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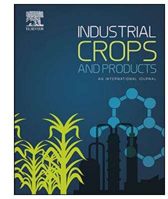

Pesticidal plants as a possible alternative to synthetic acaricides in tick control: A systematic review and meta-analysis

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A R T I C L E I N F O

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A B S T R A C T

Ticks are a large group of parasitic arthropods which transmit pathogens to animals and humans, causing great economic losses. Chemical-based antitick measures include the use of pyrethroids, carbamates, organophosphates, formamidines and macrocyclic lactones, which all have associated costs, resistance-development and environmental hazards. Some plant-based alternatives may have good efficacy, low toxicity and reduced environmental impacts. A review of published scientific articles was conducted for medicinal plants with in vitro tick repellent or acaricidal activities against immature and adult stages of ticks. Veterinary databases (All Databases, CAB Abstracts and Global Health, PubMed, Web of Science, BIOSIS Citation Index, Science Direct, Current Content Connect and Google Scholar) were used. The search words were "acaricidal", "tick repellent", "medicinal plants", "phytochemical constituents" and "antitick assays". To investigate correlations, meta-analysis was conducted using the Fixed-effect model in an Excel programme.The different plant parts, extractants used and their efficacies, where available are listed. Extracts of some species including *Azadirachta indica, Gynandropsis gynandra, Lavandula angustifolia, Pelargonium roseum* and *Cymbopogon* species have good acaricidal and larvicidal effects with 90–100% efficacy, comparable to those of currently used synthetic acaricides. Bioassays used in the determination of repellent, acaricidal, larvicidal, inhibition of oviposition and hatchability include tick climbing repellency, Petri dish, larval packet and immersion tests amongst others. Using a total of 1 428, 1 924, 574, 281 and 68 events, the median efficiency value for acaricidal, larvicidal, egg hatching inhibition, inhibition of oviposition, repellency, acaricidal effects of the Lamiaceae and Asteraceae families were 80.12 ($CI_{95\%}$: 79.20–81.04), 86.05 ($CI_{95\%}$: 85.13–86.97), 83.39 ($CI_{95\%}$: 82.47–84.31), 53.01 ($CI_{95\%}$: 52.08–53.93), 92.00 ($CI_{95\%}$: 91.08–92.93), 80.79 ($CI_{95\%}$: 79.87–81.71) and 48.34% ($CI_{95\%}$: 47.42–49.26) respectively. Among the 26 isolated active compounds identified, some such as azadirachtin, carvacrol, linalool, geraniol and citronellal and their potential uses are discussed. While plant species used in ethnoveterinary medicine hold vast potential as parasiticides, the variations in testing methodologies and assay conditions make comparison among studies very problematic. The standardization of components, extraction techniques and experimental design is urgently required to fully explore their potential.

Abbreviations: Cl-, Chloride; CNS, Central Nervous System; Conc, Concentration; DDT, Dichlorodiphenyltrichloroethane; DEET, *N,N*-Diethyl-meta-toluamide; EC, Effective concentration; Fig, Figure; GABA, γ- Aminobutyric acid; GluCl, Glutamate-gated chloride; LC, Lethal concentration; LD, Lethal dose; MEV, Median efficiency value; ND, Not determined; Picaridin, 1-Piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester; PMD, Para-menthane-3,8-diol; SS220, 1S,2S-2-Methylpiperidinyl-3-cyclohexene-1-carboxamide

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1. Introduction

Ticks are a diverse group of haematophagous arthropods, with at least 898 recognized species, distributed among three families: Argasidae (194 species), Ixodidae (703 species) and Nuttalliellidae (1 species) (Norval et al., 2004). They parasitize a wide range of hosts, and are ranked closely with mosquitoes in their capacity to transmit disease agents of importance (protozoa, bacteria, rickettsia and viruses) to livestock, domestic animals and humans (Sonenshine et al., 2002). Ticks are the most economically important ectoparasites and the most widespread species include *Amblyomma testudinarium*, *Dermacentor auratus*, *Haemaphysalis bispinosa*, *Rhipicephalus* (*Boophilus*) *microplus*, *Ixodes acutitarsus*, *Ixodes ovatus*, *Nosomma monstrosum*, *Rhipicephalus haemaphysaloides*, *Rhipicephalus sanguineus* and *Rhipicephalus turanicus* (Mans and Neitz, 2004). Economic loss caused by ticks and tick-borne diseases in cattle is estimated to be more than 7 billion USD worldwide (Zahir et al., 2010).

Tick control programmes are largely based on the use of commercially available ectoparasiticides such as the organochlorines, organophosphates, pyrethroids and more recently, the insect growth regulators and isoxazolines on or in the animals or in the environment (de Oliveira et al., 2012; McTier et al., 2016) (Table 1). Limiting exposure to tick-infested areas and the use of repellents is also considered effective in preventing ticks and tick-borne diseases in companion animals and humans (Cisak et al., 2012). At present, the most commonly used repellents include *N*, *N*-diethyl-meta-toluamide (DEET) and 1-piperidinecarboxylic acid 2-(2-hydroxyethyl)-1-methylpropylester (picaridin) (Table 2).

The sale and procurement of ectoparasiticides accounted for 22% of the annual veterinary market of 872 million ZAR (73 million USD) in 2003 in South Africa (Peter et al., 2005). In other countries such as Kenya, Zambia, Zimbabwe, Nigeria, Tanzania and Uganda, the annual cost of importing ectoparasiticides had been estimated at 16 million, 10 million, 9.3 million, 30 million, 26 million and 26 million USD respectively (Kaaya and Hassan, 2000). The global parasiticide market was valued at 6 509.1 million USD in 2013. This is expected to reach 8 918.1 million USD by 2019 growing at a rate of 5.4% (www.marketsandmarkets.com).

Commercial repellents and/or acaricidal agents are available for use on companion animals, livestock and humans, in different formulations, including tablets, sprays, soaps, shampoos, powders, impregnated collars, dip solutions, pour-on and spot-on applications (Gassel et al., 2014). Appropriate use of these chemicals is beneficial in controlling ticks, but improper application and misuse may lead to poisoning of humans and animals, emergence of resistant strains, issues of drug residues in animal food products (meat and milk) as well as environmental hazards (Babar et al., 2012). To overcome these obstacles, the development of an effective and environmentally friendly alternative of low toxicity to replace the synthetic agents is required. Research and Development orientated towards alternative methods of tick control that are consistent with the principles of sustainable agriculture, includes the use of tick antigens as vaccines (Shahein et al., 2013), entomopathogenic fungi (Nana et al., 2015, 2016) and plant-based alternatives (Benelli et al., 2017a,b).

Plants have long provided mankind with a source of medicinal agents, with natural products once serving as the major provider of all therapeutic drugs (Balandrin et al., 1993). Many plant secondary metabolites are synthesized to provide protection against pathogens, predators and pests. These agents act in one or more of the following ways: counteraction of growth regulatory hormones, anti-feeding effects, inhibition of egg development, disruption of mating and sexual communication, inhibition of chitin formation and repellent action (Benelli et al., 2016b). It should be kept in mind that plant-produced chemicals that deter invertebrates and vertebrates primarily target herbivores and not blood feeders, such as ticks. Probably because of their shared arthropod lineage with herbivorous insects, ticks are also susceptible to some plant-produced deterrents. For example, the pyrethrins, which are a class of organic compounds derived from the dried flower heads of *Chrysanthemum cinerariifolium* (Trev.) Vis, have been used for centuries for their acaricidal and tick repellent properties (Dhang and Sanjayan, 2014). They also provide a structural backbone for the synthetic pyrethroids which are components of many household, agricultural and industrial insecticides (Dhang and Sanjayan, 2014).

In some countries, plant-based ectoparasitic formulations are commercially available (Freitag and Kells, 2013). MyggA® Natural (Bioglan, Lund, Sweden), contains 30% of *Corymbia citriodora* (Hook.) oil with a minimum of 50% para-menthane-3,8-diol (PMD); Citriodiol®, manufactured by Citrefine International Limited, UK contains 64% PMD; Economist®, a natural alternative to permethrin, which contains pyrethrins and D-limonene, obtained from *Citrus* species is available in South Africa; BioUD®, with the active ingredient 7.75% 2-undecanone, originally derived from *Lycopersicon hirsutum* subsp *glabratum* C.H. Mull (wild tomato plants), registered by the United States Environmental Protection Agency in 2007 and TT-4302 (Guardian®Wilderness; Tyratech, Inc. Morrisville, NC, U.S.A) containing 5% geraniol (Bissinger et al., 2009, 2016).

In an attempt to find safe and efficient compound(s) with tick repellent and/or acaricidal properties, research on plant extracts used traditionally in tick control has grown in recent years as seen in many reviews (Atanasov et al., 2015; Adenubi et al., 2016; Benelli et al., 2016b; Pavela et al., 2016; Katz and Baltz, 2016; Benelli and Lukehart, 2017; Benelli et al., 2017a,b). Renewed interest in natural compounds derived from plants and microorganisms to develop non-synthetic medications for the veterinary industry using newer methodologies such as combinatorial chemistry, computational biology and high throughput screening, could yield new repellents/acaricides (Sparks et al., 2016). Tick repellents or acaricides with mechanisms of action targeting previously unexplored metabolic pathways can be developed that may overcome multi-acaricide resistant populations.

The market for plant-based tick repellents and acaricides is extremely promising considering the high level of synthetic acaricide consumption (Borges et al., 2011). Plant-based products could be useful for organic livestock production as well as providing alternatives for controlling resistant strains. As prevention of contamination of food and the environment is one of the sustainable development goals to transform our world, it is essential to invest in developing a pharmaceutical phytotherapy industry, with interdisciplinary approaches towards finding solutions to the menace caused by ticks and tick-borne diseases.

In this review, we provide information from selected studies that include plant species used in traditional veterinary medicine globally for tick infestation as repellents or acaricides, including those with antifeedant and growth-inhibition properties. Plant species cited are reviewed for efficacy, bioactive constituents and possible mechanism of action to validate their traditional use in animal health. We have summarized and harmonized the most important results of the tests of plant extract efficacy against different tick species and life stages (eggs, larvae, nymphs or adults), To investigate correlations, meta-analysis was conducted. Plant species and compounds therein showing very good efficacy are highlighted. Bioactive products based on plant extracts or isolated compounds may constitute prototypes for the development of promising alternatives to chemical acaricides.

2. Materials and methods

The keywords used to collect relevant literature for the review were: “tick repellent”, “acaricidal”, “medicinal plants”, “isolated compounds” and “antitick assays”. Veterinary databases (All Databases, CAB Abstracts and Global Health, PubMed, Web of Science, BIOSIS Citation Index, Science Direct, Current Content Connect and Google Scholar) were searched. Specifically, the plant species tested, the effective concentrations and concentration killing 50% of the population (LC_{50}), extractants, possible mechanism of action, species and life stage of ticks