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Tools to fight ticks: A never-ending story? News from the front of green acaricides and photosensitizers

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ABSTRACT

Nowadays, parasitology is facing a number of crucial challenges, including the urgent request of effective control tools against arthropod vectors of medical and veterinary importance. Ticks transmit at least the same amount or even more pathogen species than any other group of blood-feeding arthropods worldwide affecting humans and animals. Besides the development of vaccines against viruses vectored by ticks, integrated pest management practices aimed at reducing tick interactions with livestock, emerging pheromone-based control tools, and few biological control agents have been also proposed. The extensive employ of acaricides and tick repellents still remains the two most effective and ready-to-use strategies. However, the use of synthetic acaricides is limited by the development of resistance in several tick species as well as by heavy environmental concerns. In this scenario, the exploitation of botanicals as cheap and effective sources of tick repellents may represent a valid alternative, and the preservation of ethnobotanical information on the repellent and acaricidal potential of plants is crucial. On the other hand, novel photodynamic acaricides have been recently described, with a toxicity against ticks which far exceed some of the acaricides currently marketed (*e.g.* tetramethrin). In this brief review, I provide a focus on some hot news in tick control, with special reference to tick repellents of botanical origin and new photodynamic fluorescent acaricides. To my mind, knowledge on both the mentioned research issues may help researchers to build valuable roadmaps to boost tick control programs worldwide.

1. Introduction

Currently, parasitology is facing a number of key challenges, including the urgent request of effective control tools against arthropod vectors of medical and veterinary importance[1-3]. Ticks transmit at least the same amount or even more pathogen species than any other group of blood-feeding arthropods worldwide affecting humans and animals[3]. Currently, almost 900 tick species have been described. Some genera include several common species, which transmit several important agents of diseases. Ticks are divided into three families: Argasidae, also known as soft ticks (191 species), Ixodidae, commonly known as hard ticks (701 species), and Nuttalliellidae, consisting of only one species, *Nuttalliella namaqua*[4,5].

In Europe, several tick species, such as *Ixodes ricinus* and *Ixodes persulcatus*, attack humans and numerous animal species. They are important vectors of agents of dangerous pathogens, including *Borrelia* bacteria (Figure 1), viruses of spring-summer meningoencephalitis and Rickettsiales, which especially occur in Russia and neighbouring countries[6,7]. Moreover, in North America, ticks act as vectors of a wide number of pathogens causing human diseases, including anaplasmosis, babesiosis, borreliosis, Colorado tick fever, Rocky Mountain spotted fever (Figure 2), tick-borne relapsing fever, southern tick-associated rash illness, ehrlichiosis, heartland virus, Lyme disease, Powassan

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disease, tularemia and rickettsiosis[8]. From a livestock's point of view, at least 80% of the world's cattle population are at risk from ticks and tick-borne diseases[9]. Ticks affect cattle directly by causing skin damage opening up wounds, which make the animal susceptible to secondary infection, and cause toxicosis and paralysis in some instances. Indirectly and more importantly, ticks act as vectors of fatal diseases, for example babesiosis and theileriosis[10,11] (Figure 3).

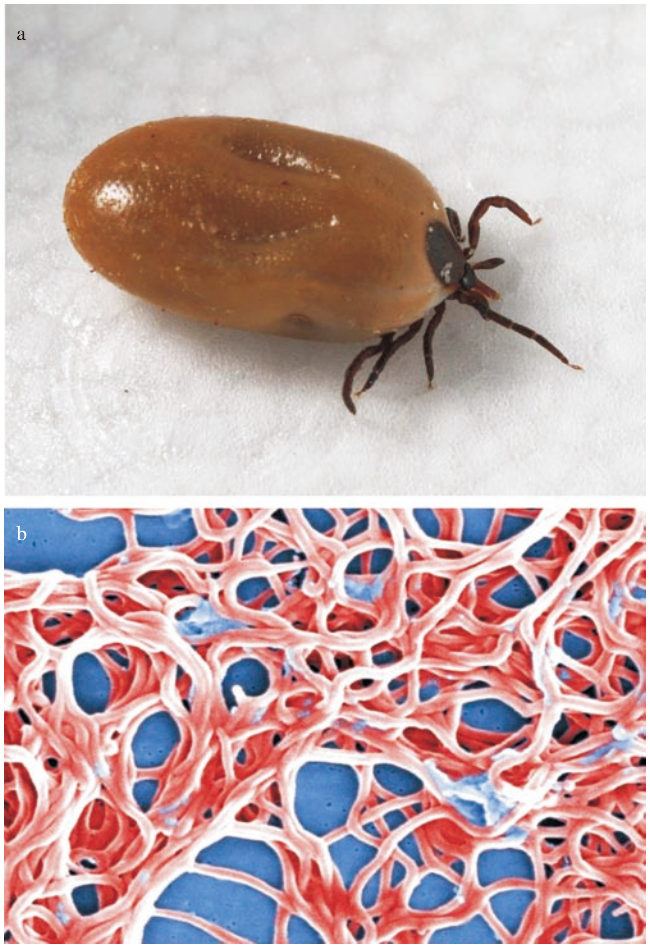

Figure 1. Engorged female of *Ixodes scapularis*, commonly known as the blacklegged or deer tick (a). This tick transmits Lyme disease, a disease caused by a spiral shaped bacterial microbe, *Borrelia burgdorferi* (b), which is widespread in Europe, Africa, Asia, and in almost all the United States (photo credit: Centers for Disease Control and Prevention, Dr. Gary Alpert and Dr. Janice Haney Carr, respectively).

2. News from the tick control front

Besides vaccines against the arbovirus vectored by ticks[12], as well as the development of biological control programs[13], and integrated pest management strategies[9], including pheromone-based control tools[14], the use of repellents and acaricides against ectoparasites is a traditional mode of treatment of people and animals[15,16]. Arsenic dips were the first effective method for controlling ticks and tick-borne diseases, and were used in many parts of the world for over 50 years before resistance to the chemical became a problem. Since the discovery of organochlorines, virtually every chemical group of pesticides developed for the control of arthropods represented among the list of products employed for the control of ticks on cattle[17]. In recent years, effective improvements in the development of acaricides with low mammalian toxicity (*e.g.* pyrethroids and avermectins) enhanced the efficacy of treatments against ticks, but at greatly increased cost[9]. Furthermore, the evolution of tick resistance to acaricides has been a major determinant of the need for new products[17]. In addition, a number of problems are associated with the use of acaricide, such as environmental pollution, contamination of meat and milk from livestock and expense especially in the developing world[3,18].

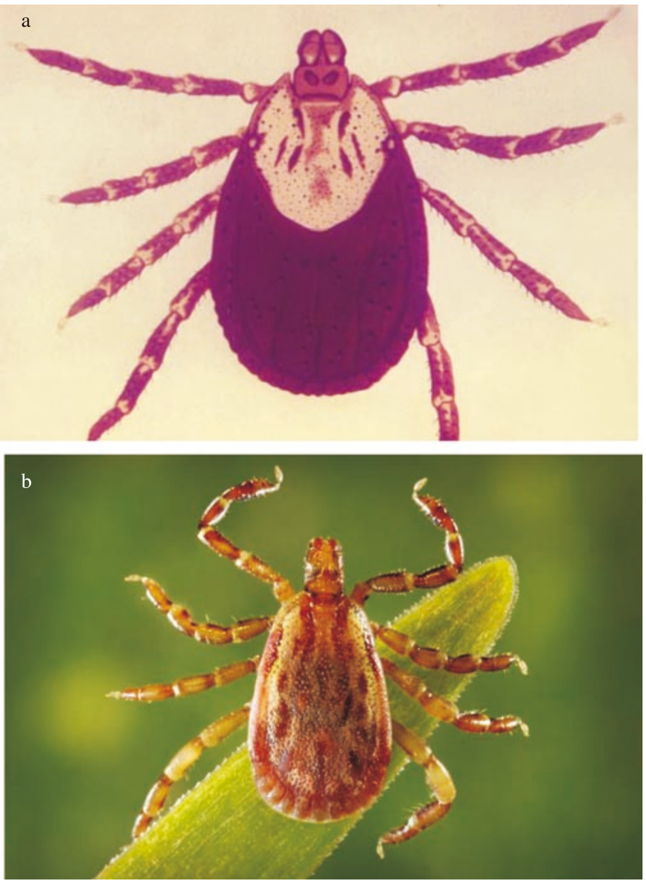

Figure 2. A female Rocky Mountain wood tick, *Dermacentor andersoni* (a), and a male yellow dog tick, *Amblyomma aureolatum* (b).
These species are major vectors of *Rickettsia rickettsii*, the agent of Rocky Mountain spotted fever in North America and Brazil, respectively (photo credit: Centers for Disease Control and Prevention, Dr. Andre J. Brooks and Dr. James Gathany, respectively).

2.1. Botanical acaricides and repellents

In this scenario, the exploitation of botanicals as cheap and effective sources of tick repellents may represent a valid alternative, and the preservation of ethnobotanical information on the repellent and acaricidal potential of plants is crucial. Current knowledge concerning the effectiveness of plant extracts as acaricides and/or repellents against tick vectors of public health importance has been recently reviewed[3], with special emphasis to *Ixodes ricinus, Ixodes persulcatus, Amblyomma cajennense, Haemaphysalis bispinosa, Haemaphysalis longicornis, Hyalomma anatolicum, Hyalomma marginatum rufipes, Rhipicephalus appendiculatus, Rhipicephalus (Boophilus) microplus, Ranunculus pulchellus, Rhipicephalus sanguineus* and *Rhipicephalus turanicus*. Study by Benelli *et al.*[3] identified 83 plant species from 35 botanical families. The most frequent botanical families exploited as sources of acaricides and repellents against ticks are Asteraceae (15% of the selected studies), Fabaceae (9%), Lamiaceae (10%), Meliaceae (5%), Solanaceae (6%) and Verbenaceae (5%). In the above-cited systematic review, regression equation analyses showed that the literature on botanicals and tick control grew by approximately 20% per year, from 2005 to 2015[3].

Figure 3. The camel tick, *Hyalomma dromedarii* (a), feeds mainly on camels (b), even if other domestic animals can be also used as hosts, nymphs and larvae parasitizing the same hosts as adults, especially camels, as well as birds, rodents and hedgehogs. This tick plays a key role in transmitting the bovine tropical theileriosis, a haemoprotozoan disease caused by *Theileria annulata* (photo credit: Ms. Maria Fremlin).

The most promising acaricidal plant extracts include the ones from *Piper tuberculatum* and *Cassia auriculata*. Some extracts also exhibit a significant effect on fertility of the tick females, or on larval hatchability from eggs laid by the treated females[3]. The highest inhibition of hatchability is provided by extracts obtained from the fruits of *Guarea kunthiana* and *Guarea guidonia*, where the concentration of $\leqslant$ 0.2% applied to the females causes larval hatching inhibition higher than 90%. In terms of preventive application of products against tick infestation, information on repellent effects of the extracts is important. *Callicarpa americana*, *Cymbopogon nardus* and *Ageratum conyzoides* have been selected in the study by Benelli *et al.*[3], due to LC_{90} estimated as $\leqslant$ 1.0 mg/cm^2 for their extracts.

2.2. Photosensitizers as novel acaricides

A photosensitizer accumulates within the arthropod's body, and then the exposure to visible light induces lethal photochemical reactions and death of the organism[19]. To the best of my knowledge, little knowledge is available on photodynamic materials acting as pesticides against arthropod vectors of medical and veterinary importance. Very recently, novel photodynamic acaricides have been investigated. Interestingly, their toxicity against ticks far exceeds the ones of some compounds currently marketed, such as tetramethrin. Safranin, a fluorescent dye, has been tested as acaricide for the first time, studying its toxicity on *Hyalomma dromedarii*, the predominant tick species infesting camels[20] (Figure 3). The toxicity of safranin has been compared to that of classic tetramethrin on engorged females of *Hyalomma dromedarii*, through *in vitro* immersion assays. The effect of safranin exposure was also evaluated on the reproductive potential of tick females. Khater *et al.*[20] administered different aqueous solutions of safranin (0.03%, 0.06%, 0.3%, 1% and 4%, w:v) and tetramethrin (0.03%, 0.13%, 0.5%, 2% and 4%) to engorged females of *Hyalomma dromedarii*. Ticks were then illuminated with a light source for 30 min post-treatment. Then, the photophysical properties of safranin were studied and the relative efficacy of the used light source and sunlight was calculated. Khater *et al.*[20] highlighted that LC_{50} values of 8 and 24 h post-treatment were 0.08%, 0.03% and 0.78%, 0.20%, for safranin and tetramethrin respectively. Comparing the LC_{50} and LC_{90} 2 h post-treatment, safranin was 33 and 22 times more potent than tetramethrin. In addition, treatments with the lowest concentrations of safranin and tetramethrin induced reduction of the number of ovipositing females, eggs per female, ticks laying viable eggs and hatching eggs[20]. Taken together, these results highlighted that safranin is highly effective compared to tetramethrin, allowing to candidate it for the development of novel and safer acaricides.

3. Conclusion and future insights

Overall, here I have provided a brief perspective on recent hot news about effective tick repellents of botanical origin and new photosensitizers with high toxicity against ticks. Concerning the evaluation of botanical repellents and acaricides, Benelli *et al.*[3] developed some recommendations for future data collection and analysis, which are worthy of attention. Concisely, the issues of major importance deal with (i) not uniform methods used, which prevent proper comparison of the results, (ii) inaccurate tested concentrations, frequently 100% of concentration corresponded to the gross extract, where the exact amounts of extracted substances are unknown, (iii) not homogeneous size of tested tick instars and species[3]. In addition, the discovery of new photodynamic acaricides, with toxicity rates far exceeding the ones of products currently marketed, is also worth of further research attention, as recently highlighted by research on safranin and camel ticks[20]. To my mind, basic toxicological knowledge on both the mentioned research issues may help researchers to build valuable roadmaps to boost tick control programs worldwide.

Conflict of interest statement

I declare that I have no conflict of interest.

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