Rhipicephalus*. Different nanoparticles like gold, silver, copper, etc. have been used to control ticks and further research is going on to determine the exact mechanism of action of these nanoparticles and their specificity to control known species of ticks.

CONCLUSION

High costs of acaricidal drugs divert the attention of local farmers towards the utilization of indigenous methods to control ticks. The way ticks infest animals depends upon the climatic condition, that’s why there is an urgent need to generate other strategies that involve vaccination, botanical control, and nanoparticles with minimum use of chemical acaricides. Multi-tick infestation is common in different regions of the world and essential oils contain special compounds that are very effective against *H. a. anatolicum*, *H. m. isaaci*, *R. microplus*, *R. haemaphysaloides*, and *H. bispinosa* infesting cattle, buffaloes, sheep, and goats. Continuous efforts are needed to identify the tick resistance genes in various breeds which can be managed for the future prospect of developing new animal stock with genetic resistance to tick and tick-borne diseases. To include more working groups in this area of study, government and private financing for ticks and tick-borne diseases research and its control needs to be increased.

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