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Review Article

Ticks and Tick-Borne Diseases: Multiple Facets of Tick Control

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Abstract

Ticks are haematophagous ectoparasites that feed on a wide range of vertebrate hosts. Risks posed due to tick infestations are alarming as the ticks attack in great numbers onto a single host leading to cascade of skin disorders such as focal dermal necrosis, haemorrhage and irritation. Besides, anaemia due to their blood sucking behaviour and the transmission of life-threatening diseases in humans and animals owing to their vectorial capacity also justifies the research investment to control ticks. Due to the invasion of forest regions, the spread of tick-borne zoonotic diseases has increased. Use of acaricides is the most common method employed for the control of ticks, which not only causes environmental contamination but also leads to development of acaricidal resistance. Till date many control measures have been tried and tested against these agents that have their own merits and demerits. To design a sustainable tick control strategy, knowledge on tick biology and the different control measures that were devised to control ticks are of utmost importance. This review sheds some light on the tick biology, tick borne diseases and the different control measures devised so far.

Keywords: Tick Biology; Tick Borne Zoonosis; Anti-Tick Vaccines; Semiochemical; Phytoacaricides; Anti-Tick Microbiota Vaccines

Introduction

Ticks belong to the class of Arachnida along with spiders, scorpions, and mites. There are about 900 species of ticks, majority are Ixodids (hard ticks) that are of medical and veterinary importance. Thousands of ticks can parasitize an animal, escalating the harm on the host, either through direct injury or disease transmission. Several attributes make them excellent vectors of pathogenic agents, including their wide host range and a tendency to feed on multiple hosts during their life cycle which ensures plenty of opportunities to acquire and transmit pathogens. Their hardiness and longevity allow them to survive long periods of unfavorable environmental conditions, and their high reproductive potential ensures large population maintenance and frequent host-vector contact [12]. These attributes of ticks make the control of ticks difficult to achieve. Tick control is one of the most important strategies for preventing the spread of tick-borne diseases (TBDs). To design effective tick control strategies, a thorough understanding of tick biology and host-tick-pathogen interactions is essential. Tick vaccinations targeting ticks and their microbiome, endosymbiont disruption, semiochemical assisted killing, development of new phytoacaricides, and biological control agents are some of the more recent tick control techniques.

Tick biology

Hard ticks are found all across the planet, with the exception of the Arctic and Antarctica. Hard ticks are classified as “outdoor ticks” because they reside in open areas such as grassland, heaths, or open woodland.

Life cycle

Tick life cycles are complicated, involving a regular switch between a blood feeding and free-living stage, as well as a change of host [18]. The reproductive, eight-legged adult stage is reached after a single hexapod larval stage and a single octopod nymphal stage, all of which need to suck blood. Ixodid ticks take a number of huge blood meals during their progression through these stages. On-host existence accounts for less than 10% of a tick's life in many species, whereas off-host phase, on the other hand, is concerned with survival during development and the search for a new host [18], which makes the control of ticks a bit complicated. Hard ticks adopt a strategy known as questing, in which they wait on the tips of vegetation for an appropriate host to brush past. Once contact is made the ticks transfer to the host, and then move over the surface to find their preferred attachment sites. Three-host ticks require a different host for each maturation stage. The larva and nymph of two-host ticks use the same host, but the adult uses a different one. As a larva, nymph, and adult, the one-host ticks feed on a same host. Copulation occurs on the host, with males usually copulating with many females. Only mated females become fully engorged and descend off the host and undergo a quiescent phase in the vegetation. While the bloodmeal is digested and the eggs mature, the female lay about 2000 to 20,000 eggs depending on the species of tick.

Figure 1: A group of engorged female Rhipicephalus sanguineus ticks laying eggs in tick rearing tubes.

Tick host interactions

Ticks use their specialised mouthparts to penetrate the skin of the host for obtaining a blood meal. As a prelude to the insertion of the hypostome, chelicerae lacerate the epidermis of the host's skin. The hypostome carries backwardly pointing teeth that provide a strong anchoring in the skin. Ticks with short mouthparts anchor themselves to the host skin by producing a cement-like substance around the hypostome and chelicerae, reinforcing the attachment. Capillaries and small blood vessels are injured during the initial probing and attachment process, resulting in formation of a haemorrhagic pool at the tick bite site from which they suck the blood [17]. During this process, ticks introduce saliva and possible pathogens, into the skin. The coagulation cascade, vasoconstriction, and inflammatory responses would be activated in response to skin damage and the presence of a tick, with the goal of inhibiting tick feeding and initiating wound healing. Ticks, on the other hand, are able to feed on blood because of various chemicals in tick saliva that have anticoagulant, vasodilatory, anti-inflammatory, and immunomodulatory properties that are necessary for efficient attachment and engorgement [16].

Effects of tick bites

Focal dermal necrosis and hemorrhage followed by a granulomatous inflammatory reaction including eosinophils and mixed inflammatory cell responses and fibrosis may occur at the tick bite site varying considerably. Hypersensitivity responses may develop leading to widespread damage [38]. Bite wounds can get infected with *Staphylococcus* bacteria, resulting in cutaneous abscesses and pyaemia. In moderate and changing proportions, blood loss, pain and swelling of bite wounds, secondary infection, myiasis, and toxin absorption result in a form of ill thrift known as "tick worry" [4]. Tick paralysis is a sickness caused by the presence of a neurotoxin in the saliva of feeding female ticks. By inhibiting the liberation of acetylcholine and causing damage to receptor sites, the toxin damages motor nerve synapses in the spinal cord and blocks neuro-muscular junctions. Tick paralysis can be caused by a variety of species, each with its unique toxin. Peripheral nerve dysfunction, cardiovascular consequences, breathing difficulties, vomiting, and changes in body temperature are among the symptoms, with the paralysis of the lower limbs spreading quickly to the remainder of the body [38].

Tick borne pathogens

Ticks are among the most proficient and versatile pathogen vectors, coming in second only to mosquitoes as vectors of viruses, bacteria, rickettsia, spirochetes, and other infections [12]. The majority of emerging infectious diseases are caused by zoonotic pathogens, and many of them are spread by tick vectors. In recent years, India has seen an increase in instances of Kyasanur Forest Disease (KFD), Crimean Congo Hemorrhagic Fever (CCHF), Lyme disease, and Indian Tick Typhus (Tick relapsing fever). These alterations have also been recorded in the United States, Europe, and Australia, owing to the spread of tick vectors in new places [29].

Tick borne zoonosis

As a result of feeding on a variety of hosts during different life cycle stages, pathogens can be transferred from one host to another through transovarial or transstadial transmission, manifesting as zoonotic infections. Lyme disease is tick borne meningopolyneuritis, most commonly reported in the United States, Europe and in temperate regions of the Northern hemisphere, with severe clinical manifestations [24]. Boutonneuse fever or the Indian tick typhus occurs in the Mediterranean countries with symptoms such as fever, chills, headache, rash and a characteristic button like ulcer called eschar or tacye noir. Kyasanur Forest Disease Virus (KFDV) is the causative agent of Kyasanur Forest Disease (KFD), a tick-borne viral haemorrhagic disease identified and isolated from sick and dead monkeys in the forest regions of Shimoga district situated in the State of Karnataka, India, with a case-fatality rate ranging from 3% to 5% [41]. Recent finding demonstrated that KFDV is present in states bordering Karnataka, such as Kerala, Tamil Nadu, Goa, and Maharashtra, suggests the existence or migration of the KFDV arena to neighbouring geographical places [41]. A list of the zoonotic infections along with the causative agents that are spread by different tick species is provided in the table 1 [24].

Disease	Causative agent	Primary tick vector	Affected host(s) beyond humans
Kysanur forest disease	*Flavi virus*	*Haemaphysalis spinigera*	Monkeys, small mammals, carnivores, birds, cattle
Tick borne encephalitis	*Flavi virus*	*Ixodes ricinus, I. persulcatus*	Rodents, Insectivores, carnivores, etc.
Human babesiosis	*Babesia microti, B. divergens, B. duconi, B. venatorum*	*I. scapularis, I. ricinus*	Mice, cattle
Possawan encephalitis	*Flavi viruses*	*Ixodes, Dermacentor and Haemaphysalis* spp.	Rodents, hares and carnivores
Colarado tick fever	*Coltivirus*	*Dermacentor andersoni*	Rodents, carnivores and domestic animals
Crimean-Congo hemorrhagic fever	*Nairovirus*	*Hyalomma* spp.	Hares, Hedgehogs, small mammals
Rocky mountain spotted fever	*Rickettsia rickettsii*	*Dermacentor* spp.	Small mammals, carnivores, rabbits and others
Boutonneuse fever	*Rickettsia conorii*	*Rhipicephalus sanguineus, D. marginatus, D. reticulatus,* others	Small mammals, hedgehogs, dogs
African tick bite fever	*Rickettsia africae*	*Amblyomma* spp.	Mammals
Human ehrilichiosis	*Ehrlichia chaffeensis*	*Amblyomma americanum*	Deer
Human anaplasmosis	*Anaplasma phagocitophilium*	*Ixodes* spp.	Rodents, deer, dog
Q fever	*Coxiella burnetti*	Many tick species	Large domestic livestock
Lyme disease	*Borrelia* spp.	*Ixodes* spp.	Mammals, birds
Tularemia	*Francisella tularensis*	Many tick species	Lagomorphs, Rodents, Carnivores

Table 1: Tick borne zoonotic infections.

Tick borne diseases of veterinary importance.

Ticks are of important veterinary concern because they can transmit a variety of microbial agents to livestock, companion animals, and wildlife. The impact of ticks and tick-borne diseases on the livelihood of resource poor farming communities have been ranked high. When livestock and poultry are highly infested with ticks, they may incur economically significant losses in body weight, milk or egg production, and general unthriftiness, and in certain cases, they may even die of anaemia [24]. Theileriosis, babesiosis and anaplasmosis are the most common TBD in cattle and buffaloes and have a major negative impact on productivity and can be fatal if not treated. The global loss due to TTBDs was estimated to be between US$ 13.9 and 18.7 billion annually. Due to the delicate triangular interconnections between host- vector- pathogens, multiple pathways are to be attempted to control TTBDs [12]. Table 2 shows the tick-borne infections of veterinary importance [24].

Disease	Causative Agent	Primary Tick Vector Species	Affected Host(s)
Bovine babesiosis	*Babesia bigemina* *B. bovis*	*R. (Boophilus) annulatus* *R. (B.) microplus, others*	Cattle
Canine babesiosis	*B. canis,* *B. rossi,* *B. vogeli,* *B. gibsoni*	*R. sanguineus, Haemaphysalis leachi*	Domestic dogs
East Coast fever	*Theileria parva*	*Rhipicephalus appendiculatus*	Cattle, Cape buffalo
Tropical theileriosis	*T. annulata*	*Hyalomma* spp.	Cattle, water buffalo
Malignant theileriosis	*T. lestoquardi*	*Hyalomma anatolicum,* other tick species	Sheep
Feline cytauxzoonosis	*Cytauxzoon felis*	*Amblyomma americanum, Dermacentor variabilis*	Domestic and wild cats
Louping ill	*Flavivirus*	*Ixodes ricinus*	Sheep, grouse, others
Tick-borne fever	*Anaplasma phagocytophilum*	*I. ricinus, I. scapularis,* *I. pacificus, I. persulcatus*	Domestic and wild ruminants, horses, dogs, humans
Canine ehrlichiosis	*Ehrlichia canis* *E. ewingii* *E. chaffeensis*	*R. sanguineus, I. ricinus A. americanum, others*	Dogs
Heartwater	*Ehrlichia ruminantium*	*Amblyomma hebraeum, A. variegatum,* *B. microplus*	Ruminants
Bovine ehrlichiosis	*Ehrlichia minasensis (Ehrlichia sp. UFMG-EV)*	*R. (B.) microplus*	Cattle
Anaplasmosis	*Anaplasma marginale,* *A. centrale,* *A. ovis*	*Dermacentor* spp., *R. (Boophilus)* spp., *Hyalomma* spp., *Rhipicephalus* spp.	Cattle, sheep, other ruminants

Table 2: Tick borne infections of veterinary importance.

Chemical control and acaricidal resistance

Currently the mainstay of tick control measure relies on the use of chemical acaricides. The classes of chemical acaricides which are the mainstay of tick control programme are organophosphates, pyrethroids, formamidines, phenylpyrazoles, insect growth regulators, isoxazolines and macrocyclic lactones [24]. Application of acaricides on the host is commonly practised in the form of dips, sprays, pour on, spot on, acaricidal dusts, plastic collars and plastic ear tags. Ivermectin is the only systemic acaricide that can be administered parentally [23]. The drawback of using acaricides inconsistently and indiscriminately is the selection of acaricide resistant ticks which makes existing acaricides ineffective and thereby limiting the efficacy of existing tick control methods. Globally, multi-acaricide resistant tick populations have been reported across the globe [29]. Resistance to organophosphates and synthetic pyrethroids has been documented in *R. (B.) microplus* [2,22]. High proportion of synthetic pyrethroid resistant alleles of *R. sanguineus* have been reported in India [3]. There is an urgent need to genotype the different tick species across the country for resistance to different acaricide groups to throw light on the geography wise selection of chemicals for tick control. It is needed to develop robust and efficient resistance monitoring techniques such as the bioassays and molecular assays in order to effectively employ and monitor chemical control measures. Another issue related with the usage of acaricides is environmental contamination, as well as chemical residues in milk and meat products, which can be tackled by usage of alternative control measures directed against the different physiological aspects of the ticks.

Novel tick control strategies

Anti-tick vaccines

Naturally acquired tick resistance, also known as 'tick immunity,' occurs after repeated tick infestations and can lead to a reduction in tick feeding success as the tick introduces different saliva proteins into the host, which also serve as antigens for the host to develop a successful protective immunological response [21]. There are two groups of potential vaccine antigens. The first group, exposed antigens are released in tick saliva during attachment and feeding on a host, where they stimulate an immunological response. These antigens are being exposed to the host immune system for a long time and are likely to be less immunogenic. Several proteins, including salivary gland proteins and structural components like the tick cement cone protein 64P, which has homology to mammalian skin proteins, could be used to avoid host rejection during tick infestation, which is not a desirable trait for a vaccine candidate [28]. In guinea pigs, however, truncated forms of the protein 64P, the 64TRP caused considerable adult and nymphal mortality. These 64TRPs were used in an experiment to demonstrate a robust humoral immune response increased by tick challenge [37]. The second category includes concealed or hidden antigens that are not ordinarily exposed to the immune system of the host [28]. Although hidden antigens do not elicit an immune response during tick infestation, they are immunogenic when produced as extracts or recombinant proteins and inoculated artificially into a host [28]. Bm86 is the first and the only commercialized anti-tick vaccine, it is an 89 kDa gut protein, situated with a glycosylphosphatidyl inositol anchor on the microvilli of the midgut. Extracted from the cattle tick *R.(B) microplus* [39], Bm86 is not exposed to the immune system naturally and thus represents an example of a concealed antigen. It has been established that Bm86 vaccination has an IgG and complement-mediated effect, and that protection is linked to IgG titres. GavacTM (HebertechTM, Havana, Cuba) and TickGard are two veterinary vaccines based on the Bm86 antigen produced in yeast (Merck Animal Health, Madison, NJ, USA) [7]. These antigens rely on vaccine-induced antibodies to work, and many shots may be required to achieve adequate antibody levels. Subolesins [31], vitellins, ferritins, aquaporins, calreticulin and other proteins [29] involved in structural, metabolic, reproductive and tick protective functions might act as potential vaccine candidates. Reports indicate that combining two tick or pathogen derived antigens can increase the vaccine efficacy significantly [29].

Types of vaccines

- **Dual action vaccines:** targets both exposed and concealed antigenic epitopes, 64 P of *R. appendiculatus*
- **Vaccines against multiple tick species:** Targeting multiple tick species, highly conserved antigen between tick species potentially possess the properties for cross resistance across all tick species and stages. Bm86 was found effective against *R. annulatus, B. decloratus* and is partially protective against *Hyalomma* spp.
- **Chimeric vaccines:** Chimera refers to a mixture of two form/antigens. It was proposed as the expression of different tick antigens/epitopes as a single protein that can elicit cross

protection against heterologous tick challenges. Example is the BM95-MSP1a chimeric protein employing *R. (B) microplus* BM95 antigen and *A. marginale* Major Surface Protein 1a (MSP1a) produced in E. coli [29].

- **Transmission blocking vaccines: Targets the vector in such a way that it blocks the transmission of one or more pathogens carried by the vector. Vaccination with 64 TRP prevented transmission of tick-borne encephalitis**
- **Cocktail vaccines against ticks and tick-borne diseases:** Cocktails are vaccination preparations that combine functionally distinct antigens with an adjuvant. The broad-spectrum cocktail vaccine developed by [27], contains recombinant GST (glutathione S-transferases) proteins from various tick species. They used E. coli to express the targeted proteins from *R. appendiculatus, R. decoloratus, R. microplus, A. variegatum,* and *H. longicornis* as rGST-Ra, rGST-Rd, rGST-Rm, rGST-Av and rGST-Hl.

Tick-pathogen interaction studies employing a systems biology approach can lead to the discovery of new target antigens, which can aid in the selection of the appropriate targets for controlling tick infestations and pathogen transmission. Vaccinomics combines transcriptomics, proteomics, immunogenomics, systems biology and bioinformatics to create next-generation vaccinations.

Anti-tick microbiota vaccines

Ticks coexist and interact with symbionts and commensal bacteria in addition to pathogens forming an ecological unit, the tick holobiont. The tick hologenome, which is made up of host and microbiome genomes, is complementary. Numerous bacterial genera, such as Pseudomonas, Sphingobacterium, Acinetobacter, Enterobacter, and Stenotrophomonas, are found more commonly in several hard tick species, [25] represented in figure 2. Reduced abundance of certain keystone bacteria and/or endosymbionts may cause predictable changes in the organization of tick microbial communities. Immune targeting of key members of the tick microbiome by host antibodies could result in microbial dysbiosis, impacting tick physiology and vector competence. For *A. phagocytophilum*, crosstalk between tick microbiota and tick gut structure, as well as its influence on tick-borne pathogens, was observed. In this case, [1] found that *A. phagocytophilum* causes the expression of *I. scapularis* antifreeze glycoprotein (IAGFP), which disrupts tick microbiota, reduces peritrophic membrane (PM) thickness, changes gut permeability, and reduces bacteria biofilm formation

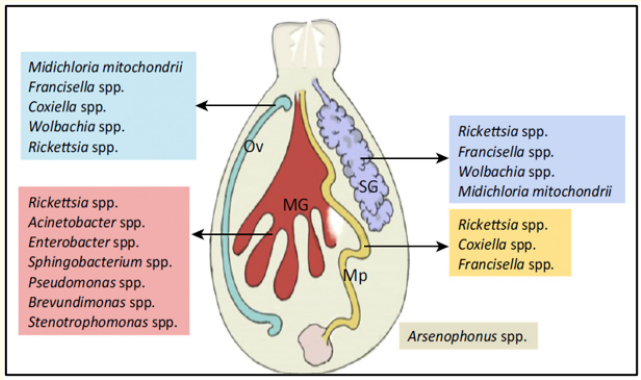

Figure 2: Predominant bacterial members of the tick microbiome. A schematic representation of bacterial genera frequently observed in the salivary glands (SG), midgut (MG), ovary (Ov), and Malphigian tubules (Mp) of ticks. [25].

capacity. To colonize successfully, *A. phagocytophilum* requires a disturbed PM. These findings suggest that there is a link between the tick microbiome and the tick gut, in which the composition of the tick microbiota influences the integrity and function of the tick gut barrier, and thus the colonization of tick-borne pathogens. Host antibodies, in combination with complement proteins, modulated the vectors microbiota [20], which not only preserve their immunological activities inside ticks, but also get access to a wide range of tick tissues, including the midguts and salivary glands [11]. Notably, no mortality was linked to antimicrobiota vaccine, and the mice showed no signs of pain following the vaccination [20].

The existence of a core tick microbiome is required for the efficient use of anti-tick microbiota vaccines in the field. If the taxonomic composition of the tick microbiome is very varied, and no bacterial core is shared among individual ticks in the population, host antibodies directed against one of its bacterial components would only affect a small percentage of ticks. Individual tick microbiomes were discovered to be so diverse in some locations that no taxon was recognised as being shared by all analysed samples [35]. Some tick species (e.g., *Ornithodoros maritimus* and *I. scapularis*) have consistent correlations with bacteria in their microbiome, implying the existence of a core microbiome [13]. These findings support the concept that at least certain tick species' microbiomes contain stable and widespread microorganisms that could be exploited as live vaccination candidates. The lack of tools for the

precise manipulation of the tick microbiome is currently a major limitation to achieve mechanistic insights into the tick microbiome [26]. Anti-tick microbiota vaccinations are thus a novel and promising technique for manipulating tick microbiota and altering tick physiology. Furthermore, because anti-tick microbiota vaccines allow for the targeting of specific bacteria, they can be utilised to investigate the role of certain bacterial species in tick physiology.

Genetic manipulation of endosymbionts

In addition to a variable microbiome, studies have revealed that adult female ticks are often dominated by a particular taxon with a high relative abundance, most likely endosymbionts. The majority of tick endosymbionts have been found in the ovaries, from whence they can reach the eggs. In contrast to the microbiome's makeup, which is tightly tied to the ticks' biological niche [40], tick endosymbionts have been found to have a high rate of transovarial transfer in various tick species [15]. Rickettsia or an unknown genus of the Enterobacteriaceae family, *Coxiella* and *Francisella*-like endosymbionts (FLE) are some of the most prominent taxa. Some of these bacteria may furnish ticks with cofactors and vitamin B (e.g., *Coxiella* and *Francisella*), amino acids and haeme (e.g., *Francisella*), or de novo-synthesised folate (e.g., Rickettsia). Antibiotic-based Francisella endosymbiont elimination from tick offspring resulted in abnormal tick development and hindered nymph growth and moulting to adults [8]. Thus, transgenerational microbial inheritance in ticks includes bacteria that are indispensable for tick development.

The endosymbiont population of tick vectors could be utilized in a variety of ways, notably as a chemotherapeutic target and a vaccine target for vector control. Expression of antiparasitic compounds by disease-transmitting vectors genetically transformed symbiotic bacteria could be a powerful way towards controlling specific arthropod-borne diseases.

- **Chemotherapeutic approach:** Exploits the endosymbionts of arthropods vectors as a chemotherapeutic target with the aim to disturb the symbiosis

- **Immunological approach:** Immunization of animals with the whole killed endosymbionts or purified antigens or recombinant antigens of the endosymbionts would render them immune to tick vectors

- **Wolbachia cytoplasmic incompatibility (CI) based approach:** It is the phenomenon in which mating between *Wolbachia* infected male insect and female insect of the same species without *Wolbachia* infection (Unidirectional CI) and mating between insects of the same species with different *Wolbachia* strain infection (Bidirectional CI), result in embryonic mortality. Reciprocal mating (infected female x uninfected male) and mating between infected individuals are fully compatible. *Wolbachia* modifies the sperm of the infected male during spermatogenesis by an unknown process. If a modified sperm enters an incompatible egg (uninfected or infected with different strain), a delay in breakdown of nuclear membrane of pronuclei of sperm occurs resulting in mitotic asynchrony and embryonic death [36].

- **Paratransgenesis:** The midgut bacteria of arthropod vectors can be engineered to express and secrete effector proteins which block the parasite invasion or kill the parasite in the midgut or hemolymph or reproductive tract. Vector that harbours the genetically transformed endosymbionts is called as paratransgenic vector. This strategy has shown promise in controlling the transmission of *Trypanosoma cruzi* by *Rhodinus prolixus*, genetically transformed *Rhodococcus rhodnii* was delivered nymph orally in such a manner to express an antimicrobial peptide, L-cecropin A, inside the gut lumen which conferred resistance status to the paratransgenic [9].

Biological control

Classical biological control entails identifying, evaluating, and importing a natural enemy from different location, as well as the conservation of local natural enemies and the enhancement of biocontrol agents. Individual inoculations or inundative releases of natural enemies are examples of application methods. 96 commercial active compounds based on microorganisms are included in the Bio Pesticide Manual [6].

- **Bacteria:** When sprayed on unfed or engorged adults of *Argas persicus* or *Hyalomma dromedarii,* [14] discovered that three commercial varieties of *Bacillus thuringiensis* (*B. t. kurstaki, B. t. israelensis*, and *B. t. thuringiensis*) caused mortality. During sporulation, *B. thuringiensis* produces crystalline d-endotoxin, which destroys insect midgut walls.

- **Fungi:** out of the 700 species of entomopathogenic fungi, the anti-tick pathogenicity of *Metarhizium anisopliae* and *Bessinia bassiana* was found to be the strongest. Tick eggs, unlike many insect eggs, are extremely vulnerable to fungi, with up to 100 percent of eggs exposed to fungi in the lab failing to hatch. The disadvantage with fungi is that they are slow in killing their host, need high humidity to germinate and sporulate, are susceptible to UV irradiation, and some strains can affect non-target arthropods

- **Entomopathogenic nematodes (EPNs):** Heterorhabditid and Steinernematid nematodes are known to be obligatory parasites of insects. The third/infective juvenile (IJ), the nematode's only free-living stage, actively seeks out and enters the host through natural openings, then releases symbiotic bacteria that kill the host insect within 24-72 hours. The nematodes subsequently grow within the host cadaver, releasing thousands of IJs into the environment 6–18 days after infection. *In vitro* experiments showed that tick hemolymph hinders the growth of EPNs but the reason(s) for nematode mortality within ticks are yet to be understood.

- **Parasitoids:** The only species that has been released for biological control of ticks is *Ixodiphagus hookeri.* Inundative releases to control ticks in limited areas (e.g., farms, recreation areas) are potentially feasible. *Ixodiphagus* spp. parasitize only ticks, as far as is known. Therefore, non-target effects would presumably be minimal if these parasites were released for tick control.

- **Predators:** Many tick bio-suppressors such as ants, beetles and many bird species are general predators that feed occasionally on ticks, therefore their populations do not depend on the sizes of the tick populations. Chickens confined with livestock can ingest ticks, hence can be maintained on small farms could help to reduce tick populations at nearly no cost. *Buphagus africanus* (the yellow-billed oxpecker, YBO) and *B. erythrorhynchus* (the red billed oxpecker, RBO), both native to Africa, are the only birds known to feed specifically on ectoparasites, especially ticks.

Phyto-acaricides

Widely available compounds with qualities such as fast degradation, non-selectivity, immunostimulatory action, low mammalian toxicity, and overall environmental friendliness. These substances work to control the population of vector flies, fleas, lice, ticks, and mites by reducing their growth, development, and reproduction in various ways. A single ectoparasiticidal plant's potency can be boosted by combining it with another plant or an active substance having adjuvant qualities.

- **Pyrethrum:** It is made up of multiple esters known as pyrethrins that are obtained from the flower of *Chrysanthenum cinerariaefolium*. Pyrethrins are neurotoxins that target sodium ion channels in insect nerve cells, causing a knockdown effect that results in repetitive and protracted nerve firings. The insect dies as a result of the loss of motor coordination and paralysis caused by the hyperexcitation [19].

- **Neem:** Physiologically active component of neem is azadirachtin. It shares structural similarities with insect hormones called "ecdysones," which are essential for insect metamorphosis leading to anti-feedant actions [5]. Neem's essential qualities include serving as a free radical scavenger and immunomodulator due to its high antioxidant content.

- **Essential oils and plant extracts:** The profound anti-tick activity of the herbal acaricide product containing Neem oil, Karanj oil, Eucalyptus oil, Rohit Gawash, and Karpura against egg and adult stages of Rhipicephalus microplus ticks was recently demonstrated, with treated females laying very few eggs and only a few of them hatching [30].

In the last few years, phytoacaricide research has made significant progress. However, the majority of the promising results have been limited to *in vitro* investigations. The reduction of efficacy of plant extracts when utilised *in vivo* is a barrier to phytoacaricide development. Hence there is a need to conduct pharmacokinetic investigations for the identification of marker compound to assure that standard extracts are used [12].

Semiochemical assisted control.

Semiochemicals are host/tick-derived chemical signal carriers that are secreted into the environment and mediate tick behavior. Semiochemical communication in nature can be classified according to the sort of behavior it mediates, rather than the molecules involved. Kairomones, allomones and pheromones are the three types of semiochemicals of which pheromones are the most stud-

ied. Ticks produce a wide range of pheromones, including those utilised for food sensing, arrestment, alarm, and sex pheromones. Different compounds are employed as pheromones, ranging from highly volatile molecules like methyl salicylate, o-nitrophenol, or 2, 6-DCP to non-volatile contact pheromones like cholesteryl esters [33]. Shown in the figure 3 are the types of pheromones:

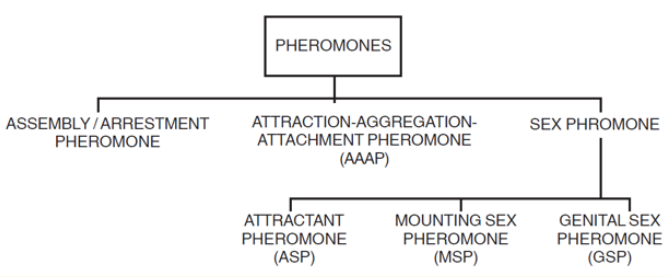

Figure 3: Classification of semiochemicals [33].

According to Sonenshine [32-34], manufacture of a long-lived control device required the continuous delivery of pheromone source by a slow-release device. Three specific types of pheromones assisted tick control devices have been developed namely arrestment's, confusants and attract and kill devices, which lure the ticks towards the device and the acaricide in the device kills the attracted ticks.

- **Arrestment pheromone impregnated devices:** Purines from the faecal wastes of the prostriate tick, I. scapularis, were incorporated into oily droplets discharged from a pump sprayer for delivery to vegetation. The oily droplets stuck to the plants where I. scapularis was questing. Ticks that come into contact with the arresting pheromone components guanine and xanthine, as well as the acaricide permethrin, attach to contaminated surfaces and acquire a deadly dose of acaricide [34].

- **2, 6-DCP as confusants:** A confusant takes advantage of the male's mate-seeking behaviour by reducing the male's capacity to locate females as the emission source. To confuse mate-seeking males, a sex pheromone–pesticide combination was applied, leading them to acquire additional pesticide as they wandered through the pheromone and pesticide-treated fur [33,34].

- **Tick decoys:** The female mimics or decoys were micro capsules, plastic decoys, or a trap made of rubber septum, hollow threads, capillary filaments, polyethylene or gelatine capsules, or multi-layer tags made of natural or synthetic polymer resins. ASP and MSP were used to lure mate-seeking males to these decoys. Small amounts of toxicant in the plastic spherules were used to kill the attracted ticks.

Tickbot is a semi-autonomous robotic device that can sweep the vegetation of host-seeking ticks in tick-infested habitats and kill them before they can attack people and/or their pet animals. Following a guide wire and assisted by dispersal of CO2, a kairomone along its predetermined pathways, the device consists of a drag cloth that is treated with acaricides, onto which the ticks cling and acquire the lethal dose. TickBot created a virtually tick-free environment within as little as 1 h following its deployment [10]. TickBot reduces the incidence of ticks in targeted treated regions without releasing toxic chemicals into the environment.

Figure 4: Image of tick bot, consisting of the robotic car and a drag cloth [10].

Conclusion

To combat the growing threat of TTBDs, it is necessary to embrace technologies that are environmentally friendly, less expensive, simple to use, and have a wider application range, these include the use of phytoacaricides, semiochemical mediated killing and BCA's. With the advent of RNAi technology, several tick proteins are being characterized, which can be used as potential vaccine candidates for immunizing the host species. Furthermore, vaccine efficacy can be increased by using 'omics' tools and techniques in the identification of novel antigens and efficient delivery into

the host, such as Lipid Nano Particle (LNP)-mRNA vaccines, viral vector vaccines, and live vector vaccines. Gene editing technologies such as the CRISPR CAS 9 could be utilized to genetically control the vector populations through manipulation of endosymbionts and the tick microbiomes, that has the potential to effectively control the TTBD's. It is also evident that effective control of vectors and slowing down of emergence of acaricidal resistance cannot be accomplished by adopting only one control strategy. An integrated vector control strategy which draws together a range of appropriate complementary tactics may offer the best approach for the future, allowing one tactic to mask the weaknesses of another.