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TICK-BORNE BACTERIAL PATHOGENS OF LIVESTOCK AND THEIR CONSEQUENCES

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Abstract: In the modern world, ticks are considered to be second only to mosquitoes as a vector of various infectious diseases in livestock as well as in humans. Most tick species preferred suitable environmental conditions and typography that establish distribution and consequently increase the risk areas for different tick-borne diseases. They have a vectorial capacity to transmit and consider reservoirs of pathogens that cause direct damage to the host during blood-feeding and through the secretion of toxins present in the saliva of the animal. The main consequence of the tick primarily depends on the different pathogens they can transmit like bacteria, protozoa, viruses, and helminths. This review explains the various aspects of tick biology, vector competence, and tick microbiome identification, mainly focused on bacterial pathogens, techniques or methods used for their characterization, and different bacterial diseases associated with it, as well as pharmaceuticals used against ticks and ticks-borne pathogens.

Keywords: Bacterium, Diseases, Livestock, Pathogens, Techniques, Ticks.

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INTRODUCTION

Ticks (Acari: Ixodida) are globally one of the most important obligate hematophagous arthropods, that parasitized and vector for infectious diseases in animals and humans (Parola and Raoult, 2015). There are primarily three tick families (Ixodidae, Argaside, and Nuttalliellidae) out of which, the majority of tick species belong to Ixodidae (hard ticks) and Argasidae (soft ticks) families (Berrada and Telford, 2009). Two major tick families are Ixodidae or 'hard ticks' so-called due to the presence of their sclerotized dorsal plate and the Argasidae or 'soft ticks' so-called because of their flexible cuticle whereas a third family 'Nuttalliellidae' is monospecific, which is found only in South Africa (Koneman *et al*., 2006). With some exceptions, mobile ticks belong to three families and feed mainly on blood.

Ticks have three fundamental life stages i.e. larva, nymph and adult (male and female). Ixodids have pronounced sexual dimorphism as adults. Adult females (and immatures) have a shortened scutum and a small pronotal shield behind the capitulum, which aids in allowing for greater distention of the idiosomal integument during

eating (Lora, 2001). Argasid and Ixodid ticks differ both anatomically and in their life cycle. Ixodids have several different characteristics that boost their vector potential. Their bite is painless and might go unnoticed for a long time. They remain firmly attached to the host and feed for reasonably extended periods of time. Argasid, on the other hand, often feeds on a single host species frequently and briefly (Reuben, 2010). They are mainly found in dry locations, and the majority of species are found in protected areas close to their hosts. These species show negative geotropism behavior hiding in crevices and roofs, being highly reproductive, and females lay 2000-3000 eggs in their entire lives. Unfed larvae can survive up to 8½ months, nymphs up to 6 months, and adults up to 19 months and hence when these larvae feed, they spread numerous bacterial, viral, and protozoan infections, some of which are zoonotic, are frequently carried by and transmitted by these species (Ram *et al*., 2004). The contact of tick with people and animals is becoming more likely as a result of habitat change and distribution pattern changes. Various pathogens associated with ticks have direct impact on livestock by causing direct and indirect damages. The damage are losses in meat and milk production, mortality, loss of weight gain, trauma, spoilage, toxicity, secondary infectious, erosive lesions in the skin, and paralysis. The indirect damages or injuries are acting as a vector of several infections and parasitic diseases (Garcia-Vazquez *et al*., 2015).

TICK BIOLOGY

Ticks as ectoparasite

Most arthropods can have a major influence on the productivity and welfare of livestock. In recent years, many countries play an important role in animal husbandry and parasite control strategies, which extensively increased the requirement for a better understanding of tick' s distribution and prevalence as livestock parasites. In some cases, these modifications have been related to moves towards increased productivity, such as higher-stocking densities, indoor confinement, large-scale rearing units, reduced genetic diversity, and large-scale movement of animals, and in others, with a move towards organic farming (Colebrook and Wall, 2004).

Among the ectoparasite, ticks have been recognized as the most important constraint for optimum production in livestock of tropical and subtropical countries. Ticks belong to the family Ixodidae (Acari: Ixodida) and are obligate hematophagous ectoparasites of domestic animals and economically important pests of cattle. These ectoparasitic arthropods feed or shelter on the host epidermis by puncturing or burrowing into the surface. Their excessive or continuous feeding may also result in blood loss, excoriation, pruritus, and alopecia in some cases which may cause death. The behavior of ectoparasites also may cause harm indirectly particularly when present at high intensities by causing a disturbance, increasing levels of behavior such as rubbing and leading to reduced time spent grazing or ruminating and in some cases, to self-wounding (Berriatua *et al*., 2001). When a large population of ticks feeds these become cause of injury to livestock and wildlife due to excessive blood loss.

The tick species have an impact on cattle because they cause tick worry, which causes an animal to weaken, lose condition, and have decreased immunity to diseases. This results in overall economic loss because the animal does not develop and produce as expected, which in turn reduces the herd's productivity (Drummond, 1983). Tick bites injure skin and teats, which results in blood loss and the formation of sores, which expose the animal to secondary bacterial infections and onset of diseases more readily. Different agro-climatic conditions of high temperature, moderate rainfall, humidity, and adequate water sources favour their perpetuation and propagation (Singh and Rath, 2013).

Identification of ticks

The correct identification of tick species and associated pathogens is a crucial step that can contribute to distinguishing tick vectors from non-vectors. Morphological identification of tick species is done by using standard taxonomic keys for endemic species. This approach of species identification in a specific geographic region is the oldest and very reliable. Singh and Rath (2013) studied morphological characters to identify different types of tick species and observed that cattle were infested with hard ticks (*Rhipicephalus (=Boophilus*) sp., *Hyalomma* sp.

and *Haemaphysalis* sp.) and observed higher infestation in female cattle (43.30%) than males. Chillar *et al*. (2014) conducted a survey and observed that out of 662 animals, 309 animals were found infested with ticks from three different genera of family Ixodidae and identified species of tick from three genera were *Hyalomma anatolicum anatolicum* Koch, 1844, *Hyalomma anatolicum excavatum* Koch, 1844, *Rhipicephalus sanguineus* (Latreille, 1806), *Rhipicephalus (Boophilus) microplus* (Canestrini, 1888), *Rhipicephalus (=Boophilus) decoloratus* (Koch, 1844) and Dermacentor spp. However, this approach is frequently difficult to determine these physical differences between closely related tick species when tick specimens are injured, engorged, or from non-adult instars (Lempereur *et al*., 2010).

Additionally, morphological classification requires for entomological knowledge, which is either non-existent or insufficient in most of the impacted countries. Therefore, if the concerned entomological staffs are not properly trained, simply and merely relying on morphological identification of tick species may lead to misidentification. Molecular tools have been more or less used to overcome the limitations of morphological identification. Additionally, molecular techniques for the identification of ticks were developed, particularly for specimens with damage where the most of morphological features are no longer distinguishable. In addition to these DNA-based techniques, which include the nuclear and mitochondrial ribosomal small subunit of RNA genes (12S and 16S) and the mitochondrially encoded cox1 gene for tick species identification, cytochrome b has also been utilised for this purpose. The cox1 sequence was found to be the most accurate and appropriate marker for differentiating tick species across several investigations on ticks through molecular methods. Conversely, there are some drawbacks to these tools, which are expensive, time-consuming, and require primer-specific targeting (Yssouf *et al*., 2016). Recently, the MALDI-TOF MS method has been recommended as an alternative and advanced tool to overcome the limitations of the above two methods in arthropod identification. Since then, studies in several laboratories have demonstrated that MALDI-TOF MS is a remarkably robust tool for identifying many species of arthropod vectors and non-vectors (Sevestre *et al*., 2021).

Tick as a vector

Ectoparasites that derive their nutrition through blood-feeding (hematophagy) are competent vectors of disease. Ticks are the most diverse ectoparasitic and adaptable vectors of pathogens considered second to mosquitoes as vectors of various human pathogens viz. viruses, bacteria, rickettsia, spirochetes, and tick-borne bacterial species of genera *Anaplasma, Borrelia, Coxiella, Ehrlichia, Francisella* and *Rickettsia*, are well-known pathogens of humans and livestock (Munderloh *et al*., 2005). The rearing of these vectors is strongly impacted by microbial interactions in the tick, which also exhibit antagonistic behaviour toward harmful bacteria as a result of their establishment and transmission.

When describing an arthropod's capacity to act as a disease vector, the terms 'vectorial capacity' and 'vector competence' are frequently employed. Despite this, behavioural and environmental factors that affect things like longevity, vector density, and competency also have an impact on vectorial capacity. A crucial element of vectorial capability, vector competence largely depends on genetic characteristics, which primarily affect a vector's power to transmit a virus (Beerntsen *et al*., 2000). Both of these factors have an impact on characteristics like the relationship between a tick, its host, and its pathogen, the length of the tick's attachment, its preferences for particular hosts, and the interactions between the microbiome and pathogens (Vayssier-Taussat *et al*., 2015).

However, the pathologies caused by these infectious organisms are frequently zoonosis, for which human serve as unintentional host, and they indicate the infectious agent has reached its end. Habitats where ticks are present are the main means of disease transmission in their host animals. Tick bites are the most common method of transmission; however other methods include contact with bodily fluids contaminated with tularemia or blood transfusions for *Babesia* species etc (Piesman and Eisen, 2008). The pathogen mostly persists in ticks for a long time because it can be transmitted from stage to stage

i.e. transstadial transmission, from females to eggs (vertical transmission) and from tick to tick through the host (horizontal transmission) depending on the pathogen. Co-feeding behaviour enables the transmission of some infectious agents, such as the tick-borne encephalitis virus and bacteria that cause Lyme disease, from an infected tick to a healthy tick at the site of the animal's bite, even in the absence of viremia or bacteremia in the host (Randolph *et al*., 1996). Determining the molecular drivers of tick-borne diseases and exposing paradigms for their management and prevention depends on the explanation of the mechanisms involved in tick-pathogen interactions that impact vector competence.

Pathogenicity/infestation of ticks

India has the largest livestock population in the world with 192.49 and 109.85 million of the world's cattle and buffalo population respectively and becomes the largest milk producer in the world (Anonymous, 2018-19). India shows a major contribution to the world's livestock resources with nearly 57% of the world's buffaloes, 16.5% cattle, 16.3% goats and 5.7% sheep. Livestock constitutes a chief source of animal protein for farm families and is also considered as draught power in agriculture and transport, moreover, their dung is used to primarily increase soil fertility. Ticks are obligate hematophagous arthropods, parasitizing every class of vertebrates in almost every region of the world, and estimated that 80% of the world's cattle population is exposed to tick infestation. In India, major damage is caused to livestock by ticks and tick-borne diseases (Ghosh *et al*., 2006).

Ticks and the pathogens they transmit have significant effects on cattle, including direct harm (death), losses in meat and milk output, fetus loss, trauma, toxicity, harm to the leather industry, and secondary infectious harm (spoiled food, erosive skin sores, paralysis, etc.). Ticks transfer the widest range of infections of all known blood-sucking arthropods, primarily viruses, protozoa, and rickettsiae. Sarkar (2007) and Rony *et al*. (2010) reported a higher prevalence of tick infestations in females as compared to male cattle. Compared to older animals, younger animals exhibit a higher infection rate.

Animal resistance increases with age, and in the earlier stages of their life cycles, animals become more resilient and adaptive. Another study found that compared to adults and older animals, calves were twice as likely to get a tick infestation. According to Sajid (2007) and Islam *et al*. (2009), this may be because juvenile animals have skin that is softer and thinner and may also have less immunity. The incidence of infestation was substantially greater in older animals with an age range of > 8 years (71.1%), followed by adults with an age range of > 2 - 8 years (65.4%), and the lowest was observed in young animals with an age range of 2 years (47.1%) (Rony *et al*., 2010). According to Kabir *et al*. (2011), native cattle (43.8%) had much more ticks than crossbred cattle (24.1%) exhibited. In another study, it was observed that the perineum, udders, and external genitalia of cattle had the highest tick infestation rates, followed by the dewlap, neck, chest, inner thighs, tail, and ears, around the eyes, flanks, and legs (Atif *et al*., 2012). This study may be related to the fact that the perineum, external genitalia, and thighs are parts of the body with abundant blood supply and that insects tend to prefer thinner skin with short hair when invading. Moreover, inevitably facilitates tick mouthpart entry into the highly vascular locations for feeding (Sajid, 2007).

Animals have reportedly developed abscesses, screwworm infestations, and sores as a result of tick bites. It was discovered that the region in consideration had a strong correlation with high levels of tick infestation. Genera *Amblyomma* and *Hyalomma* have large mouthparts, which allow them to enter tissues more deeply than *Boophilus* genera with short mouthparts. They tear the muscles, causing a few minor injuries that lead to tissue necrosis (Sonenshine, 1991). When tick bite wounds are infected with bacteria, they develop lesions that eventually rupture to form open sores. The wounds could later develop a screwworm infestation. Teat damage can cause cows to stop producing milk, which prevents new-born calves from receiving the essential colostrum, which is their first line of defence.

Tick microbiome

Arthropods that feed primarily on host blood are known as hematophagous and often have a

limited diet. The primary factor determining their microbiome composition is whether they are facultative or obligatory blood feeders (Narasimhan and Fikrig, 2015). Ticks, bugs, and tsetse flies are examples of obligate blood-feeders that have come to rely on microbial endosymbionts to supplement many B vitamins, including biotin, riboflavin, and folate, which are lacking in the blood of these species. These endosymbionts have been found in bacteriocytes, which are specialised large cells seen in some arthropods and which are connected to the gut or reproductive organs. Despite this, tick species have a rather long lifespan and just a few unique possibilities throughout their lifetime to pick up or lose microorganisms (Rio *et al*., 2016).

The first or most important opportunity for acquiring a microbiome is seeded from the adult female tick to their offspring through transovarial transmission. Ticks generally take up microorganisms in a variety of methods, including transovarial transfer, environmental contamination, blood feeding on vertebrate hosts, and mating with other ticks. Ticks come into contact with soil bacteria both before and after the feeding phase. Transovarial, oral, and cuticular pathways are the most common entry points for bacteria into ticks. In addition to Acidobacteria, the common soil microbiome also contains bacteria from the phyla Verrucomicrobia, Bacteroidetes, Gammaproteobacteria, Deltaproteobacteria, Planctomycetes, Actinobacteria, Alphaproteobacteria, and Betaproteobacteria, some of which may be connected to the tick microbiome (Narasimhan and Fikrig, 2015). It was discovered that tick larvae exposed to the field typically pick up microbial species by placing *I. pacificus* in field enclosures buried in the soil for varied lengths of time (0-6 weeks) (Couper *et al*., 2019).

Another study using mid gut immunostaining to analyse the microbiome found that certain taxa that had previously been isolated from wash samples were also recognised internally, including *Bacillus*, *Pseudomonas*, and Enterobacteriaceae. Microorganisms need to migrate from the mid gut and enter the glands after successfully entering in order to survive in the salivary glands. The interactions between specific microorganisms, ticks, and other symbioses can affect the establishment of germs in ticks (Parola *et al*., 2013). Populations of microorganisms in ticks at various phases of development fluctuate depending on the ecosystem in which they inhabit (Menchaca *et al*., 2013).

Additionally, their composition varied between organs, such as between the ovaries and mid gut. Ticks exhibit various metabolic consequences, such as the emission of some reactive oxygen species during normal aerobic respiration, as a result of the microbe (Enterobacteriaceae) residing within animals. As a result, *E. coli* has a variety of survival mechanisms, and some homologous regulators found in Proteobacteria are also well recognised to tolerate the oxidative stress that arises. According to Molina-Garza and Galaviz-Silva's (2019) observations, the majority of the bacterial population (160/54.6%) was recovered from the tick *R. microplus*. Gram-negative bacteria were found to be slightly more common (152/51.87%) among these isolates than gram-positive bacteria (141/48.12%).

TECHNIQUES USED FOR IDENTIFICATION

Different techniques including culture, staining, metabolic assay, serology, and infection studies, helps in the detection and identification of bacterial species based on their physical, biochemical, and pathogenic properties (Philip *et al*., 1978). However, when stained with Gimenez or Giemsa staining, the spotted fever group *Rickettsiae*, *Ehrlichia* and *C. burnetii* are easily seen as small rods. However, these techniques have certain significant limitations because they are time-consuming and less sensitive or specific in their detection and accurate identifying bacterial species (Busse *et al*., 1996). To overcome these said limitations, culture-independent molecular techniques are applied as a rapid and reliable method to identify microorganisms (Sparagano *et al*., 1999). In order to identify microbial communities from various habitats, culture-independent methods (CIMs) have been developed since the usage of molecular techniques.

Several techniques based on the direct amplification and analysis of the small subunit ribosomal RNA gene has been developed over the past 20 years to study environmental

microorganisms directly. In recent years, diverse methods for characterizing tick microbiome assemblages are changing rapidly, with several technologies being used to assay the DNA sequence variation in bacterial communities of ticks. The use of these molecular techniques also facilitated species identification which are previously unrecognized and difficult to culture or cannot be cultured (Clarridge, 2004). Bacteria typically infect and multiply in all of the ticks' organs and fluids, and it is quite easy to detect them in the hemolymph or salivary glands. DNA molecules that differ in sequence by one or more nucleotides are separated using mutation scanning techniques like denaturing gradient gel electrophoresis (DGGE), restriction fragment length polymorphism, terminal restriction fragment length polymorphism, quantitative polymerase chain reaction, and single-strand conformation polymorphism (SSCP) analysis. Similar to how several PCR-based molecular techniques like fluorescence in situ hybridization and microarray have also been employed for identification. Numerous unique research areas, including meta-transcriptomics, meta-genomics, meta-proteomics, and single-cell genomics, have emerged recently, partly due to the novelty and use of next-generation sequencing techniques.

Hemolymph test

Although bacteria may enter or multiply in all organs and fluids of tick species, they are relatively easy to detect in the hemolymph or salivary glands. Hemolymph tests are typically performed on live ticks after the distal leg is severed. The first step is to smear hemolymph from the area on a microscope slide, stain it, and then check it for germs.

Antigen-capture enzyme immunoassay

The antigen capture enzyme immunoassay, which mainly utilizes a monoclonal antibody that binds to antigens having a molecular weight of 135-kD considered a surface protein common with various members of the spotted fever group, is suggested for primary screening of tick samples because it is reliable and however less labor-intensive than the direct immunofluorescence and hemolymph tests (Radulovic *et al*., 1994). In the direct immune detection method, recognition of organisms was done from hemolymph or organ smear. Slides were first air-dried and fixed in acetone, then polyclonal or monoclonal antibodies conjugated with immunological fluorescent markers were applied (Xu and Raoult, 1997). The detection of *Ehrlichiae*, *C. burnetii*, *Borreliae* and *F. tularensis* species was also possible using this approach. Several useful and more sensitive molecular tools have been currently developed, such as real-time PCR and reverse line blot (RLB) assay to detect and identify Rickettsia species in hosts and vectors (Jado *et al*., 2006).

PCR amplification

PCR amplification of the 16S rRNA gene is the most commonly used method for determining bacterial community composition, with the alternating conserved and variable sequence of it, allowing the construction of universal primers bracket of short informative regions. In the microbiota, firmicutes and gamma proteo-bacteria were the dominant taxa. In another study, a total of 887 adult *Ixodes ricinus* ticks (469 females and 418 males) were screened for Rickettsia, Anaplasma, and Coxiella by DNA using PCR and gene sequencing. Out of these isolates, Rickettsial DNA was detected in 9.5-9.6% of the ticks while six of the ticks (0.7%) were infected with an Anaplasma species.

Schabereiter-Gurtner *et al*. (2003) identified the bacterial communities in ticks by using a molecular approach i.e. 16S rDNA genotyping in combination with analysis of denaturing gradient gel electrophoresis for detection and identification of bacteria infecting ticks. For phylogenetic identification, the obtained sequences were compared with 16S rDNA sequence of known bacteria listed in the Gene Bank database and analysis revealed a limited variety of genera viz. *Staphylococcus, Rhodococcus, Haemobartonella, Moraxella, Pseudomonas*, and *Borrelia*. Rudolf *et al*. (2009) recovered 151 bacterial isolates and identified them employing 16S rRNA gene sequencing from larvae, nymphs and adults of field-collected ticks, 67 strains from *Ixodes ricinus*, 38 from *Dermacentor reticulatus*, 46 from *Haemaphysalis concinna*.

Next-generation Sequencing

The advancement of next-generation sequencing (NGS) technology over the last decade has made it

possible to rapidly and inexpensively investigate the genes and genomes of single cells and communities of microbes (Buermans and den Dunnen, 2014). Amplicon sequencing and shotgun sequencing are two NGS techniques that may be used to study microbiomes (which covers transcriptomics and metagenomics). In 16S amplicon NGS research, the nine hypervariable regions (V1-V9) of the bacterial 16S ribosomal RNA gene (16S) can be used to target bacterial taxonomic identification. Regions V1-V4 has been most often sequenced in ticks. Ticks 16S amplicons have been sequenced using the 454 (Roche) pyrose quenching method, the Ion Torrent (Thermo Fisher) semiconductor ion detection method, and the MiSeq (Illumina) platform that uses fluorescent dye detection sequencing techniques. Compared to the Ion Torrent and MiSeq systems, 454 platforms, such as the 454 GS Junior + and 454 GS FLX Titanium XL+, offer the benefit of larger read lengths (up to 1 kbp), which have been employed in the majority of published bacterial microbiome investigations on ticks (Ercolini *et al*., 2012).

TICK-BORNE BACTERIAL SPECIES AND THEIR DISEASES

Ticks act as vectors for a group of pathogens that are veterinary and zoonotic significant and several tick-borne diseases (TBDs) associated with these are known to be endemic. This mainly includes bovine babesiosis which is caused by *Babesia bovis* and *Babesia bigemina* another specie *Anaplasma marginale* which cause bovine anaplasmosis and heartwater caused by *Ehrlichia ruminantium*. In addition, several other mildly pathogenic *Theileria* species such as *Theileria velifera*, mutans and orientalis have also been reported to occur (Kumsa *et al*., 2014). A list of tick-borne bacterial species and their diseases are given in table 1.

The life cycle of an ixodid tick has four distinct stages: egg, larva, nymph, and adult. Each post-embryonic stage requires blood for growth and moulting. Ticks inject saliva into the host (tick) during the feeding phase to aid in the uptake of blood. Tick saliva typically contains a variety of bioactive substances that prevent blood clotting, suppress the immune system of the host, and aid in the development of a strong attachment to the host's skin. *Ehrlichia*, *Rickettsia*, and *Anaplasma* are tick-borne infections that concentrate in the salivary glands and are then transported into the host animal's blood while feeding. In indigenous breeds of cattle, the course of this tick-borne disease is usually subclinical. However, they show a bigger challenge to vulnerable exotic breeds of cattle, thus posing a major problem in the upgrading and development of cattle production (Mekonnen *et al*., 2007).

Table 1: List of tick-borne bacterial species and their diseases.

Ticks	Isolated bacterial species	Diseases	References
Rhipicephalus sanguineus	*Rickettsia conorii*	Mediterranean spotted fever	Bernasconi *et al*. (2002)
	Coxiella burnetii	Query (Q) fever	
Ixodes spp.	*Spiroplasma*	Scrapie or Creutzfeldt-Jakob disease	Henning *et al*. (2006)
Ixodes ricinus	*Spirochete*	Lyme disease	Richter and Matuschka (2006)
Ixodid	*Rickettsiae*	Rickettsioses	Raoult and Roux (1997)
Amblyomma americanum, Ixodes scapularis	*Ehrlichia*	Ehrlichiosis	Dumler and Bakken (1995)
Dermacentor variabilis	*Anaplasma marginale*	Bovine anaplasmosis	Kocan *et al*. (2003)
Ixodes (Amblyomma)	*Rickettsia ruminantium, Ehrlichia ruminantium*	Heartwater	Latif *et al*. (2020)

Major impacts of vector-borne diseases

Numerous costs are associated with the transmission of infectious diseases by bacterial and protozoal vectors. Financial cost incurred in the raising of farm animals, time spent due to illness or injury, and, most cruelly, the loss of human life among them. One of the biggest worries is the spread of vector-borne diseases from wildlife reservoir species to domestic animals or humans. The most important vectors, pathogens, environmental exposures, or ecological and evolutionary elements that enable the genesis of VBZDs have not been comprehensively defined, irrespective of the fact that they are acknowledged as a substantial category of emerging diseases.

New infections that have the ability to spread across species boundaries and from one host to another are continually a threat to both human and animal health. Zoonotic pathogens, like *Borrelia burgdorferi*, *Babesia microti* and *A. phagocytophilum*, are strongly associated with endemic periods of infection involving wild rodents and ticks. These illnesses may also be carried by ticks or animal hosts (Adelson *et al*., 2004). Modifications to the host, environment, or pathogen are frequently to blame for the re-emergence of vector-borne illnesses.

TICK CONTROL METHODS

The incidence and geographic distribution of the disease may be permanently changed by interventions that target the reservoir hosts or vectors. For bacteria that allow infections to move from reservoir hosts to people, particularly tick-borne illnesses, the tick species serves as the link. Targeting a particular infection at the vector, a tick, provides the advantage of potentially reducing all diseases spread by that vector. Instead of eradicating all ticks at once, the main objective of tick control strategies is to reduce a particular species due to its unique role (Laing *et al*., 2018). For the effective implementation of reasonable and sustainable tick control programmes in grazing animals, a full understanding of the ecology or epidemiology of the tick as it interacts with the host in particular climatic, management, and production situations is essential.

However, the majority of effective strategies for managing cattle ticks and tick-borne disease (TBD) rely on the administration of an acaricide medication, sometimes with only a basic knowledge of the relevant ecology or epidemiology. Prior to selecting a control programme, it's crucial to take into account all of these factors, including accessibility, advantages and disadvantages, and cost-benefit evaluations (De Meneghi *et al*., 2016). In an ideal situation, these measures should concentrate on the free-living and parasitic phases of the life cycle, and it is crucial to acknowledge their essential role in TBD transmission. In order to provide integrated control methods against the tick and associated hemoparasites, a number of strategies have been developed and are being explored.

Acaricide

Acaricide pesticides are commonly used to kill ticks and mite's species present on livestock as a parasite. Acaricides mostly include chlorinated hydrocarbons (e.g. dichloro diphenyl trichloroethane (DDT), pyrethroids (permethrin, flumethrin), organophosphorus compounds (diazinon), carbamates (carbaryl), formamidines and avermectins. Most of the organochlorines pesticides are persistent in the environment, like DDT, BHC, and cyclodienes as they accumulate in the body fat of livestock (Ware, 2000).

Organophosphates are generally considered the most toxic among all pesticides to vertebrates (Verma and Prakash, 2018; Prakash and Verma, 2021). Carbamate acaricides (carbaryl and promacyl) mainly work by inhibiting the target's cholinesterase but have very little mammalian and dermal toxicity. Among these, pyrethroids are the safest and most effective pesticides for the control of tick species. When an infestation is at its worst, acaricide techniques are usually utilised as a suppressive strategy, with multiple treatments applied at regular intervals. In a short amount of time, this suppressive technique is the most effective since it helps to maintain animals almost tick-free, minimising the direct impact of ticks and the danger of disease transmission. By using one of the several available acaricides, the tick population can be decreased. But frequent acaricide use also created resistant in tick species (George *et al*., 2008).

An ideal acaricide would be simple to use, inexpensive, and have a powerful knockdown ability. It would also have a strong enough residual

effect on females to stop them from laying eggs and safeguard animals from reinfestation by larvae. Additionally, it should not have any lasting effects on the quality of the meat or milk and shouldn't be hazardous to humans or animals. Unfortunately, no products of this form of acaricide have yet been created. But before it is widely used, further research would be needed to understand how this method would affect animal welfare in the short and long-term, including physiological changes, altered behavioural situations and prolonged breeding seasons. The development of resistance to these acaricides is the main drawback of the acaricidal strategy. Additionally, these may be extremely harmful to a range of species in the ecosystem (Van wieren *et al*., 2016).

Biocontrol

In recent decades, interest in creating anti-tick biocontrol agents has grown, including entomopathogenic bacteria, fungi, parasitoids, birds, and nematodes. In this control method, chalcid flies (*Hunterellus* sp.) function as hyperparasites, although they are difficult to assess and much tougher to handle or multiply for practical purposes. Ticks can be killed by fungus, viruses, and bacteria that are both naturally occurring and created specifically for this purpose. The fungus *Metarhizium brunneum* is an entomopathogenic fungus that has been discovered to kill a range of insects and arachnids, including *Ixodes* and isolated from moths (Bharadwaj and Stafford, 2010).

Various investigations indicate that it is an efficient biocontrol agent with little influence on non-target species (Fischhoff *et al*., 2017). Other biocontrol agents are entomopathogenic nematodes, which can have reduced oviposition, larval hatching, and egg production in *Rhipicephalus microplus* and other tick species (de Mendonca *et al.*, 2019). The biological agents, which commonly include predators like birds, spiders, ants, rodents, lizards, and beetles as well as parasitoids and parasites (Nematodes and fungi), are effective at attacking the soil-dwelling stages of the ticks, and based on the situation, these predators can ingest a significant number of ticks. *Ixodiphagus hookeri*, a parasitoid wasp, can be used as a biocontrol tool against pathogens carried by ticks by parasitizing the larval and nymphal stages of Ixodes ticks when the wasp lays its eggs in engorged ticks, their larvae consume them, and then further attacks another tick as the adult emerges (Krawczyk *et al*., 2020). Despite this, the management of dipterous insects or plant pests, which are harmful to both humans and animals, has gained significance over the development of biological tick control methods.

Anti-tick vaccines

Ixodes ticks are thought to be a vector for numerous diseases and frequently carry a variety of infections. Typically, a vaccination can protect a number of diseases while also focusing on a certain vector. Cows are effectively protected from tick feeding by the application of a commercially available vaccine against the BM86 protein from boophilus ticks (Fragoso *et al*., 1998). A number of Ixodes proteins, including salivary proteins, tick salivary lectin pathway inhibitors, and tick histamine release factor, demonstrate promise as potential vaccines (Narasimhan *et al*., 2020).

However, their ability to stop the spread of disease has proven to be just moderate to ineffective. This places strong evolutionary pressure on these proteins during the co-evolutionary process and makes protein development more challenging. The effectiveness of anti-tick immunisation could be increased by combining a number of moderately effective antigens with diverse activities (Rego *et al*., 2019).

Genetic control of ticks

The most popular strategy used to manage cattle ticks is the use of acaricides. However, improper use of these substances leads to the development of resistance against certain pesticides, which ultimately reduces the chemical compound's effectiveness. In addition to this, the primary issue is due to the presence of chemical residues in meat, milk, and their products (Castro-Janer *et al*., 2010). Therefore, a significant alternative management strategy to deal with this issue is to use cow breeds that have a genetic resistance to ticks (Ibelli *et al*., 2011).

Bos indicus cattle have been proven to be more resilient to tick species than *Bos taurus* cattle. These two breeds differ significantly in how vulnerable they are to cow ticks (Bianchin *et al*., 2007). Recently, more research has been conducted by mating these two groups in an effort

to create animals that are more resilient to the circumstances encountered in tropical regions (Graf *et al*., 2005).

Use of genetic engineering

Bacillus thuringiensis (Bt), a less established chemical that is used extensively in agriculture to control many insect species, also exhibits toxicity to *Ixodes* and *Dermacentor* ticks (Verma, 2017; Szczepa ska *et al*., 2018). A genetically modified virus called baculovirus produces chitinase to attack Ixodes ticks (*Haemaphysalis longicornis*). These genetically modified baculoviruses have been widely used in agriculture to control insects since they are believed to be environmentally safe (Szewczyk *et al*., 2006). However, ticks are not infected by the most common baculoviruses. An analogous genetic engineering approach might be applied with a focus on ticks. Removal of certain proteins necessary for vector competence or engineering ticks to just have one sex could also reduce tick populations.

Antimicrobials

Due to an alarming increase in the incidence of new and re-emerging infectious diseases, simultaneous development of resistance to antibiotics due to excessive clinical use, there is a continuous and urgent need to discover new effective antimicrobial compounds with novel mechanisms of action (Rajendran and Ramakrishnan, 2009). Antimicrobial peptides are now thought to be the best candidate agents for the creation of novel antibacterial drugs, which is badly needed. The innate immune system of every living thing, including mammals, plants, and insects, depends on antimicrobial peptides (Palmer and Jiggins, 2015).

Strong natural resistance in arthropods is produced by antimicrobial peptides, especially those from the defensin family that is found in the silk moth and beetle Chrudimska *et al*. (2010). Tick antimicrobial peptide persulcatusin, which is present in the midgut of *Ixodes persulcatus*, has an antimicrobial effect against Gram-positive pathogens like *S. aureus* (Nakajima *et al*., 2002). Furthermore, it has been reported previously that *S. aureus* strains could not be isolated from *I. persulcatus* during feeding. This is attributable to the antimicrobial activity of *I. persulcatus*, which is highly expressed during blood feeding.

Pharmaceuticals of plant origin

Plants of Indian origin are a rich source of a wide variety of secondary metabolites viz. tannins, terpenoids, alkaloids, and flavonoids possessing enormous antimicrobial properties (Suresh *et al*., 1992) and are capable of inhibiting or slowing the growth of bacteria, yeasts, and molds. Essential oils and their components act against a variety of targets, particularly the membrane and cytoplasm, and completely change the morphology of the cells. Approximately 25 to 50% of current pharmaceuticals are derived from plants and were found effective against many pathogenic bacteria (Bilgrami *et al*., 1992). Mostly two plants were considered as effective against tick species, these are *Aloe ferox* and *Pityrodia obliquum* which are widely distributed to eastern parts of Africa (Van Wyk *et al*., 2002).

Need for plant products

Multiple drug resistance in microbial pathogens has become a severe health issue for humanity because of the widespread and recurrent use of antimicrobial medications by insufficient illness treatment (Peng *et al*., 2006). By gaining novel enzyme systems to break the antibiotic and render it ineffective for infection control, micro-organisms have acquired drug resistance (Ritch-Kro *et al*., 1996). As a result, herbal medications made from plants are regarded as secure substitutes for synthetic treatments. Many plant species have been used in recent years for possible therapeutic antimicrobial uses, and many regions of the world now use these antimicrobials as a fundamental component of primary healthcare (Cowan, 1999).

Antibacterial activity of various solvent extracts viz., petroleum ether extract, benzene, chloroform, methanol and ethanol from roots of *Operculina turpethum* (L.) were tested against six bacterial species viz., *Escherichia coli, Enterobacter aerogenes, Klebsiella oxytoca*, *Proteus vulgaris*, *Bacillus cereus* and *Staphylococcus aureus* at 500, 1000, 1500 and 2000 ppm concentration (Kiran *et al*., 2018). The study conducted by Burt and Reinders (2003) revealed that Oregano (*Origanum vulgare*) and thyme (*Thymus vulgaris*; light and red varieties) essential oils had the strongest bactericidal and bacteriostatic properties, followed by bay (*Pimenta racemosa*) and clove bud (*Eugenia caryophyllata* synonym: *Syzygium aromaticum*).

CONCLUSION

In the past few years, a bigger issue related to the parasitic association between animal and ticks, and approximately 20 million heads of animals are exposed to the disease. This review explains that economically critical ticks are prevalent throughout the world and their occurrence in abundance is alerting. Bacterial pathogens use some strategies that infect both ticks and their associated ticks. Identification of interaction that helps their transmission also provides opportunities to disrupt these interactions and lead to a decrease in tick load and incidence of tick-borne diseases.

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