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Background on the control of the cattle tick *R. (B.) microplus* and the use of coumarin substances as an alternative

Abstract

Rhicephalus (Boophilus) microplus (R. (B.) microplus) is a hematophagous ectoparasite of Indo-Asian origin that is found in tropical and subtropical regions, which has expanded its geographical distribution as a result of climate change, migrating to northern latitudes and higher altitudes. This species creates estimated economic losses between $13.9 and 18.7 million dollars per year, generating direct and indirect effects on livestock such as low productivity and production rates, decreased reproduction, and even death through the transmission of diseases associated with this species, including diseases known as TBD (tick borne diseases), which are a public health problem in countries with high rates of occurrence, such as the United States, the United Kingdom, Russia, France, Australia and Brazil.

The chemical control of cattle ticks began in 1895 with the use of arsenic baths that reduced infestation of this species in herds in Australia. Today, many formulations and techniques have been developed to control of this species; however, malpractice, underdosing and/or overuse of these substances have allowed this species to develop different types of resistance, which have documented worldwide. Countries with a high number of resistance reports include Mexico, Brazil and Australia.

These factors serve as a starting point for research that seeks to provide economically and environmentally viable alternatives for the control of cattle ticks, which make use of different types of plant extracts obtained from many species. As a result, high control rates at different stages of this species using various compounds with a less harmful effect on the environment have been achieved, such as with coumarins, which are obtained from chemical reactions using methodologies designed with the concept of green chemistry. This paper sought to provide an overview and approximation of the traditional control of *R. (B.) microplus* and control alternatives that use coumarin compounds.

Keywords: coumarins, control, resistance, acaricides, vector, environmentally viable alternatives

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Introduction

The cattle tick *R. (B.) microplus* is a hematophage ectoparasite of great importance worldwide because it causes considerable economic losses to the meat and dairy industry,[1] losses that they are directly associated with a lower weight gain and milk production.[2] In addition, it is a vector of zoonotic diseases, including anaplasmosis, babesiosis, ehrlichiosis and Lyme disease.[3,4]

Given the importance of this pest, chemically synthesized acaricides have traditionally been used to reduce infestations in cattle, generating a series of problems associated with environmental pollution, loss of food quality through the presence of agrochemicals in meat and milk, and significant economic losses worldwide.[5,6] Different authors have reported that *R. (B.) microplus* has generated resistance to acaricides as a result of continuous and improper use,[7] generating interest in investigating plant extracts with ixodicidal properties as a sustainable alternative with low or no toxicity to mammals, rapid degradation in the environment and greater impediment for the development of resistance that is economically viable.[8,9] Studies have used different species, showing high levels of developmental inhibitory action for eggs and adult control, suggesting that they are a viable alternative for the control of this tick.[9-11]

Secondary metabolites such as isoflavones, flavones, flavonols, neoflavones and coumarins have been isolated from plant extracts.[12]

Coumarins have been studied since 1860, revealing wide range of antiviral, antiparasitic, antifungal, and insecticidal activities, among others.[13] Because of their importance in different types of industries, there is a large amount of research on obtaining them, isolating them naturally or through chemical synthesis. As a result, there are approximately 1300 coumarins isolated from different plant families.[14-16] The various procurement processes have generated variations in structure and possible use, so the insecticidal activity has been studied, demonstrating great potential for the control of different species of mosquitoes, ticks and other pests that transmit diseases in humans, animals and plant species.[17]

Materials and methods

This paper was developed with a review of research literature and publications of scientific importance that have impacted knowledge on the cattle tick *R. (B.) microplus*, mainly through exploration of types of control with an emphasis on plant extracts containing coumarins. The cited articles were considered for this review, but not all studies on which the research was based were included.

The objective was to provide an overview and approximation of the traditional control of *R. (B.) microplus* and control alternatives that use coumarin compounds, taking into account the literature and discussions on the use of plant extracts for controlling this ectoparasite.

Rhipicephalus (Boophilus) microplus

The cattle tick *R. (B.) microplus* is a species of Indo-Asian origin[18] that is widely distributed in tropical and subtropical regions between 32°N and 35°S latitude, in areas with an average annual rainfall of 750 to 1000 mm, a temperature range between 12°C and 24°C and altitudes from 250 to 1600 meters above sea level;[9,19] however, as a result of climate change, *R. (B.) microplus* has expanded its geographical distribution to northern latitudes and higher altitudes,[20] as reported by Pulido-Herrera et al.,[18] who observed the presence of *R. (B.) microplus* at altitudes above 2,750 m.a.s.l., with temperatures below 12°C and 500 mm of rainfall, in the Cundiboyacense highlands of Colombia.

This ectoparasite lives on the surface of a host,[21] feeding on the blood without mortality but can transmit different pathogens.[22] Its life cycle is divided into two phases: the non-parasitic phase comprised of pre-oviposition, oviposition, pre-hatching and hatching, and the parasitic phase with feeding, molting and mating. The duration of the cycle is influenced by environmental factors such as climate and vegetation;[23] however, the duration of the cycle under controlled conditions (28±3^{0}C and 80±5% RH) has an approximate duration of 49 to 81 days.[24]

Transmitted diseases

Ticks are the second most important vector worldwide, after mosquitoes, and are carriers of causative or infectious agents of diseases, called tick borne diseases (TBD).[5] TBD incidence has increased through the spread of ticks linked to climatic changes. Rodríguez et al.,[25] made a conglomerate of global reports of diseases related to tick bites with a geographical distribution that included countries such as the US, UK, Russia, France, Argentina, Brazil, Spain, and Israel, among others. NCEZID,[26] in turn, reported on the increase of cases of Lyme disease that has occurred in the US from 2016 to 2017, from 26,203 to 29,513. In addition, it has been estimated that effects from ticks are seen in 80% of the cattle population worldwide.[27]

These diseases can be transmitted from ticks to vertebrates,[4] the more important being the Jiangmen tick virus (JMTV), Lihan tick virus (LITV) and Wuhan tick virus (WTV-2), among other viruses,[28-30] bacteria, such as rickettsia (Rickettsia spp), causative agents of spotted rocky mountain fever, and spotted Mediterranean fever,[31,32] and Anaplasma marginale, which is the causative agent of bovine anaplasmosis and human granulocytic anaplasmosis.[33,34] The bacteria transmitted by ticks include spirochetes (Borrelia spp), which cause Lyme disease, recurrent fever and rash disease, associated with the southern tick.[35,36]

Economic importance

The cattle tick has a great economic impact on the livestock industry through blood feeding and the transmission of pathogens. According to Meng & Sluder,[23] a reliable number of economic losses worldwide caused by cattle ticks was indicated by Brown & Askenase,[37] who reported economic losses estimated at US $8 billion caused by ticks in 1984; however, Betancur Hurtado & Giraldo-Ríos,[38] observed US $18.7 million in annual losses caused by *R. (B.) microplus* worldwide. Several authors have presented varying values depending on the country (Table 1). Finally, Lew-Tabor & Rodríguez Valle,[39] stated that the total estimated economic loss per animal per year (production plus control cost) can reach US $22-30 thousand per year.

Table 1 Report of economic losses caused by *R. (B.) microplus*, according to different sources

Country	Losses in $ USD	Author/Year
Brazil	$3,240,000,000	Grisi et al.,[40]
USA	$3,000,000,000	Graham & Hourrigan[41]
Mexico	$573,610,000	Rodríguez-Vivas et al.,[42]
India	$498,700,000	Senbill et al.,[24]
Australia	$62,000,000	Manjunathachar et al.,[27]
Colombia	$25,300,000	Puerta et al.,[43]
Puerto Rico	$6,700,000	Senbill et al.,[24]
Zambia	$5,000,000	Senbill et al.,[24]

Chemical control of *R. (B.) microplus*

Historically, tick infestations in cattle have been controlled using chemical acaricides with various active ingredients and application methods, such as immersion or sprinkling.[23] This type of control began at the end of the 19th century with the use of arsenic and then advanced to formulations produced from active ingredients such as organochlorines, organophosphates, carbamates, amidines, pyrethroids, phenylpyrazoles, cyclic lactones, and growth regulators of insects and isoxazolines (Table 2).[8,23,44-46]

Table 2 Introduction, mode and point of action of active ingredients used as acaricides worldwide

Active Ingredient/ year of introduction[23]	Formulations	Action Mechanism	IRAC Grouping according to the action mechanism and point
Arsenic 1895	Arsenic Trioxide, Potassium Arsenite, Dihydro-1, 3, 2, -dithiarsenol-2-mercaptoacetic acid	Inhibit pyruvate dehydrogenase, competing with phosphate, decoupling oxidative phosphorylation, causing reduced energy-linked nicotinamide dinucleotide, mitochondrial respiration and the synthesis of adenosine triphosphate, leading to death.[47]	Pyruvate dehydrogenase (NADP +)/respiratory system inhibitors
Organophosphates 1955	Ethion, Chlorpyrifos, Chlorphenvinphs And Coumaphos	Act at the synapse of nerve junctions and inhibit the activity of acetylcholinesterase irreversibly, producing continuous nerve discharges that cause paralysis and death.[48]	Acetylcholinesterase/nervous system inhibitors

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Table Continued...

Active Ingredient/ year of introduction[23]	Formulations	Action Mechanism	IRAC Grouping according to the action mechanism and point
Carbamates 1956	Carbaryl, Aldicarb, Carbofuran, Ethienocarb, Fenobucarb, Oxamyl, Propoxur		
Organochlorines 1939	Chlorinated Ethane Derivatives: DDT,	Binding to the picrotoxin site in the gamma aminobutyric acid chloride (Cl -) ionophores complex (GABA), which inhibits the flow of Cl into the nerve and causes hyperexcitation and death[49]	GABA receptor (chlorine channel)/nervous system antagonists
	DDE (Dichloro-diphenyldichloro-ethane) and DDD (Dicofol, Methoxychloro)		
	Cyclodiene, Chlordane, Aldrine, Dieldrin, Hepatochlor, Endrin, Toxaphene.		
	Hexachlorocyclohexanes (HCH): Benzene Hexachloride (BHC) that includes γ-isomer, lindane		
Pyrethroids 1978	Cypermethrin, Deltamethrin, Cyhalotrin and Flumethrin	Block the movement of sodium ions along the axon of the nerve fiber. Stimulate repetitive nerve discharges that lead to paralysis and death.[50]	
Phenylpyrazoles 1995	Fipronil, Pyriprole	Binds to the allosteric sites of the GABAA and GluCl channels, acting as an antagonist (non-competitive inhibition), which prevents the opening of the Cl channels normally promoted by GABA[49]	
Isoxazolines 2013	Afoxolaner, Fluralaner, Sarolaner, Lotilaner, CPD 1	Non-competitive GABA receptor antagonists that bind to Cl-channels in nerve and muscle cells blocking the transmission of neuronal channels, paralysis and death.[49]	
Amidines 1975	Amitraz, Clordimeform, Clenpirin, Chloromethurgon	Competing with octopamine for its receptor site, guanosine diphosphate is replaced by guanosine triphosphate, which induces the production of cyclic adenosine monophosphate that leads to inhibition of binding and, finally, to blood feeding, with the final death.[47]	Octopamine/nervous system receptor agonist
Cyclic Lactones 1981	Avermectin: Doramectin, Selamectin, Abamectin, Ivermectin and Eprinomectin.	Bind to GABA and glutamate-regulated chloride channels (GluCl), which opens chloride channels in the nerves, resulting in disruption of activity and loss of function in these cells that lead to paralysis and Death.[51]	Nicotinic acetylcholine receptor agonists/antagonists
	Milbemycins: Moxidectin, Milbemycin Oxima		
	Spinosyns: Spinosad		
Growth Regulators 1994	Chitin synthesis inhibitors (Benzoylphenylureas),	Structural resemblance to the molting hormone, 20-hydroxyecdsyone, thus interrupting the molting, metamorphosis and development of the female reproductive system. Surviving ticks are unable to produce a progeny.[45]	Chitin biosynthesis inhibitors-Acetyl CoA carboxylase inhibitors/hormone imbalance
	Chitin inhibitors (Triazine/Pyrimidine derivatives)		
	Juvenile Hormone Analogs		

Resistance to chemical control

The intensive use of chemical acaricides has resulted in populations of ticks that exhibit resistance, understood as a characteristic or set of specific inherited traits resulting from the contact of said population with an acaricide, which results in significant increases of the percentage of the population that survives exposure to a certain concentration.[42] In 2019, the Insecticide Resistance Action Committee (IRAC)[47] defined resistance as an inheritable change in the sensitivity of a population of a pest that is reflected in repeated failures of a product to reach the expected levels of control when used in accordance with the label recommendations for that pest.

The evaluation of the effectiveness of these products has shown the time that has elapsed from introduction until the development of resistances. Meng & Sluder[23] developed a timeline (Figure 1) that

shows the years that have elapsed since introduction of an acaricide until the first report of resistance. The first evidence of a population of resistant ticks was presented by Mackerras,[53] who, based on evidence received 10 years earlier from the Ayr district in Queensland (Australia), reported a decrease in the number of dead ticks after arsenic immersion baths, a situation that, according to the same author, was seen in South Africa and Argentina.

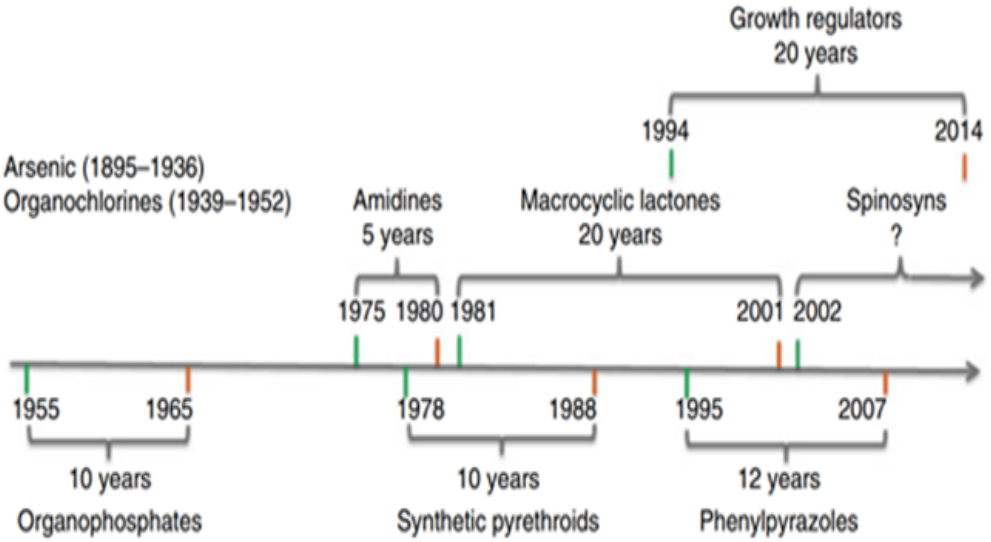

Figure 1 Chronological order of the introduction of acaricides used for tick control (green marker date) and the first resistance report according to the respective group (red marker date).[23]

The review by Adenubi et al.,[12] in 2018, which has been modified by the authors, including reports from 2019 (Table 3), showed that there are 204 studies that show resistance to different active ingredients and formulations in *R. (B.) microplus*, with 134 of the studies from the Americas, where Mexico has the highest number of resistance reports, 42 in total, followed by Brazil (27) Australia (23), India (18) and Colombia (17). On the other hand, the active ingredient with the highest number of reports is cypermethrin.

Table 3 Historical reports of resistance generated by *R. (B.) microplus* worldwide

Continent	Country	Reference	Year	Acaricide or active ingredient
Africa	Benin	Adehan et al.,[54]	2016	Alpha-cypermethrin
Africa	Benin	Adehan et al.,[54]	2016	deltamethrin
Africa	Benin	Adehan et al.,[54]	2016	Amitraz
Africa	Egipto	Aboelhadid et al.,[50]	2018	deltamethrin
Africa	South Africa	Ntondini et al.,[55]	2008	Amitraz
Africa	South Africa	Ntondini et al.,[55]	2008	Cypermethrin
Africa	South Africa	Ntondini et al.,[55]	2008	chlorfenvinphos
Africa	South Africa	Baron et al.,[56]	2015	Amitraz
Africa	South Africa	Lovis et al.,[57]	2013	Pyriprol
Africa	South Africa	Lovis et al.,[57]	2013	Cypermethrin
Africa	South Africa	Lovis et al.,[57]	2013	fenvalerate
Africa	Tanzania	Kagaruki[58]	1991	Dieldrin
Africa	Tanzania	Kagaruki[58]	1991	lindane
Africa	Zambia	Muyobela et al.,[59]	2015	Amitraz
Africa	Zambia	Muyobela et al.,[59]	2015	Cypermethrin
S America	Argentina	Mangold et al.,[59]	2004	Flumethrin
S America	Argentina	Cutullé et al.,[60]	2013	Amitraz

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Table Continued...

Continent	Country	Reference	Year	Acaricide or active ingredient
S America	Argentina	Cutullé et al.,[60]	2013	Cypermethrin
S America	Argentina	Cutullé et al.,[60]	2013	Flumethrin
S America	Argentina	Lovis et al.,[61]	2013	Amitraz
S America	Argentina	Lovis et al.,[61]	2013	Cypermethrin
S America	Argentina	Lovis et al.,[61]	2013	Flumethrin
S America	Argentina	Cutullé et al.,[60]	2013	Amitraz
S America	Argentina	Cutullé et al.,[60]	2013	deltamethrin
S America	Bolivia	Villarroel-Alvarez et al.,[62]	2006	Flumethrin
S America	Bolivia	Villarroel-Alvarez et al.,[62]	2006	deltamethrin
S America	Bolivia	Villarroel-Alvarez et al.,[62]	2006	Cypermethrin
S America	Brazil	Martins & Furlong[63]	2001	Doramectin
S America	Brazil	Martins & Furlong[63]	2001	moxidectina
S America	Brazil	Li et al.,[64]	2004	Amitraz
S America	Brazil	Klafke et al.,[6]	2006	Ivermectin
S America	Brazil	Mendes et al.,[65]	2007	Cypermethrin
S America	Brazil	Mendes et al.,[65]	2007	deltamethrin
S America	Brazil	Mendes et al.,[65]	2007	Chlorpyriphos
S America	Brazil	Castro-Janer et al.,[49]	2010	Fipronil
S America	Brazil	Klafke et al.,[6]	2010	Ivermectin
S America	Brazil	Klafke et al.,[6]	2011	Ivermectin
S America	Brazil	Andreotti et al.,[66]	2011	Alpha-cypermethrin
S America	Brazil	Andreotti et al.,[66]	2011	Cypermethrin
S America	Brazil	Andreotti et al.,[66]	2011	Amitraz
S America	Brazil	Mendes et al.,[67]	2011	Deltamethrin
S America	Brazil	Mendes et al.,[67]	2011	Chlorpyriphos
S America	Brazil	Mendes et al.,[67]	2011	Cypermethrin
S America	Brazil	Reck et al.,[68]	2014	Chlorpyriphos
S America	Brazil	Reck et al.,[68]	2014	Amitraz
S America	Brazil	Reck et al.,[68]	2014	Cypermethrin
S America	Brazil	Reck et al.,[68]	2014	fipronil
S America	Brazil	Reck et al.,[68]	2014	Ivermectin
S America	Brazil	Reck et al.,[68]	2014	Fluazuron
S America	Brazil	Klafke et al.,[6]	2016	Amitraz
S America	Brazil	Klafke et al.,[6]	2016	Chlorpyriphos
S America	Brazil	Klafke et al.,[6]	2016	Cypermethrin
S America	Brazil	Klafke et al.,[6]	2016	Fipronil
S America	Brazil	Klafke et al.,[6]	2016	ivermectin
S America	Colombia	Benavides et al.,[69]	2000	Cypermethrin
S America	Colombia	Benavides et al.,[69]	2000	deltamethrin
S America	Colombia	Benavides et al.,[69]	2000	coumaphos
S America	Colombia	Benavides et al.,[69]	2000	chlorfenvinphos

Table Continued...

Continent	Country	Reference	Year	Acaricide or active ingredient
S America	Colombia	Benavides et al.,[69]	2000	diazinon
S America	Colombia	Benavides et al.,[69]	2000	Amitraz
S America	Colombia	Diaz & Vallejo[70]	2013	Cypermethrin
S America	Colombia	Lopez-Arias et al.,[71]	2014	Cypermethrin
S America	Colombia	Lopez-Arias et al.,[71]	2014	Amitraz
S America	Colombia	Araque et al.,[72]	2014	Amitraz
S America	Colombia	Araque et al.,[72]	2014	ethion
S America	Colombia	Puerta et al.,[43]	2015	Cypermethrin
S America	Colombia	Puerta et al.,[43]	2015	Amitraz
S America	Colombia	Villar et al.,[73]	2016a	Ivermectin
S America	Colombia	Villar et al.,[74]	2016b	Deltamethrin
S America	Colombia	Villar et al.,[74]	2016b	Amitraz
S America	Colombia	Villar et al.,[74]	2016b	Chlorpyriphos
N America	Costa Rica	Hagen et al.,[75]	1999	Flumethrin
N America	Costa Rica	Alvarez & Hernandez[76]	2010	Chlorpyriphos
N America	Costa Rica	Alvarez & Hernandez[76]	2010	coumaphos
N America	Costa Rica	Alvarez & Hernandez[76]	2010	Flumethrin
N America	Costa Rica	Alvarez & Hernandez[76]	2010	deltamethrin
N America	Costa Rica	Alvarez & Hernandez[76]	2010	ivermectin
N America	Costa Rica	Alvarez & Hernandez[76]	2010	Amitraz
N America	Cuba	Valdez et al.,[77]	1999	Chlorfenvinphos Cyamizol
N America	El Salvador	Hagen et al.,[75]	1999	Flumethrin
N America	Guatemala	Hagen et al.,[75]	1999	Deltamethrin
N America	Guatemala	Hagen et al.,[75]	1999	Flumethrin
N America	Guatemala	Hagen et al.,[75]	1999	cyfluthrin
N America	Jamaica	Rawlins & Mansingh[78]	1978	Carbaryl
N America	Jamaica	Rawlins & Mansingh[78]	1978	Lindane
N America	Jamaica	Rawlins & Mansingh[78]	1978	chlorfenvinphos
N America	México	Ortiz et al.,[79]	1995	Dieldrin
N America	México	Ortiz et al.,[79]	1995	Cypermethrin
N America	México	Ortiz et al.,[79]	1995	deltamethrin
N America	México	Ortiz et al.,[79]	1995	Lindane
N America	México	Ortiz et al.,[79]	1995	coumaphos
N America	México	Ortiz et al.,[79]	1995	diazinon
N America	México	Ortiz et al.,[79]	1995	dioxathion
N America	México	Ortiz et al.,[79]	1995	dimethoate
N America	México	Ortiz et al.,[79]	1995	ethion
N America	México	Fragoso et al.,[80]	1995	Amitraz
N America	México	Soberanes et al.,[81]	2002	Amitraz
N America	México	Li et al.,[64]	2004	Carbaryl
N America	México	Rodriguez-Vivas et al.,[82]	2006b	Amitraz

Table Continued...

Continent	Country	Reference	Year	Acaricide or active ingredient
N America	México	Rodríguez-Vivas et al.,[83]	2007	Diazinon
N America	México	Rodríguez-Vivas et al.,[83]	2007	coumaphos
N America	México	Rodríguez-Vivas et al.,[83]	2007	chlorfenvinphos
N America	México	Rodríguez-Vivas et al.,[83]	2007	Flumethrin
N America	México	Rodríguez-Vivas et al.,[83]	2007	deltamethrin
N America	México	Rodríguez-Vivas et al.,[83]	2007	Cypermethrin
N America	México	Rosado-Aguilar et al.,[84]	2008	Amitraz
N America	México	Fernández-Salas et al.,[85]	2012c	Cypermethrin
N America	México	Fernández-Salas et al.,[86]	2012b	Diazinon
N America	México	Fernández-Salas et al.,[86]	2012b	Flumethrin
N America	México	Fernández-Salas et al.,[86]	2012b	deltamethrin
N America	México	Fernández-Salas et al.,[86]	2012b	Cypermethrin
N America	México	Perez-Cogollo et al.,[87]	2010a	Ivermectin
N America	México	Rodríguez-Vivas et al.,[88]	2011	Cypermethrin
N America	México	Olivares-Pérez et al.,[89]	2011	Amitraz
N America	México	Olivares-Pérez et al.,[89]	2011	Flumethrin
N America	México	Olivares-Pérez et al.,[89]	2011	deltamethrin
N America	México	Olivares-Pérez et al.,[89]	2011	Cypermethrin
N America	México	Olivares-Pérez et al.,[89]	2011	Chlorpyriphos
N America	México	Olivares-Pérez et al.,[89]	2011	coumaphos
N America	México	Olivares-Pérez et al.,[89]	2011	diazinon
N America	México	Miller et al.,[90]	2013	Fipronil
N America	México	Rodríguez-Vivas et al.,[91]	2013	Ivermectin
N America	México	Rodríguez-Vivas et al.,[91]	2013	Amitraz
N America	México	Rodríguez-Vivas et al.,[91]	2013	Chlorpyriphos
N America	México	Rodríguez-Vivas et al.,[91]	2013	coumaphos
N America	México	Rodríguez-Vivas et al.,[91]	2013	Cypermethrin
N America	México	Rodríguez-Vivas et al.,[91]	2013	permethrin
N America	México	Rodríguez-Vivas et al.,[91]	2013	fipronil
N America	Panama	Hagen et al.,[75]	1999	Flumethrin
N America	Panama	Torrijos et al.,[92]	2015	Cypermethrin
N America	Dominican Republic	Hagen et al.,[75]	1999	Deltamethrin
N America	Dominican Republic	Hagen et al.,[75]	1999	Flumethrin
N America	Dominican Republic	Hagen et al.,[75]	1999	cyfluthrin
S America	Uruguay	Castro-Janer et al.,[93]	2009	Fipronil
S America	Uruguay	Castro-Janer et al.,[94]	2011	Ivermectin
S America	Uruguay	Cuore & Solari[95]	2014	Ethion
S America	Uruguay	Cuore & Solari[95]	2014	Cypermethrin
S America	Uruguay	Cuore & Solari[95]	2014	Amitraz
S America	Uruguay	Cuore & Solari[95]	2014	fipronil
S America	Uruguay	Cuore & Solari[95]	2014	ivermectin

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Table Continued...

Continent	Country	Reference	Year	Acaricide or active ingredient
S America	Uruguay	Castro-Janer et al.,[96]	2015	Fipronil
S America	Uruguay	Castro-Janer et al.,[96]	2015	Lindane
N America	USA	Miller et al.,[97]	2007b	Permethrin
N America	USA	Busch et al.,[98]	2014	Coumaphos
N America	USA	Busch et al.,[98]	2014	permethrin
N America	USA	Busch et al.,[98]	2014	Amitraz
N America	USA	Busch et al.,[98]	2014	ivermectin
N America	USA	Busch et al.,[98]	2014	fipronil
N America	USA	Klafke et al.,[6]	2017	permethrin
N America	USA	Klafke et al.,[6]	2017	Cypermethrin
N America	USA	Klafke et al.,[6]	2017	deltamethrin
N America	USA	Klafke et al.,[6]	2017	Flumethrin
S America	Venezuela	Coronado[99]	1999	Amitraz
Asia	India	Chaudhuri & Naithani[100]	1964	BHC
Asia	India	Kumar et al.,[101]	2011	Diazinon
Asia	India	ALT Sharma et al.,[102]	2012	Deltamethrin
Asia	India	ALT Sharma et al.,[102]	2012	Cypermethrin
Asia	India	Shyma et al.,[103]	2013	Deltamethrin
Asia	India	Shyma et al.,[103]	2013	Cypermethrin
Asia	India	Shyma et al.,[103]	2013	diazinon
Asia	India	Singh et al.,[104]	2014	Cypermethrin
Asia	India	Jyoti Singh et al.,[105]	2014	Malathion
Asia	India	Singh et al.,[106]	2015	Amitraz
Asia	India	Ghosh et al.,[107]	2015	Deltamethrin
Asia	India	Ghosh et al.,[107]	2015	diazinon
Asia	India	Shyma et al.,[108]	2015	Deltamethrin
Asia	India	Shyma et al.,[108]	2015	fipronil
Asia	India	Shyma et al.,[108]	2015	Flumethrin
Asia	India	Gaur et al.,[109]	2016	Deltamethrin
Asia	India	Gaur et al.,[109]	2016	diazinon
Asia	India	Khangembam et al.[51]	2018	ivermectin
Asia	Iran	Ziapour et al.,[1]	2016	lambda-cyhalothrin
Asia	Iran	Ziapour et al.,[1]	2016	Cypermethrin
Australia	Australia	Mackerras[53]	1936	arsenic tetroxide
Australia	Australia	Stone & Webber[110]	1960	BHC
Australia	Australia	Stone & Webber[110]	1960	DDT
Australia	Australia	Stone & Webber[110]	1960	dieldrin
Australia	Australia	Stone & Meyers[110]	1957	Dieldrin
Australia	Australia	Shaw[111]	1966	Carbophenothion
Australia	Australia	Shaw[111]	1966	dioxathion

Table Continued...

Continent	Country	Reference	Year	Acaricide or active ingredient
Australia	Australia	Shaw[111]	1966	diazinon
Australia	Australia	Shaw[111]	1966	parathion
Australia	Australia	Shaw[111]	1966	carbaryl
Australia	Australia	Nolan et al.,[112]	1989	Cypermethrin
Australia	Australia	Nolan et al.,[112]	1989	cyhalothrin
Australia	Australia	Roulston et al.,[113]	1981	Dimethoate
Australia	Australia	Roulston et al.,[113]	1981	dioxathion
Australia	Australia	Roulston et al.,[113]	1981	coumaphos
Australia	Australia	Roulston et al.,[113]	1981	cyanophos
Australia	Australia	Roulston et al.,[113]	1981	Chlorpyriphos
Australia	Australia	Roulston et al.,[113]	1981	dieldrin
Australia	Australia	Roulston et al.,[113]	1981	DDT
Australia	Australia	Jonsson & Hope[114]	2007	Amitraz
Australia	Australia	Lovis et al.,[57]	2013	Flumethrin
Australia	Australia	Lovis et al.,[57]	2013	Cypermethrin
Australia	Australia	Lovis et al.,[57]	2013	pyriprol
Australia	New Caledonia	Brun et al.,[115]	1983	Ethion
Australia	New Caledonia	Beugnet & Chardonnet[116]	1995	Fenvalerate
Australia	New Caledonia	Beugnet & Chardonnet[116]	1995	deltamethrin
Australia	New Caledonia	Beugnet & Chardonnet[116]	1995	Flumethrin
Australia	New Caledonia	Bianchi et al.,[117]	2003	Deltamethrin
Australia	New Caledonia	Bianchi et al.,[117]	2003	ethion
Australia	New Caledonia	Ducornez et al.,[118]	2005	Amitraz
Australia	New Caledonia	Petermann et al.,[119]	2016	deltamethrin
Australia	New Caledonia	Petermann et al.,[119]	2016	Amitraz

The latest reports on resistance in *R. (B.) microplus* include resistance to deltamethrin, where the use of the recommended dose (200 ppm) caused 33.33% mortality in ticks, and the application of double the recommended dose caused 56% mortality, while for the use of ivermectin, there are high resistance factors in treatments performed both in the laboratory and in the field.[50,51] These and other reports on ticks with resistance to different chemical acaricide formulations elucidate the difficulty that comes with the development of new molecules capable of exercising efficient control.[120]

Factors that lead to the development of resistance

The FAO, in 2013,[121] established that the development of resistance is not only linked to operational factors but is also largely due to genetic and biological factors of the pest. In arthropods, development is partly dependent on factors related to the use of acaricides and the life cycle of the organism.[122] Therefore, internal and external factors influence the development of resistance in *R. (B.) microplus*.

Biological factors refer to the duration of the life cycle, population densities, reproductive capacity, type of reproduction and host range of the pest.[121] *R. (B.) microplus*, which is a single host tick, has a shorter life cycle than the ticks of several hosts and produces a high amount of eggs, which means that this species produces a greater number of offspring annually. Therefore, a large variety of acaricides is needed to effectively control infestations,[122] resulting in a high potential for resistance development.

A clear explanation of the operational activities that lead to the development of resistance in cattle ticks was given by Vudriko et al.[123], who reported that Ugandan producers employ activities that are not effective in the long term, with an increase of 2 to 4 times the concentrations in applications and an increase in the frequency of the use of acaricides, along with mixing two or more acaricides and not correctly rotating the products that are used, activities that are contrary to the integrated management approach for pests as presented by the Insecticide Resistance Action Committee[47] and the FAO for several years.

Rodríguez-Vivas et al.,[52] studied the genetic behavior of resistance in *R. (B.) microplus* according to phenotype and genotype, following the distinction made by Guerrero et al.,[122] who established that the resistant phenotype is given by the susceptibility or resistance of a group of individuals to the effects of an application of a certain acaricide, while the resistance genotype refers to the genetic composition of the tick, which leads to the expression of the resistance phenotype.

These genetic factors occur because of the modification of a specific gene or group of genes linked to responses that will prevent the expected acaricidal effect from occurring in the pest.[121] In order to understand the way in which genetics acts in the development of different types of resistance, studies have been carried out that associate genetic alterations with the resistance mechanism.

Resistance mechanisms

Genetic changes promote the development of resistance in tick populations. These changes generate resistance mechanisms in individuals, described as follows: modifications at the target site, increased metabolism, acaricide sequestration, or reduced ability of acaricide to penetrate through the outer protective layers of the tick body (Table 4).[122]

In the identification of resistance mechanisms in *R. (B) microplus*, there have been advances that show the way in which the enzymatic, metabolic, genetic and proteomic activities are involved (Table 4). There are also reports that have demonstrated the presence of combinations of different resistance mechanisms.[96,125,126,6] This type of resistance is known as "cross resistance," which occurs when a single defense mechanism against an insecticide also confers resistance to other insecticides, even if the insect has not been previously exposed to the other products.[130]

Table 4 Types of resistance generated by *R. (B.) microplus*

Resistance mechanism	Definition		Resistance studies on R. B. microplus
Metabolic detoxification (enzymatic)	Development of high levels of a particular enzyme or altered forms of it with higher catalytic rates, which eliminate naturally occurring toxins in hosts, these enzymes include esterases, cytochrome P450 monooxygenases, and glutathione S-transferases.[124]		Increase in the activity of the enzymes β-naphthol, β-esterase and cytochrome P450, in pyrethroid, organophosphorus and phenylpyrazole resistant ticks.[125]
Reduced sensitivity at the site of action	Change of pesticide fixation site, eliminating or significantly reducing effectiveness[121]	KDR (shock resistance): sodium channel interference in nerve cells. Commonly developed in resistance to DDT and pyrethroids.[47]	Mutations in the s4-5 gene of domain II of the sodium channel, given by conversion of glycine to valine at position 72, generate resistance to DDT and malathion[126]
		MACE (modified acetylcholinesterase): modifies the structure of acetylcholinesterase so that it is no longer affected by the insecticide.[121]	Development of resistance to organophosphorus by modified acetylcholinesterase as a result of fluctuations in the increase in transcription of the achE2 and pAChE2 genes[48]
		RDL (resistance to dieldrin) is a mutation point that reduces the binding of dieldrin to the GABA receptor.[49]	Alanine substitutions (A286S / L) in populations resistant to fipronil[49]
Sequestration	Metabolic enzymes increase considerably (up to 15% of the total body of the protein) and fixed to the insecticide, but the insecticide is not metabolized, that is, it is not sequestered.[122]		-
Behavioral Resistance	The modification of the behavior helps to avoid the lethal effect of the pesticides since feeding simply stops if the individual becomes close to some insecticides or can leave the area that has been treated.[126]		The study of behavioral resistance in R. (B). microplus has not been addressed, however Soares & Borges,[127] studied the behavior of Amblyomma Cajennense, identifying sensory odor neurons that presented positive responses (movement towards) to 2,6-dichlorophenol (2,6-DCP)
Reduced penetration	This mechanism retards the penetration of the pesticide through the cuticle of resistant insects, producing low levels of resistance, which by delaying the penetration of the toxic through the cuticle greatly increases the impact of other resistance mechanisms.[47]		Kluck et al.,[128] verified the presence of a candidate hemolymphatic protein, called Rhipicephalus microplus lipid carrier protein (RmLCP), this lipoprotein binds and transports free cholesterol and is presumed to be involved in lipid modification that promotes reduced penetration resistance

Use of bio-extracts for the control of *R. (B.) microplus*

This species has been a favorite organism for evaluating different types of extracts worldwide, given its distribution and importance in animal and human health. Therefore, these evaluations are based on the effect that these extracts produce in adult, nymph and larval mortality, along with the effect on oviposition and hatching.[12]

There is a global trend to reduce the use of chemical insecticides and acaricides, mainly caused by the development of resistance and the presence of traces of chemical residues in food that damage human and animal health, The loss of biodiversity and ecosystem degradation, and costs are other drawbacks of the use of acaricides.[8]

Therefore, in order to control tick infestations, alternatives for their control have been developed, based on the use of plants that are

recognized for their antiparasitic characteristics[131] and that generally have a lower value and are safer and more friendly to the environment, promoting interest in the use and study of extracts obtained from these plants.[132]

Worldwide there is a wide variety of plant extracts of various species, prepared through different methodologies that use leaves, roots, stems, flowers, fruits and seeds, obtaining extracts based on water,[9,131] oil[133] or different types of alcohols.[11,132,134] Essential oils have been obtained and used[135,136] in spray dried powder[6] for the control of this important ectoparasite.

According to a review by Adenubi et al.,[8] in the use of plant extracts for the control of different species of ticks worldwide from 1914 to 2014, 30 species of plants were used. Two years later, Adenubi et al.,[12] found that the number of species used for the elaboration of extracts with a tick effect increased from 30 to 55. These extracts are distributed as follows: according to the families to which they belong: Lamiaceae 20%, Asteraceae 13%, Rutaceae and Fabaceae 9% and Solanaceae 7%. This study clarified that, of the studies conducted on bio-extracts for the control of ticks, only 17% focused on how these extracts act or their mode of action, which should be addressed since this information theoretically and scientifically reinforces the use of plant extracts in the control of pests and diseases.

Coumarins as an alternative in the control of *R. (B.) microplus*

The presence of secondary metabolites that are related to the control of ticks has been evidenced from plant extracts, including flavonoids, terpenes, spilanthol and coumarins.[13,137-139] The latter are the most important within this document since they are one of the largest classes of natural compounds and are present in many plants as secondary metabolites in roots, stems, leaves, branches and seeds.[140]

Development and employment of coumarins

Coumarins have been thoroughly studied because of their potential for fighting diseases and pests, both in plants and animals, and their anti-inflammatory, antioxidant, antimicrobial, antiviral, anticoagulant and anticancer activities.[141,142] This family of secondary plant-derived metabolites was first isolated in 1820 by Voguel from a Fabaceae called Coumarouna odorata, now known as Dipteryx odorata, commonly known as cumarú.[142] Its main use was the cosmetic industry.[143]

It took 40 years for Perkin in 1868 to design a reaction using salicylaldehyde and acetic anhydride to synthesize coumarin, a methodology that is still used today.[142] In 1947, Seshadri & Murti[144] compared coumarin derivatives to natural flavones to reveal the level of toxicity of these compounds because they had previously been associated with hemorrhagic diseases in cattle, resulting in 3-phenyl and 4-phenylumbelliferone and its methyl esters, which are highly toxic in fish. By 1948, the efforts of Karl Link[145] and his collaborators took the use of coumarins a step further when warfarin (3-phenylacetyl ethyl, 4-hydroxycoumarin) was isolated from coumarin compounds, which was used as rodenticide, the most potent form of synthetic coumarins at the time.[146] Warfarin, in addition to being used for rodenticide, was also included in the prevention of thromboembolic diseases, demonstrating greater efficiency than dicumarol and heparins.[147]

On March 5, 1954, the use of coumarins in food[148] was regulated because liver diseases related to high doses of coumarins were reported, where prolonged doses of 2500 ppm caused pathologies in the livers of mice.[149,150] In the 1960s, significant advances were reported for the use of different types of coumarins as growth regulators in plants, such as antispasmodic and analgesic agents, breathing stimulants, vasodilators, antibacterial, anthelmintic, and antifungal agents, and insecticides;[151] many others are still studied today. The study of biosynthetic routes for coumarins began with Kosuge & Conn in 1959,[152] who demonstrated that the shikimic acid route is the pathway for the metabolization of o-coumaric acid, which is a precursor of Coumarins and is associated with the synthesis of the aromatic ring of the molecule. Another study was carried out by Brown during the 60s and 70s that focused on the study of the biosynthetic routes of coumarins, conducting experiments that identified precursors involved in the formation of coumarins, such as L-phenylalanine and p-coumaric acid, and pointing out reactions such as methylation, lactonization, and hydroxylation, among others.[153,154]

Parallel to these investigations and as the result of the development of resistance to the use of these compounds in anticoagulant treatments and in the use as rodenticide, from 1975 to 1978, the second generation of coumarins was developed,[155] which were based on the replacement of stereochemically similar side chains in the 4 hydroxycoumarin, known as difenacoum and brodifacoum.[156] In the late 1980s, research on coumarins focused on new ways of synthesizing the molecule and its use in medicine, with contributions from Harvey et al.,[157] who, in 1988, developed a new type of synthesis based on Ortho-directed methylation, obtaining a series of coumarins with substituents in positions 6 and 7, which were used in bioassays to reveal their antitumor activity, resulting in polycyclic coumarins with a chemo preventive cancer activity.

By 2002, Lake et al.,[158] demonstrated with live studies in both mice and Drosophila melanogaster that coumarin compounds are not genotoxic agents. However, *in vitro* tests on human liver cultures with high doses of coumarins resulted in genotoxicity. Kostova[159] reported a considerable number of tests carried out *in vivo* and *in vitro* on cytotoxicity related to the use of coumarins, which may present a greater or lesser degree of cytotoxicity according to the type of substituent that is used.[160]

Research on the possible uses and characteristics of coumarins are still valid. In fact, there are a large number of reports aimed at alternative uses of coumarins; more than 1300 coumarins have been isolated from plants, bacteria and fungi,[14-16] with antioxidant,[161] anti-HIV,[162] anticancer,[163] antiviral,[164] antituberculosis,[165] insecticide and fungicide properties,[166] among others.

Obtaining coumarins

Natural coumarins

Coumarins occur naturally in plants. These secondary metabolites are associated with defense functions against fungi and insects, Coumarin compounds are a class of lactones structurally constructed by a benzene ring fused with an α-pyrone ring.[167]

Coumarins are naturally synthesized phenolic compounds, through the shikimic acid pathway. This metabolic pathway occurs from the reaction of l-phenylalanine, which is catalyzed by the enzyme phenylalanine ammonium lyase (PAL), resulting in cinnamic acid. Once this acid has been formed, a series of reactions that includes hydroxylation, methylation and dehydration occurs, the most important being the reactions that take place in the ortho and para positions, which in turn involve processes in which enzymes intervene, such as cinnamate 4 hydroxylase, in the putative P450

and P450 metabolic pathways, along with the independent routes of these enzymes and others, in which the lactonization process occurs, resulting in various types of coumarins.[168,169]

Voguel, in 1820, was the first to report the successful extraction of coumarins from Dipteryx odorata;[142,151] however, it was not until years later that the methodologies for obtaining them were known,[170] using different species of plants[146] and different plant parts. These methodologies are based on obtaining plant extracts from the maceration of plant material and the addition of solvents of increasing polarity, such as petroleum ether and bicarbonate or sodium carbonate, which then allow direct crystallization from the concentrated extract, either during Soxhlet extraction or at rest at a higher concentration and cooling of the extract.[171]

Currently, the isolation of coumarins is carried out with techniques that combine different types of maceration, either using ultrasound, liquid nitrogen, infusions, or solvents of different polarities, such as hexane, chloroform, ethyl acetate and methanol, resulting in concentrates with vacuum distillation using Soxhlet, supercritical CO2 extraction,[172] pressurized hot water extraction,[173] microwave-assisted extraction,[174] or dispersion in the solid phase of the effervescence-assisted matrix (EA-MSPD).[175]

Synthesis of coumarins

Research developed with the objective of synthesizing new coumarins has been widely addressed. The first methodology for obtaining coumarins was proposed by Perkin in 1868.[142] Perkin used different temperatures, an alkaline salt as a catalyst, and acetic acid, which resulted in a type of aldol condensation from an interaction between a carbanion and a carboxyl group.[176,177] This was followed by methodologies such as condensation by Knoevenagel, which used the reaction between an aldehyde or its derivative and an ester, in the presence of the amine as a catalyst. This reaction synthesizes coumarins through cyclisation of the lactone group without the presence of solvents in processes carried out with microwaves[178] or the Reformatsky reaction, which generates the condensation of aldehydes (or ketones) with α-halo esters in the presence of metallic zinc, forming β-hydroxy esters that are dehydrated in subsequent steps to produce an unsaturated ester.[179,180]

On the other hand, the Wittig reaction synthesizes an alkene from the reaction of an aldehyde or ketone with the ilium generated from a phosphonium salt.[181] Claisen also developed a decarboxylative condensation reaction, where, starting from an ester and a strong base used as a catalyst, a single carbon-carbon bond is produced.[182] Pechmann used the esterification/transesterification of phenols with β-ketoesters with acids such as Bronsted or Lewis.[183,184] These methodologies laid the foundation for the development of processes that obtain coumarin compounds.[171] These new methodologies are based on the use of different reactions and catalytic processes in which the precursors and materials used to obtain coumarins vary, involving ecological approaches, new technologies, such as microwaves[184] and ultrasound,[185] new catalysts,[186,187] ecological solvents,[188] reactions without Solvents[189] and molecular coupling,[190,191] among others, resulting in coumarins with greater yields and better activity, demonstrating the importance of coumarin compounds in different industries and providing coumarin derivatives in recent years that are much more easily obtained, economical and environmentally responsible.

Use of coumarins for tick control

Many of the extracts evaluated for the control of ticks use coumarns; hence, they are associated with the effect on ticks. The cases in which mortality and/or repellency were greater than 60% were compiled, given that this effect resulted from the direct use of coumarins or by the presence of coumarins in bio-extracts.

Tunón et al.,[192] evaluated an extract of Artemisia abrotanum obtained from toluene and the essential oil of Dianthus caryophyllum, which, based on identification with thin layer chromatography, contains coumarins. This extract produced 93% mortality rates in Ixodes ricinus nymphs after 4 hours from the start of the test.

Mortality values obtained from the use of Ocotea elegans essential oil in *R. (B.) microplus* larvae and adults were 70% mortality with a concentration of 100mg/ml in the larvae and, in the adults, were greater than 60% with a concentration of 6.2 mg/ml, along with 97% mortality at 25 mg/ml. Although no coumarins were detected in the essential oil of Ocotea elegans, Figueiredo et al.,[138] it has been previously reported as containing them.[193,194]

It has been shown that the use of coumarins for the control of Rhipicephalus appendiculatus larvae has been successful, with up to 90% mortality when two types of coumarin compounds isolated from Acokanthera schimperi were mixed.[17]

On the other hand, Rosado-Aguilar et al.,[195] stated that studies on the effects of essential oils and extracts of plants with coumarins showed an efficacy of 5 to 100%, with the genus Rhipicephalus being the most studied. In addition, tests on the inhibition of egg hatching showed efficiencies of 60-100%, and tests on larvae and adults produced mortality of 5 to 100% and 60 to 100%.[132] The results obtained by Dantas et al.,[132] and reported by Rosado-Aguilar et al.,[195] confirmed that coumarins are a promising alternative for the control of ticks that are susceptible and resistant to conventional acaricides.

Mode of action of coumarins in ticks

Whatever the mechanism of action of coumarins, the strength of their binding to the target is increased by additional interactions involving the substituents present in the coumarin scaffold. The type of substituents and the substitution pattern determine, along with the general binding energy and potency, the selective interactions of coumarin derivatives with specific objectives.[170]

The use of plants with high tannin contents and the presence of cumaronochromones[196] causes darkening of the cuticle, lack of movement in the Malpighi tubes and hemorrhagic skin lesions in *R. (B.) microplus* adults. A possible mode of action in coumarins was evidenced in a study by Enan,[197] who evaluated the behavior of Periplaneta americana after being treated with three essential oils with cinnamic alcohol, which has been associated with coumarins by Ntalli et al.,[198] resulting in some signs of toxicity, such as hyperactivity, followed by hyperextension of the legs and abdomen, then rapid immobilization and finally death, symptoms that were compared with treatments with induced octopamine, finding similar signs of toxicity.

Conclusions

Because of the capacity not only of this species but of other types of ticks to expand distribution worldwide, it is necessary to develop and subsequently implement strategies with high viability and easy acceptance by producers since the use of acaricides and control techniques based on chemical compounds have lost their level of effectiveness, causing an increase in costs in relation to the effectiveness in the control of this species.

The use of plant extracts obtained from different plant species through different techniques has proven promising for the control of *R. (B.) microplus*, demonstrating even better behavior than the

active ingredients used today for the control of this pest; however, more research is needed for the point and mode of action that these extracts have on the individual, either at the biochemical, molecular, proteomic or physiological levels.

Although coumarins are present in several plant extracts obtained from different species, there are very few studied on their acaricidal activity, a topic of great interest for future research, which can take into account the methodologies and raw materials used for obtaining them and their mode of action in *R. (B.) microplus* since the effect they have depends on, among other things, their chemical structure.

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Conflicts of interest

We declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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