Acta Scientiae Veterinariae, 2023. 51: 1900.

REVIEW ARTICLE
Pub. 1900

ISSN 1679-9216

Mechanisms of Acaricide Resistance in Ticks

Jéssica Waldman[1], Guilherme Marcondes Klafke[2,3] & Itabajara da Silva Vaz Jr.[1,3,4]

ABSTRACT

***Background*:** In several countries, including Brazil, the livestock industry plays a key role in the country's economy. Brazil has the second largest bovine herd in the world and the biggest commercial herd. Ticks are an ongoing problem for both large operation cattle producers and small family farmers. *Rhipicephalus microplus* causes expressive losses in cattle breeding, since it occurs in important beef production zones like South America, Africa, and Oceania. Some of the negative consequences of tick infestation to cattle breeding are anemia, loss in milk and beef production, and transmission of Babesia bovis and *B. bigemina*. Significant losses are caused by the cattle tick (*R. microplus*) in several regions of the world, costing around US$ 3.3 billion per year to the Brazilian livestock industry alone. The tick control methods are mainly based on synthetic acaricides. However, the improvement of current tick control requires the identification of new molecular targets in tick physiology and development of molecule compounds to target important physiology pathways. The strategies proposed to address this issue are expand the knowledge about the molecules involved in the detoxification of chemicals to enhance the efficacy of the acaricides as well as to develop new compounds for chemical control.

***Review*:** Tick control is currently based on chemical acaricides; however, effective control and prevention of tick infestation remain distant goals. In recent decades, a progressive decrease in the efficiency of acaricides due to drug resistance has been observed. Acaricide resistance is an evolutionary adaptation, which implies the existence of behavioral and physiological mechanisms that allow the survival of resistant individuals. Four resistance mechanisms are described: behavioral resistance, reduced drug penetration, target site insensitivity and increased drug detoxification. Augmented drug detoxification may be due to increased activity of enzymes or transporters due to increased gene expression or mutations in some genes. Research focus on mechanisms of acaricide resistance in ticks characterized detoxification pathways based on (1) increased activity of enzymes (cytochrome p450, esterase and GST) which play a role in biochemically altering acaricides towards decreased toxicity and, (2) enhanced excretion of the modified less toxic compounds. To bypass the current problems, a better understanding of the biology, physiology, and molecular biology of the mechanisms of resistance to acaricides is fundamental to prolong their efficiency in controlling ticks. Moreover, identifying the genes and proteins associated with resistance can support in the development of more sensitive diagnostic methods to identify acaricide resistance, as well as improving control strategies.

***Discussion*:** In the last years, many researchers have been studying resistance mechanisms and important advances have been made which showed that, in several tick species, ABC transporters, esterases, P-450 cytochromes and glutathione-S-transferases participate in acaricide resistance. The characterization of the alterations in the targets in tick physiology and identification of new drugs with potential to tick control are crucial goals to increase tick control

Keywords: esterases, glutathione S transferases, pyrethroids, organophosphate, acaricide, resistance, parasite, *Rhipicephalus microplus*, bovine.

DOI: 10.22456/1679-9216.128913

Received: 4 October 2022 Accepted: 16 December 2022 Published: 5 January 2023

[1]Centro de Biotecnologia (Cbiot), Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, RS, Brazil. [2]Instituto de Pesquisas Veterinárias Desidério Finamor (IPVDF) - Centro de Pesquisa em Saúde Animal Desidério Finamor (CEPVDF), Secretaria da Agricultura, Pecuária e Desenvolvimento Rural, Eldorado do Sul, RS. [3]Instituto Nacional de Ciência e Tecnologia em Entomologia Molecular (INCT-EM), Rio de Janeiro, RJ, Brazil. [4]Faculdade de Veterinária, UFRGS, Porto Alegre. CORRESPONDENCE: I.S. Vaz Júnior [itabajara.vaz@ufrgs.br]. Laboratório de Imunologia Aplicada à Sanidade Animal, CBiot - UFRGS. Campus do Vale. Av. Bento Gonçalves n. 9500. CEP 9150-970 Porto Alegre, RS, Brazil.

I. INTRODUCTION

Ticks are ectoparasites worldwide distributed that infest a variety of vertebrate hosts, presenting a hematophagous behavior and could affect the animal and human health [37,38,126]. The parasitism caused by the cattle tick, *Rhipicephalus microplus*, and the transmission of *Babesia bovis* and *B. bigemina* could lead to host anemia and, consequently, decrease in milk and meat production, with economic annual losses for livestock production reaching US$ 3.2 billion in Brazil [59,72].

Currently, there are 7 classes of commercially available pesticides to control ticks' infestation: organophosphates, synthetic pyrethroids, macrocyclic lactones, formamidines, benzoylphenyl ureas, phenylpyrazoles and isoxazolines [110,118]. The main targets of pesticides are present in the central nervous system of arthropods having neurotoxic activity [99]. Most of them have a role on ion channels, like Gamma-aminobutyric acid gated chloride channel (GABA-Cl), glutamate-gated chloride channel (Glu-Cl) [13-15,91] and voltage-sensitive sodium channels (Na^+) [80], acetylcholinesterase enzyme [19,20] and arthropod octopamine receptors (AOR) [49,50]. However, there is an increasing global concern about tick acaricide resistance, since the application of chemical acaricides, over the years, has led to an increase in the reports of resistant populations to these compounds [71], including multiresistant populations to all commercial acaricides in different countries [52,61,76,107,110,134]. In Brazil, a field population of *R. microplus* has already been identified as resistant to 6 acaricides (cypermethrin, chlorpyriphos, fipronil, amitraz, ivermectin and fluazuron) that belong to different classes [107], also resistance to deltamethrin, fipronil and ivermectin was reported in the brown dog tick, *Rhipicephalus sanguineus* [10].

Until now, 3 main factors have been identified to contribute to resistance selection: cuticle thickening (reducing or delaying the pesticide penetration) [117], target-site insensitivity [22] and detoxification pathways [84], but in ticks the studies are focused on last two. Thus, knowledge and understanding of tick metabolism and the target pathways that contribute resistance selection can help in the identification of new targets, as well as in the development of novel control strategies to overcome increasing resistance to pesticides.

II. TARGET-SITE INSENSITIVITY

1. Voltage channels

Voltage-gated Na+ and K+ channels are responsible for the generation of action potentials in neurons and propagation of electrical signals [140]. In ticks, the synganglion, a mass of fused nerves, is the central nervous system, [108] and is an important target of the current acaricides [111]. However, multiple studies revealed that acaricide resistance occurs in many different species of arthropods, including ticks [25,61,97,139]. Acaricide resistance can be determined by different mechanisms, including the metabolic inactivation or degradation of the active molecule. However, most of the times, acaricide resistance is caused by changes in the drug targets [27,45,113]. The concept of drug resistance was first considered when mosquitoes and housefly became resistant to DDT in Italy in 1946 [62].

Pyrethroids are broad-spectrum acaricides and their major mode of action is via interactions with the voltage-gated sodium channel [125]. Mutation mediated knockdown resistance (kdr) is the most common and a frequent cause of resistance to pyrethroids in ticks [22,31]. Several studies on ticks, especially *R. microplus*, have documented several point mutations in the sodium channel associated with reduce sensitivity to pyrethroids [1,21,31,77,127]. Gamma-aminobutyric acid gated chloride channel (GABA-Cl) and glutamate-gated chloride channels (Glu-Cl) are other essential players in the central nervous system functions [124,138,145]. GABA-Cl are targets for several pesticides, including fipronil, lindane and cyclodienes and the novel acaricide class of isoxazolines [22,142,146].

The hyperexcitation caused by antagonist drugs blocks the GABA current leading to arthropod death [142]. Interestingly, fipronil and fipronil sulfone were reported as inhibitors of both channels, GABA-Cl and Glu-Cl [143,144]. The Glu-Cl channel receptors are part of ion channel protein superfamily detected in invertebrates, but not in vertebrates [26], and appears to be the target of macrocyclic lactones in *Caenorhabditis elegans*, and in *Drosophila melanogaster*, potentiating the glutamate activated current [33,34]. On the other hand, it was not identified cross-resistance between fipronil and ivermectin in *R. microplus*, suggesting that these acaricides do not present the same target-site [23].

Resistance to dieldrin gene (*rdl*) from *Drosophila* was the first member of GABA-Cl channel genes described in invertebrates [53]. In ticks, it was shown that GABA current was blocked when fipronil was administrated in *Xenopus* oocytes that expressed *rdl* gene from *Dermacentor variabilis*, suggesting a role of this pesticide as blocking the opening of GABA-Cl channels and indicate a potential target to tick control [145]. It was identified that ala to glycine (*gly*) substitution in *Anopheles gambiae rdl* locus for GABA receptor conferred resistance to dieldrin [43]. Also, mutations in GABA-Cl gene led to dieldrin and fipronil resistance in *R. microplus* [22,70]. However, a study showed that no significant association was found between presence of rdl mutations and fipronil resistant phenotypes in cattle tick isolates from Uruguay and Argentina [21,115]. Meanwhile, point mutations in Glu-Cl gene which led to the substitution from alanine (ala) to valine (val) and from gly to aspartic acid (asp) were identified in *Plutella xilostella* and *Tetranychus urticae* resistant to abamectin, respectively, both modifications promote a change in the channel conformation interfering with binding of this pesticide to the channel receptor [81,137], but in ticks this resistance mechanism is still unknown.

2. Acetylcholinesterase

The acetylcholinesterase is a serine hydrolase that degrade acetylcholine and terminate neurotransmission [93]. However, tick exposition to organophosphate acaricides result in inhibition of cholinesterase, so acetylcholine accumulates at the cholinergic synapse, keeping the receptors activated causing paralysis and death of tick [54].

In *R. microplus*, single nucleotide polymorphism in 2 acetylcholinesterase genes (*AchE1* and *AchE3*) has been associate to organophosphates resistance [11,133] since the mutation is present in *R. microplus* resistant strains [132]. Interesting, it was observed that in insects and ticks multiple simultaneous mutations can occur in the same acetylcholinesterase gene increasing the level of resistance [54,75,88,92,104].

Amitraz belongs to another class of acaricides that is extensively used for tick control, but resistance to this pesticide have been detected since the 1990's [73]. In the same way of organophosphates, there are still questions about the mechanisms involved in amitraz resistance.

3. Octopamine receptors

Formamidines are a class of acaricides that act as agonists by stimulating the octopamine receptors (AOR), the consequence is a decrease in intracellular Ca^{2+} and activation of K+ efflux leading to interruption of nervous transmission and death [7,49,96]. These pesticides have a role mainly against the βAOR, despite the arthropods have 3 AOR: α-adrenergic-like octopamine receptors (αAOR), octopamine/tyramine receptors (OCT/TYR) and β-adrenergic-like octopamine receptors (βAOR) [29,50,63,95]. In addition, formamidines have also been shown to interfere in octopamine / tyramine receptors activated [60].

Therefore, although OCT/TYR gene has been sequenced in *Rhipicephalus australis* from Australia, mutations in these sequences from susceptible and resistant strains to amitraz were not initially identified in that country, suggesting that other pathways could be involved in this pesticide resistance [9]. However, posteriorly, point mutations in OCT/TYR sequences related to amitraz resistance were detected in resistant ticks from Brazil, Mexico, South Africa, Zimbabwe and India [4,22,24,109,129]. Also, the intragenic recombination of OCT/TYR could be suggested as important in the emergence of resistant populations [8]. Another work associated non-synonymous mutations (from ile to phe) in βAOR sequence from *R. microplus* to amitraz resistance, but not all resistant populations presented this genotype, suggesting the involvement of other mechanisms in resistance pathway [28,73], but this mutation was confirmed to reduce the effect of N2–(2,4-dimethylphenyl)-N1-methyformamidine, an amitraz metabolite, in *Bombyx mori* and their resistance potential needs to be confirmed in ticks [130].

III. DETOXIFYING PROTEINS AND DETOXIFICATION PATHWAYS

The best-known mechanism in acaricide-resistant ticks is the metabolic detoxification [30,39,113]. This pathway is characterized by increased activity of enzymes, such as esterase (phase I), cytochrome P450 (CYP450) (phase I) and glutathione S-transferase (GST) (phase II) [2], playing a role in modifying acaricides toward decreased toxicity, forming more hydrophilic molecules and enhancing excretion of the less toxic compounds out of the cells (phase III) [103].

1. Esterases

Two beta-carboxylesterases (serine hydrolases) sequences were identified in *R. microplus* and a point mutation (G1120A) was found in one of these genes from pyrethroid resistant Mexican strains [64,68]. Carboxylesterases have a role in pesticide detoxification and besides the presence of mutations in their sequence, an overexpression of these enzymes has also been described in other arthropods, like *Musca domestica* [51]. In ticks, an increased hydrolysis capacity of carboxylesterase was detected in *R. microplus* resistant to the organophosphate coumaphos, which is possibly associated to resistance to this pesticide [135]. Increased activity of alpha- and beta-carboxylesterases was also shown in *R. microplus* larvae resistant to fluazuron [56]. Meanwhile, another study analyzed the transcription level of an esterase gene in 2 pyrethroid resistant tick strains. In 1 strain, a higher number of transcripts was observed in larvae and in the hemolymph collected from resistant engorged females, in comparison to pyrethroid-susceptible ticks. However, in the second strain no differences were observed in the expression of the esterase encoding gene in relation to susceptible ticks. Therefore, these results suggest that different pathways can contribute to resistance to the same acaricide [67].

2. Cytochromes P450

Cytochromes P450 metabolize xenobiotics, being a common detoxification mechanism in several arthropod species, and has also been linked to pyrethroid resistance in insects and other arthropods [69]. In several arthropods, CYP450-mediated resistance is characterized by the gene overtranscription, resulting from alterations in the factors that regulate its expression [86,116]. In the red flour beetle, *Tribolium castaneum*, populations resistant to phosphine showed increased susceptibility to this pesticide when a CYP450 inhibitor (piperonyl butoxide - PBO) was used. Also, a significant up-regulation of CYP346B subfamily genes was described in this resistant insect species [136]. In *Drosophila melanogaster* lineages over-expressing *CYP6G1*, *CYP6G2* and *CYP12D1*, increased survival to insecticides DDT, nitenpyram, dicyclanil and diazonin was detected [35]. In *A. gambiae* a CYP450 enzyme was located in oenocytes and it is related to hydrocarbon production, which leads to the thickening of the cuticle of pyrethroids-resistant mosquitoes and consequently insecticide uptake reduction [6]. Also, in *R. microplus*, a proportional increase in transcription of CYP450 was identified in pyrethroids-resistant populations [30]. Similar results were described in *R. sanguineus sensu lato*, since when PBO was used in synergist bioassay, an increase in tick mortality was shown, restoring the permethrin toxicity in pyrethroid-resistant isolates, indicating a role of CYP450 in metabolic detoxification. However, the same pattern has not been described in fipronil-resistant populations, suggesting that another mechanism may be involved in this resistance pathway [46]. In contrast, some CYP450-encoding genes presented decreased transcripts levels, while other CYP450 genes were over transcribed when *R. microplus* resistant to pyrethroids were exposed to deltamethrin. This could be explained by the need of the high transcription of genes necessary for survival post-acaricide treatment [94].

The exposure to PBO slightly increased (1.4-fold) amitraz toxicity in susceptible *R. microplus*, however, the synergistic effect of PBO was significantly increased (2.9-fold) in an amitraz-resistant isolate, suggesting a role of P450s in resistance to the formamidine in cattle ticks [82].

Besides their detoxification role, CYP450 can also act in metabolization and consequent activation and enhancement of the pesticide toxicity, like organophosphates. It was observed that CYP450 activity was reduced in organophosphate-resistant tobacco budworm (*Heliothis virescens*) [78]. The use of PBO decreased the coumaphos toxicity in acaricide-susceptible *R. microplus*, while synergistic effect was shown in resistant isolates, however, the same synergic activity with diazinon was not identified when PBO was used in resistant isolates [85]. On the other hand, it was not detected significantly differences in the CYP450 gene expression levels in organophosphate-resistant and

susceptible *R. microplus*, suggesting a multifactorial resistance mechanism to this acaricide [32].

3. Glutathione S-transferase

The tick GST catalyzes the conjugation of reduced glutathione (GSH) with a wide variety of endogenous and exogenous electrophilic compounds, protecting the cell from oxidative damage [3]. Thus, this enzyme could have a role in the tick resistance to acaricide. While GST enzyme overexpression is frequently associated with drug resistance [10], reports on the participation in acaricide resistant ticks are sparse. However, there is data of increased GST transcription in acaricide resistant tick populations [55,66]. Excitingly, GST-gene RNAi silencing is shown to induce acaricide susceptibility in ticks [44]. Currently, 7 classes of these enzymes are known in mammals, named Alpha, Mu, Pi, Sigma, Theta, Zeta and Omega, according to their chromosomal location [119]. In insects, Delta and Epsilon classes are also present, and are implicated in *Anopheles gambiae* detoxification pathways [105,106]. GST enzymes are subdivided in cytosolic, microsomal, and mitochondrial (Kappa) categories [120], however the last one was not identified in insects so far, but are present in other arthropods, like crustaceans [112]. In insects, cytosolic class are subdivided in Delta, Epsilon, Omega, Theta, Sigma and Zeta [47]. In *Tribolium castaneum*, 36 putative cytosolic GSTs and 5 microsomal GSTs were identified, while in *Bombyx mori*, only 23 cytosolic *GSTs* were observed, it is interesting to highlight that the class which contains the highest number of detected sequences was the *Epsilon* for both insect species [121,141], also in *Drosophila* the main classes are Epsilon followed by Delta [58]. These cytosolic enzymes act by catalyzing the conjugation to glutathione (GSH), facilitating that more hydrophilic substrate to be transported out of the cell [120]. In *Tenebrio molitor*, it was hypothesized that cytosolic GSTs act by sequestration and binding to the pyrethroids, thus allowing the detoxification process. However, no relationship was found between GSH concentration and resistance to insecticides [79]. High transcript levels of Delta *GST* were found in *D. melanogaster* chemosensory organs, after isothiocyanate exposition. This enzyme was over transcribed, suggesting an insecticide protection role [58].

Also, in *Haemaphysalis longicornis*, 2 GSTs-encoding gene transcripts were identified in several organs of larvae, nymph and adults, it is interesting to note that during blood feeding, higher transcript levels were observed, however protein levels decrease after engorgement, moreover location of GST in midgut and salivary glands depends on the feeding, and GST may be related to oxidative stress [66]. The expression of this enzyme is induced by heme, not by iron present in the blood, thereby reducing the cytotoxic effects caused by blood components [100]. Recombinant GSTs (rGSTs) from *H. longicornis* and *Rhipicephalus appendiculatus* had their activity inhibited by acaricides [123]. Similar effects were observed rGST from *R. microplus* using different acaricides. However, coumaphos shown to increase rGST activation, suggesting different interaction mechanisms between acaricide and detoxification enzymes [122]. Furthermore, increasing flumethrin doses led to increase of GST gene transcription in tick males, while GST knockdown decreased the larval survival rate after acaricide treatment [65], accordingly, permethrin has been shown to have more toxic effects on *R. sanguineus sensu lato* knockdown for *GST*, thus suggesting this protein as an alternative control target for ticks [44]. Natural compounds [12,89,131] or synthetic molecules [98] can alter GST activities and can consequently lead to the improvement and development of new acaricides.

4. ABC transporters

Lastly, P-glycoproteins (P-gps) are ABC transporters that influence drug uptake and excretion, interacting with different agents and have been related as a protection mechanism against pesticide in mosquitoes, including a multidrug resistance pathway, may be the first line of defense of cells [5,17,36,57,74]. Nevertheless, ABC transporters are poorly understood in arthropods and only some species present a characterization of putative ABC genes. These were grouped into 8 families (from ABCA to ABCH), in *Tribolium castaneum*, *Tetranychus urticae*, *Bombyx mori*, *Anopheles gambiae*¸ *Daphnia pulex* and *Drosophila melanogaster* [16,40,42,87,114,128]. In *Anopheles stephensi*, *ABCB* and *ABCG* augmented transcription has been associated with permethrin resistance, since when mosquitoes were exposed to ABC inhibitors and to the insecticide an increase in larval mortality was observed. Also, an over-transcription was detected in ABCG-encoding genes when the mosquitos were exposed to permethrin alone, but similar results were not identified for ABCB-encoding genes [48]. In contrast, a *D. melanogaster* lineage knocked-out to homologous

of mammalian ABCB-encoding genes (*Mdr65*) was more susceptible to several insecticides than other genes tested, showing synergistic activity with ABC transporter inhibitor, whereas flies knocked-out to other Mdr genes were resistant to some pesticides [41].

Although little is known about these transporters in insects, in ticks the knowledge is even scarcer. The first association between ABC transporters and acaricide resistance was demonstrated in *R. microplus* resistant to ivermectin. The exposure of the ticks to compounds that interfere with ABC proteins (cyclosporin-A) in association with the acaricide treatment, lead to the reduction in oviposition and egg viability of treated engorged female ivermectin-resistant ticks. In addition, a decrease in ivermectin lethal concentration was observed [102]. Similar results were observed in *R. sanguineus sensu lato* (exposed to fipronil and ivermectin) [18] and with a multiple acaricide resistant strain of *R. microplus* (exposed to ivermectin, abamectin, moxidectin and chlorpyriphos) [103], suggesting that ABC transporters could act as a multidrug detoxification mechanism, with the ABC transporters inhibition as an approach for tick control. Interestingly, an up-regulation in the transcription of the ABCB-encoding gene was detected for resistant population (Juarez) exposed or not to ivermectin, the same was not identified for ABCC-encoding gene and for susceptible strain (Porto Alegre) [102]. A cell line from *Ixodes ricinus* exposed to 3 acaricides (amitraz, permethrin, and fipronil) showed differences in up- and down-regulation for ABCB and ABCC-encoding genes depending on the pesticide treatment, showing different pathways and cell responses according to the drugs tested [90]. *In vitro* assays were also performed using ivermectin-resistant *R. microplus* embryonic cell line. An increase in ABCB transcriptional level was observed in resistant cells exposed to acaricide, while the resistance decreased after treatment with ABC transporters inhibitor, demonstrating the role of these transporters in resistance to ivermectin, however once again similar results were not observed to ABCC [101]. Moreover, an association between amitraz detoxification and heme transportation in midgut was proposed for *R. microplus* ABCB transporters, suggesting that resistance to acaricides may be a consequence of endogenous compound detoxification pathway [83]. Confirming that several physiological mechanisms can act on pesticide resistance, in *Rhipicephalus microplus*, toxicological assays confirmed that esterases and ABC transporters contribute to ivermectin resistance, followed by GSTs and CYP450 [84].

IV. CONCLUSIONS

Ticks and tick-borne diseases are significant impediments to livestock production. Current tick control methods are mainly based on chemical acaricides; however, effective control and prevention of tick infestation remain distant goals. In recent decades, a progressive decrease in the efficiency of acaricides due to drug resistance has been observed. To bypass the current problems, a better understanding of the physiology and molecular biology of the mechanisms of resistance to acaricides is fundamental to prolong their efficiency in controlling ticks, as well as improving control strategies.

This includes, expand the knowledge about the molecules directly involved in the detoxification of chemicals to enhance the efficacy of the acaricides as well as to develop new compounds for chemical control.

Acknowledgments. This work received financial support from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) #159522/2019-6, 405763/2018-2 and #465678/2014-9 INCT-EM (Instituto Nacional de Ciência e Tecnologia de Entomologia Molecular), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) #88882.346657/2019-01, and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul (FAPERGS)# 21/2551-0002221-3 (Brazil).

Declaration of interest. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this manuscript.

REFERENCES

1 Aguilar G. 2018. SNPs and other polymorhisms associated with acaricide resistance ini *Rhipicephalus microplus*. *Frontiers in Bioscience*. 23(1): 65-82.

2 Agwunobi D.O., Pei T., Yang J., Wang X., Lv L., Shen R., Yu Z. & Liu J. 2020. Expression profiles of glutathione S-transferases genes in semi-engorged *Haemaphysalis longicornis* (Acari: Ixodidae) exposed to *Cymbopogon citratus* essential oil. *Systematic and Applied Acarology*. 25(5): 918-930.

3 **Allocati N., Masulli M., Di Ilio C. & Federici L. 2018.** Glutathione transferases: substrates, inihibitors and pro-drugs in cancer and neurodegenerative diseases. *Oncogenesis*. 7(1): 8. DOI: 10.1038/s41389-017-0025-3

4 **Anon J., Singh N.K., Singh H. & Rath S.S. 2021.** Adult bioassay based Amitraz resistance status in *Rhipicephalus microplus* populations of Punjab, India. *Exploratory Animal and Medical Research*. 11(1): 49. DOI: 10.52635/EAMR/11.1.49-54

5 **Bain L.J. & LeBlanc G.A. 1996.** Interaction of structurally diverse pesticides with the human MDR1 gene product P-glycoprotein. *Toxicology and Applied Pharmacology*. 141(1): 288-298.

6 **Balabanidou V., Kampouraki A., MacLean M., Blomquist G.J., Tittiger C., Juárez M.P., Mijailovsky S.J., Chalepakis G., Anthousi A., Lynd A., Antoine S., Hemingway J., Ranson H., Lycett G.J. & Vontas J. 2016.** Cytochrome P450 associated with insecticide resistance catalyzes cuticular hydrocarbon production in *Anopheles gambiae*. *Proceedings of the National Academy of Sciences*. 113(33): 9268-9273.

7 **Baron S., Barrero R.A., Black M., Bellgard M.I., van Dalen E.M.S., Fourie J. & Maritz-Olivier C. 2018.** Differentially expressed genes in response to amitraz treatment suggests a proposed model of resistance to amitraz in *R. decoloratus* ticks. *International Journal for Parasitology: Drugs and Drug Resistance*. 8(3): 361-371.

8 **Baron S., van der Merwe N.A., Madder M. & Maritz-Olivier C. 2015.** SNP Analysis Infers that Recombination Is Involved in the Evolution of Amitraz Resistance in *Rhipicephalus microplus*. *PLOS ONE*. 10(7): e0131341. DOI: 10.1371/journal.pone.0131341

9 **Baxter G.D. & Barker S.C. 1999.** Isolation of a cDNA for an octopamine-like, G-protein coupled receptor from the cattle tick, *Boophilus microplus*. *Insect Biochemistry and Molecular Biology*. 29(5): 461-467.

10 **Becker S., Webster A., Doyle R.L., Martins J.R., Reck J. & Klafke G.M. 2019.** Resistance to deltamethrin, fipronil and ivermectin in the brown dog tick, *Rhipicephalus sanguineus* sensu stricto, Latreille (Acari: Ixodidae). *Ticks and Tick-Borne Diseases*. 10(5): 1046-1050.

11 **Bendele K.G., Guerrero F.D., Miller R.J., Li A.Y., Barrero R.A., Moolhuijzen P.M., Black M., McCooke J.K., Meyer J., Hill C.A. & Bellgard M.I. 2015.** Acetylcholinesterase 1 in populations of organophosphate-resistant North American strains of the cattle tick, *Rhipicephalus microplus* (Acari: Ixodidae). *Parasitology Research*. 114(8): 3027-3040.

12 **Bezerra W.A. dos S., Tavares C.P., Rocha C.Q. da, Vaz Junior I. da S., Michels P.A.M., Costa Junior L.M. & Soares A.M. dos S. 2022.** Anonaine from *Annona crassiflora* inhibits glutathione S-transferase and improves cypermethrin activity on *Rhipicephalus* (*Boophilus*) *microplus* (Canestrini, 1887). *Experimental Parasitology*. 243: 108398. DOI: 10.1016/j.exppara.2022.108398

13 **Bloomquist J.R. 1993.** Toxicology, mode of action and target site-mediated resistance to insecticides acting on chloride channels. *Comparative Biochemistry and Physiology Part C: Pharmacology, Toxicology and Endocrinology*. 106(2): 301-314.

14 **Bloomquist J.R. 1994.** Cyclodiene resistance at the insect GABA receptor/chloride channel complex confers broad cross resistance to convulsants and experimental phenylpyrazole insecticides. *Archives of Insect Biochemistry and Physiology*. 26(1): 69-79.

15 **Bloomquist J.R. 2003.** Chloride channels as tools for developing selective insecticides. *Archives of Insect Biochemistry and Physiology*. 54(4): 145-156.

16 **Broehan G., Kroeger T., Lorenzen M. & Merzendorfer H. 2013.** Functional analysis of the ATP-binding cassette (ABC) transporter gene family of *Tribolium castaneum*. *BMC Genomics*. 14(1): 6. DOI: 10.1186/1471-2164-14-6.

17 **Buss D.S., Mccaffery A.R. & Callaghan A. 2002.** Evidence for p-glycoprotein modification of insecticide toxicity in mosquitoes of the *Culex pipiens* complex: P-glycoprotein modification of insecticide toxicity. *Medical and Veterinary Entomology*. 16(2): 218-222.

18 **Cafarchia C., Porretta D., Mastrantonio V., Epis S., Sassera D., Iatta R., Immediato D., Ramos R.A.N., Lia R.P., Dantas-Torres F., Kramer L., Urbanelli S. & Otranto D. 2015.** Potential role of ATP-binding cassette transporters against acaricides in the brown dog tick *Rhipicephalus sanguineus* sensu lato: ABC transporters in *R. sanguineus*. *Medical and Veterinary Entomology*. 29(1): 88-93.

19 **Casida J.E. 1956.** Mode of Action of Pesticides, Metabolism of Organophosphorus Insecticides in Relation to Their Antiesterase Activity, Stability, and Residual Properties. *Journal of Agricultural and Food Chemistry*. 4(9): 772-785.

20 **Casida J.E. & Durkin K.A. 2013.** Neuroactive Insecticides: Targets, Selectivity, Resistance, and Secondary Effects. *Annual Review of Entomology*. 58(1): 99-117.

21 **Castro Janer E., Díaz A., Fontes F., Baraibar F., Saporiti T. & Olhagaray M.E. 2021.** Molecular survey of pyrethroid and fipronil resistance in isolates of *Rhipicephalus microplus* in the north of Uruguay. *Ticks and Tick-Borne Diseases*. 12(5): 101747. DOI: 10.1016/j.ttbdis.2021.101747.

22 **Castro Janer E., Klafke G.M., Fontes F., Capurro M.L. & Schumaker T.S.S. 2019.** Mutations in *Rhipicephalus microplus* GABA gated chloride channel gene associated with fipronil resistance. *Ticks and Tick-Borne Diseases*. 10(4): 761-765.

23 **Castro-Janer E., Rifran L., González P., Niell C., Piaggio J., Gil A. & Schumaker T.T.S. 2011.** Determination of the susceptibility of *Rhipicephalus* (*Boophilus*) *microplus* (Acari: Ixodidae) to ivermectin and fipronil by Larval Immersion Test (LIT) in Uruguay. *Veterinary Parasitology*. 178(1-2): 148-155.

24 **Chen A.C., He H. & Davey R.B. 2007.** Mutations in a putative octopamine receptor gene in amitraz-resistant cattle ticks. *Veterinary Parasitology*. 148(3-4): 379-383.

25 **Chitombo L., Lebani K. & Sungirai M. 2021.** Acaricide resistance in *Rhipicephalus appendiculatus* ticks collected from different farming systems in Zimbabwe. *Tropical Animal Health and Production*. 53(4): 431. DOI: 10.1007/s11250-021-02881-2

26 **Cleland T.A. 1996. I**nhibitory glutamate receptor channels. *Molecular Neurobiology*. 13(2): 97-136.

27 **Coles T.B. & Dryden M.W. 2014.** Insecticide/acaricide resistance in fleas and ticks infesting dogs and cats. Parasites & Vectors. 7(1): 8. DOI: 0.1186/1756-3305-7-8

28 **Corley S.W., Jonsson N.N., Piper E.K., Cutulle C., Stear M.J. & Seddon J.M. 2013.** Mutation in the Rm AOR gene is associated with amitraz resistance in the cattle tick *Rhipicephalus microplus*. *Proceedings of the National Academy of Sciences*. 110(42): 16772-16777.

29 **Corley S.W., Piper E.K. & Jonsson N.N. 2012.** Generation of Full-Length cDNAs for Eight Putative GPCnR from the Cattle Tick, *R. microplus* Using a Targeted Degenerate PCR and Sequencing Strategy. *PLoS ONE*. 7(3): e32480. DOI: 0.1371/journal.pone.0032480

30 **Cossío-Bayúgar R., Martínez-Ibañez F., Aguilar-Díaz H. & Miranda-Miranda E. 2018.** Pyrethroid Acaricide Resistance Is Proportional to P-450 Cytochrome Oxidase Expression in the Cattle Tick *Rhipicephalus microplus*. *BioMed Research International*. 2018: 1-6. DOI: 10.1155/2018/8292465

31 **Cossío-Bayúgar R., Miranda-Miranda E., Martínez-Ibañez F., Narváez-Padilla V. & Reynaud E. 2020.** Physiological evidence that three known mutations in the para-sodium channel gene confer cypermethrin knockdown resistance in *Rhipicephalus microplus*. *Parasites & Vectors*. 13(1): 370. DOI: 10.1186/s13071-020-04227-7

32 **Cossio-Bayugar R., Miranda-Miranda E., Ortiz-Najera A.O.-N., Neri-Orantes S. & Olvera-Valencia F. 2008.** Cytochrome P-450 Monooxygenase Gene Expression Supports a Multifactorial Origin for Acaricide Resistance in *Rhipicephalus microplus*. *Research Journal of Parasitology*. 3(2): 59-66.

33 **Cully D.F., Paress P.S., Liu K.K., Schaeffer J.M. & Arena J.P. 1996.** Identification of a *Drosophila melanogaster* Glutamate-gated Chloride Channel Sensitive to the Antiparasitic Agent Avermectin. *Journal of Biological Chemistry*. 271(33): 20187-20191.

34 **Cully D.F., Vassilatis D.K., Liu K.K., Paress P.S., Van der Ploeg L.H.T., Schaeffer J.M. & Arena J.P. 1994.** Cloning of an avermectin-sensitive glutamate-gated chloride channel from *Caenorhabditis elegans*. *Nature*. 371(6499): 707-711.

35 **Daborn P.J., Lumb C., Boey A., Wong W., ffrench-Constant R.H. & Batterham P. 2007.** Evaluating the insecticide resistance potential of eight *Drosophila melanogaster* cytochrome P450 genes by transgenic over-expression. *Insect Biochemistry and Molecular Biology*. 37(5): 512-519.

36 **Danø K. 1973.** Active outward transport of daunomycin in resistant ehrlich ascites tumor cells. *Biochimica et Biophysica Acta (BBA) - Biomembranes*. 323(3): 466-483.

37 **Dantas-Torres F., Chomel B.B. & Otranto D. 2012.** Ticks and tick-borne diseases: A One Health perspective. *Trends in Parasitology*. 28(10): 437-446.

38 **Dantas-Torres F., Fernandes Martins T., Muñoz-Leal S., Onofrio V.C. & Barros-Battesti D.M. 2019.** Ticks (Ixodida: Argasidae, Ixodidae) of Brazil: Updated species checklist and taxonomic keys. *Ticks and Tick-Borne Diseases*. 10(6): 101252. DOI: 0.1016/j.ttbdis.2019.06.012.

39 **De Marco L., Sassera D., Epis S., Mastrantonio V., Ferrari M., Ricci I., Comandatore F., Bandi C., Porretta D. & Urbanelli S. 2017.** The choreography of the chemical defensome response to insecticide stress: insights into the *Anopheles stephensi* transcriptome using RNA-Seq. *Scientific Reports*. 7(1): 41312. DOI: 10.1038/srep41312

40 Dean M., Rzhetsky A. & Allikmets R. 2001. The human ATP-binding cassette (ABC) transporter superfamily. *Genome Research*. 11(7): 1156-1166.

41 Denecke S., Fusetto R. & Batterham P. 2017. Describing the role of *Drosophila melanogaster* ABC transporters in insecticide biology using CRISPR-Cas9 knockouts. *Insect Biochemistry and Molecular Biology.* 91: 1-9. DOI: 10.1016/j.ibmb.2017.09.017

42 Dermauw W., Osborne E., Clark R.M., Grbić M., Tirry L. & Van Leeuwen T. 2013. A burst of ABC genes in the genome of the polyphagous spider mite *Tetranychus urticae*. *BMC Genomics*. 14(1): 317. DOI: 10.1186/1471-2164-14-317

43 Du W., Awolola T.S., Howell P., Koekemoer L.L., Brooke B.D., Benedict M.Q., Coetzee M. & Zheng L. 2005. Independent mutations in the *Rdl* locus confer dieldrin resistance to *Anopheles gambiae* and *An. arabiensis*. *Insect Molecular Biology*. 14(2): 179-183.

44 Duscher G.G., Galindo R.C., Tichy A., Hummel K., Kocan K.M. & de la Fuente J. 2014. Glutathione S-transferase affects permethrin detoxification in the brown dog tick, *Rhipicephalus sanguineus*. *Ticks and Tick-Borne Diseases.* 5(3): 225-233.

45 Dzemo W.D., Thekisoe O. & Vudriko P. 2022. Development of acaricide resistance in tick populations of cattle: A systematic review and meta-analysis. *Heliyon*. 8(1): e08718. DOI: 10.1016/j.heliyon.2022

46 Eiden A.L., Kaufman P.E., Oi F.M., Dark M.J., Bloomquist J.R. & Miller R.J. 2017. Determination of metabolic resistance mechanisms in pyrethroid-resistant and fipronil-tolerant brown dog ticks: *R. sanguineus* metabolic resistance. *Medical and Veterinary Entomology*. 31(3): 243-251.

47 Enayati A.A., Ranson H. & Hemingway J. 2005. Insect glutathione transferases and insecticide resistance. *Insect Molecular Biology*. 14(1): 3-8.

48 Epis S., Porretta D., Mastrantonio V., Comandatore F., Sassera D., Rossi P., Cafarchia C., Otranto D., Favia G., Genchi C., Bandi C. & Urbanelli S. 2014. ABC transporters are involved in defense against permethrin insecticide in the malaria vector *Anopheles stephensi*. *Parasites & Vectors*. 7(1): 349. DOI: 10.1186/1756-3305-7-349

49 Evans P.D. & Gee J.D. 1980. Action of formamidine pesticides on octopamine receptors. *Nature*. 287(5777): 60-62.

50 Evans P.D. & Maqueira B. 2005. Insect octopamine receptors: a new classification scheme based on studies of cloned *Drosophila* G-protein coupled receptors. *Invertebrate Neuroscience*. 5(3-4): 111-118.

51 Feng X., Li M. & Liu N. 2018. Carboxylesterase genes in pyrethroid resistant house flies, *Musca domestica*. *Insect Biochemistry and Molecular Biology*. 92: 30-39.

52 Fernández-Salas A., Rodríguez-Vivas R.I. & Alonso-Díaz M.A. 2012. First report of a *Rhipicephalus microplus* tick population multi-resistant to acaricides and ivermectin in the Mexican tropics. *Veterinary Parasitology*. 183(3-4): 338-342.

53 Ffrench-Constant R.H., Mortlock D.P., Shaffer C.D., MacIntyre R.J. & Roush R.T. 1991. Molecular cloning and transformation of cyclodiene resistance in *Drosophila*: an invertebrate gamma-aminobutyric acid subtype A receptor locus. *Proceedings of the National Academy of Sciences*. 88(16): 7209-7213.

54 Fournier D. 2005. Mutations of acetylcholinesterase which confer insecticide resistance in insect populations. *Chemico-Biological Interactions*. 157-158: 257-261.

55 Freitas D.R.J. de, Vaz Junior I. da S. & Masuda A. 2008. Expressão e atividade enzimática de glutationa s-transferase em tecidos de fêmeas de *Boophilus microplus*. *Revista Brasileira de Parasitologia Veterinária*. 17(2): 99-104.

56 Gaudêncio F.N., Klafke G.M., Tunholi-Alves V.M., Ferreira T.P., Coelho C.N., da Fonseca A.H., da Costa Angelo I. & Pinheiro J. 2017. Activity of carboxylesterases, glutathione-S-transferase and monooxygenase on *Rhipicephalus microplus* exposed to fluazuron. *Parasitology International*. 66(5): 584-587.

57 Germann U.A. & Chambers T.C. 1998. Molecular analysis of multidrug transporter, P-glycoprotein. *Cytotechnology*. 27(1/3): 31-60.

58 Gonzalez D., Fraichard S., Grassein P., Delarue P., Senet P., Nicolaï A., Chavanne E., Mucher E., Artur Y., Ferveur J.-F., Heydel J.-M., Briand L. & Neiers F. 2018. Characterization of a *Drosophila glutathione* transferase involved in isothiocyanate detoxification. *Insect Biochemistry and Molecular Biology*. 95: 33-43.

59 Grisi L., Leite R.C., Martins J.R. de S., Barros A.T.M. de, Andreotti R., Cançado P.H.D., León A.A.P. de, Pereira J.B. & Villela H.S. 2014. Reassessment of the potential economic impact of cattle parasites in Brazil. *Revista Brasileira de Parasitologia Veterinária*. 23(2): 150-156.

60 Gross A.D., Temeyer K.B., Day T.A., De León A.A.P., Kimber M.J. & Coats J.R. 2015. Pharmacological characterization of a tyramine receptor from the southern cattle tick, *Rhipicephalus* (*Boophilus*) *microplus*. *Insect Biochemistry and Molecular Biology*. 63: 47-53.

61 Guerrero F.D., Lovis L. & Martins J.R. 2012. Acaricide resistance mechanisms in *Rhipicephalus* (*Boophilus*) *microplus*. *Revista Brasileira de Parasitologia Veterinária*. 21(1): 1-6.

62 Hammerstrom R.J. 1958. Insect resistance to insecticides. *Public Health Reports (Washington, D.C.: 1896)*. 73(12): 1126-1131.

63 Han K.-A., Millar N.S. & Davis R.L. 1998. A Novel Octopamine Receptor with Preferential Expression in *Drosophila* Mushroom Bodies. *The Journal of Neuroscience*. 18(10): 3650-3658.

64 Hemingway & Karunaratne. 1998. Mosquito carboxylesterases: a review of the molecular biology and biochemistry of a major insecticide resistance mechanism. *Medical and Veterinary Entomology*. 12(1): 1-12.

65 Hernandez E.P., Kusakisako K., Talactac M.R., Galay R.L., Hatta T., Fujisaki K., Tsuji N. & Tanaka T. 2018. Glutathione S-transferases play a role in the detoxification of flumethrin and chlorpyrifos in *Haemaphysalis longicornis*. *Parasites & Vectors*. 11(1): 460. DOI: 10.1186/s13071-018-3044-9

66 Hernandez E.P., Kusakisako K., Talactac M.R., Galay R.L., Hatta T., Matsuo T., Fujisaki K., Tsuji N. & Tanaka T. 2018. Characterization and expression analysis of a newly identified glutathione S-transferase of the hard tick *Haemaphysalis longicornis* during blood-feeding. *Parasites and Vectors*. 11(91): 2018. DOI: 10.1186/s13071-018-2667-1

67 Hernandez R., Guerrero F.D., George J.E. & Wagner G.G. 2002. Allele frequency and gene expression of a putative carboxylesterase-encoding gene in a pyrethroid resistant strain of the tick *Boophilus microplus*. *Insect Biochemistry and Molecular Biology*. 32(9): 1009-1016.

68 Hernandez R., He H., Chen A.C., Waghela S.D., Wayne Ivie G., George J.E. & Gale Wagner G. 2000. Identification of a point mutation in an esterase gene in different populations of the southern cattle tick, *Boophilus microplus*. *Insect Biochemistry and Molecular Biology*. 30(10): 969-977.

69 Hodgson E., Rose R.L., Goh D.K.S., Rock G.C. & Roe R.M. 1993. Insect cytochrome P -450: metabolism and resistance to insecticides. *Biochemical Society Transactions*. 21(4): 1060-1065.

70 Hope M., Menzies M. & Kemp D. 2010. Identification of a Dieldrin Resistance-Associated Mutation in *Rhipicephalus* (*Boophilus*) *microplus* (Acari: Ixodidae). *Journal of Economic Entomology*. 103(4): 1355-1359.

71 Jongejan F. & Uilenberg G. 2004. The global importance of ticks. *Parasitology*. 129(Suppl): S3-S14. DOI: 10.1017/s0031182004005967

72 Jonsson N.N. 2006. The productivity effects of cattle tick (*Boophilus microplus*) infestation on cattle, with particular reference to Bos indicus cattle and their crosses. *Veterinary Parasitology*. 137(1-2): 1-10.

73 Jonsson N.N. 2018. Molecular biology of amitraz resistance in cattle ticks of the genus *Rhipicephalus*. *Frontiers in Bioscience*. 23(2): 796-810.

74 Juliano R.L. & Ling V. 1976. A surface glycoprotein modulating drug permeability in Chinese hamster ovary cell mutants. *Biochimica et Biophysica Acta (BBA) - Biomembranes*. 455(1): 152-162.

75 Jyoti, Singh N.K., Singh H., Singh N.K. & Rath S.S. 2016. Multiple mutations in the acetylcholinesterase 3 gene associated with organophosphate resistance in *Rhipicephalus* (*Boophilus*) *microplus* ticks from Punjab, India. *Veterinary Parasitology*. 216: 108-117.

76 Klafke G.M., Miller R.J., Tidwell J., Barreto R., Guerrero F.D., Kaufman P.E. & Pérez de León A.A. 2017. Mutation in the Sodium Channel Gene Corresponds With Phenotypic Resistance of *Rhipicephalus sanguineus sensu lato* (Acari: Ixodidae) to Pyrethroids. *Journal of Medical Entomology*. 54(6): 1639-1642.

77 Klafke G.M., Miller R.J., Tidwell J.P., Thomas D.B., Sanchez D., Feria Arroyo T.P. & Pérez de León A.A. 2019. High-resolution melt (HRM) analysis for detection of SNPs associated with pyrethroid resistance in the southern cattle fever tick, *Rhipicephalus* (*Boophilus*) *microplus* (Acari: Ixodidae). *International Journal for Parasitology: Drugs and Drug Resistance*. 9: 100-111.

78 Konno T., Hodgson E. & Dauterman W.C. 1989. Studies on methyl parathion resistance in *Heliothis virescens*. *Pesticide Biochemistry and Physiology*. 33(2): 189-199.

79 Kostaropoulos I., Papadopoulos A.I., Metaxakis A., Boukouvala E. & Papadopoulou-Mourkidou E. 2001. Glutathione S–transferase in the defence against pyrethroids in insects. *Insect Biochemistry and Molecular Biology*. 31(4–5): 313-319.

80 Kumar R., Klafke G.M. & Miller R.J. 2020. Voltage-gated sodium channel gene mutations and pyrethroid resistance in *Rhipicephalus microplus*. *Ticks and Tick-Borne Diseases*. 11(3): 101404. DOI: 10.1016/j.ttbdis.2020.101404

81 Kwon D.H., Yoon K.S., Clark J.M. & Lee S.H. 2010. A point mutation in a glutamate-gated chloride channel confers abamectin resistance in the two-spotted spider mite, *Tetranychus urticae* Koch: Abamectin resistance in *T. urticae*. *Insect Molecular Biology*. 19(4): 583-591. DOI: 10.1111/j.1365-2583.2010.01017.x

82 La Canal L.H., Dall'Agnol B., Webster A., Reck J., Martins J.R. & Klafke G.M. 2021. Mechanisms of amitraz resistance in a *Rhipicephalus microplus* strain from southern Brazil. *Ticks and Tick-Borne Diseases*. 12(5): 101764. DOI: 10.1016/j.ttbdis.2021.101764.

83 Lara F.A., Pohl P.C., Gandara A.C., Ferreira J. da S., Nascimento-Silva M.C., Bechara G.H., Sorgine M.H.F., Almeida I.C., Vaz I. da S. & Oliveira P.L. 2015. ATP Binding Cassette Transporter Mediates Both Heme and Pesticide Detoxification in Tick Midgut Cells. *PLOS ONE*. 10(8): e0134779. DOI: 10.1371/journal.pone.0134779.

84 Le Gall V.L., Klafke G.M. & Torres T.T. 2018. Detoxification mechanisms involved in ivermectin resistance in the cattle tick, *Rhipicephalus* (*Boophilus*) *microplus*. *Scientific Reports*. 8(1): 12401. DOI: 10.1038/s41598-018-30907-7

85 Li A.Y., Davey R.B., Miller R.J. & George J.E. 2003. Resistance to Coumaphos and Diazinon in *Boophilus microplus* (Acari: Ixodidae) and Evidence for the Involvement of an Oxidative Detoxification Mechanism. *Journal of Medical Entomology*. 40(4): 482490.

86 Liu N., Li M., Gong Y., Liu F. & Li T. 2015. Cytochrome P450s – Their expression, regulation, and role in insecticide resistance. *Pesticide Biochemistry and Physiology*. 120: 77-81.

87 Liu S., Zhou S., Tian L., Guo E., Luan Y., Zhang J. & Li S. 2011. Genome-wide identification and characterization of ATP-binding cassette transporters in the silkworm, *Bombyx mori*. *BMC Genomics*. 12(1): 491. DOI: 10.1186/1471-2164-12-491

88 Lokeshwari D., Krishna Kumar N.K. & Manjunatha H. 2016. Multiple Mutations on the Second Acetylcholinesterase Gene Associated With Dimethoate Resistance in the Melon Aphid, *Aphis gossypii* (Hemiptera: Aphididae). *Journal of Economic Entomology*. 109(2): 887-897.

89 Luns D.A.R., Martins R., Pombal S., Rodilla J.M.L., Githaka N.W., Vaz I. da S. & Logullo C. 2021. Effect of essential oils against acaricide-susceptible and acaricide-resistant *Rhipicephalus* ticks. *Experimental and Applied Acarology*. 83(4): 597-608.

90 Mangia C., Vismarra A., Genchi M., Epis S., Bandi C., Grandi G., Bell-Sakyi L., Otranto D., Passeri B. & Kramer L. 2018. Exposure to amitraz, fipronil and permethrin affects cell viability and ABC transporter gene expression in an *Ixodes ricinus* cell line. *Parasites & Vectors.* 11(1): 437. DOI: 10.1186/s13071-018-3020-4

91 Matsumura F. & Ghiasuddin S.M. 1983. Evidence for similarities between cyclodiene type insecticides and picrotoxinin in their action mechanisms. *Journal of Environmental Science and Health, Part B*. 18(1): 1-14.

92 Menozzi P., Shi M., Lougarre A., Tang Z. & Fournier D. 2004. Fournier D. Mutations of acetylcholinesterase which confer insecticide resistance in *Drosophila melanogaster* populations. *BMC Evolutionary Biology*. 4(1): 4. DOI: 10.1186/1471-2148-4-4

93 Mladenović M., Arsić B., Stanković N., Mihović N., Ragno R., Regan A., Milićević J., Trtić-Petrović T. & Micić R. 2018. The Targeted Pesticides as Acetylcholinesterase Inhibitors: Comprehensive Cross-Organism Molecular Modelling Studies Performed to Anticipate the Pharmacology of Harmfulness to Humans *In Vitro*. *Molecules*. 23(9): 2192. DOI: 10.3390/molecules23092192.

94 Nagar G., Upadhaya D., Sharma A.K., Kumar R., Fular A. & Ghosh S. 2021. Association between overexpression of cytochrome P450 genes and deltamethrin resistance in *Rhipicephalus microplus*. *Ticks and Tick-Borne Diseases*. 12(2): 101610. DOI: 10.1016/j.ttbdis.2020.101610

95 Nagaya Y., Kutsukake M., Chigusa S.I. & Komatsu A. 2002. A trace amine, tyramine, functions as a neuromodulator in *Drosophila melanogaster*. *Neuroscience Letters*. 329(3): 324-328.

96 Nathanson J.A. 1985. Characterization of octopamine-sensitive adenylate cyclase: elucidation of a class of potent and selective octopamine-2 receptor agonists with toxic effects in insects. *Proceedings of the National Academy of Sciences*. 82(2): 599-603.

97 Obaid M.K., Islam N., Alouffi A., Khan A.Z., da Silva Vaz I., Tanaka T. & Ali A. 2022. Acaricides Resistance in Ticks: Selection, Diagnosis, Mechanisms, and Mitigation. *Frontiers in Cellular and Infection Microbiology*. 12: 941831. DOI: 0.3389/fcimb.2022.941831

98 Ozelame K.P.C., Mattia M.M.C., Dedavid e Silva L.A., Randall L.M., Corvo I., Saporiti T., Seixas A., da Silva Vaz I. & Alvarez G. 2022. Novel tick glutathione transferase inhibitors as promising acaricidal compounds. *Ticks and Tick-Borne Diseases*. 13(5): 101970. DOI: 10.1016/j.ttbdis.2022.101970

99 Pereira M.C., Gasparotto A.E., Jurgilas J.P., da Silva L.A.C., Pereira M.C., Silveira S.S., Silva T.N., Arnosti A. & Camargo-Mathias M.I. 2017. Detrimental effect of deltamethrin on the central nervous system (synganglion) of *Rhipicephalus sanguineus* ticks. *Experimental and Applied Acarology*. 71(2): 159-169.

100 Perner J., Kotál J., Hatalová T., Urbanová V., Bartošová-Sojková P., Brophy P.M. & Kopáček P. 2018. Inducible glutathione S-transferase (Ir GST1) from the tick *Ixodes ricinus* is a haem-binding protein. *Insect Biochemistry and Molecular Biology*. 95: 44-54.

101 Pohl P.C., Carvalho D.D., Daffre S., da Silva Vaz Jr I. & Masuda A. 2014. *In vitro* establishment of ivermectin-resistant *Rhipicephalus microplus* cell line and the contribution of ABC transporters on the resistance mechanism. *Veterinary Parasitology*. 204(3-4): 316-322.

102 Pohl P.C., Klafke G.M., Carvalho D.D., Martins J.R., Daffre S., da Silva Vaz I. & Masuda A. 2011. ABC transporter efflux pumps: A defense mechanism against ivermectin in *Rhipicephalus* (*Boophilus*) *microplus*. *International Journal for Parasitology*. 41(13-14): 1323-1333.

103 Pohl P.C., Klafke G.M., Júnior J.R., Martins J.R., da Silva Vaz I. & Masuda A. 2012. ABC transporters as a multidrug detoxification mechanism in *Rhipicephalus* (*Boophilus*) *microplus*. *Parasitology Research*. 111(6): 2345-2351.

104 Qian W., Liu N., Yang Y., Liu J., He J., Chen Z., Li M. & Qiu X. 2021. A survey of insecticide resistance-conferring mutations in multiple targets in *Anopheles sinensis* populations across Sichuan, China. *Parasites & Vectors*. 14(1): 169. DOI: 10.1186/s13071-021-04662-0

105 Ranson H., Claudianos C., Ortelli F., Abgrall C., Hemingway J., Sharakhova M.V., Unger M.F., Collins F.H. & Feyereisen R. 2002. Evolution of Supergene Families Associated with Insecticide Resistance. *Science*. 298(5591): 179-181.

106 Ranson H., Rossiter L., Ortelli F., Jensen B., Wang X., Roth C.W., Collins F.H. & Hemingway J. 2001. Identification of a novel class of insect glutathione S-transferases involved in resistance to DDT in the malaria vector *Anopheles gambiae*. *Biochemical Journal*. 359(2): 295-304.

107 Reck J., Klafke G.M., Webster A., Dall'Agnol B., Scheffer R., Souza U.A., Corassini V.B., Vargas R., dos Santos J.S. & de Souza Martins J.R. 2014. First report of fluazuron resistance in *Rhipicephalus microplus*: A field tick population resistant to six classes of acaricides. *Veterinary Parasitology*. 201(1-2): 128-136.

108 Rispe C., Hervet C., de la Cotte N., Daveu R., Labadie K., Noel B., Aury J.-M., Thany S., Taillebois E., Cartereau A., Le Mauf A., Charvet C.L., Auger C., Courtot E., Neveu C. & Plantard O. 2022. Correction: Transcriptome of the synganglion in the tick *Ixodes ricinus* and evolution of the cys-loop ligand-gated ion channel family in ticks. *BMC Genomics*. 23(1): 502. DOI: 10.1186/s12864-022-08669-4

109 Robbertse L., Baron S., van der Merwe N.A., Madder M., Stoltsz W.H. & Maritz-Olivier C. 2016. Genetic diversity, acaricide resistance status and evolutionary potential of a *Rhipicephalus microplus* population from a disease-controlled cattle farming area in South Africa. *Ticks and Tick-Borne Diseases*. 7(4): 595-603.

110 Rodriguez-Vivas R.I., Jonsson N.N. & Bhushan C. 2018. Strategies for the control of *Rhipicephalus microplus* ticks in a world of conventional acaricide and macrocyclic lactone resistance. *Parasitology Research*. 117(1): 3-29.

111 Roma G.C., Camargo Mathias M.I., Nunes P.H. & Bechara G.H. 2014. Ultrastructure of the synganglion in the larvae and nymphs of tick *Rhipicephalus sanguineus* (Latreille, 1806) (Acari: Ixodidae). *International Journal of Acarology*. 40(3): 207-213.

112 Roncalli V., Cieslak M.C., Passamaneck Y., Christie A.E. & Lenz P.H. 2015. Glutathione S-Transferase (GST) Gene Diversity in the *Crustacean Calanus finmarchicus* – Contributors to Cellular Detoxification. *PLOS ONE*. 10(5): e0123322. DOI: 10.3390/jmse9091025

113 Rosario-Cruz R. 2009. Genetic basis and impact of tick acaricide resistance. *Frontiers in Bioscience*. 14: 2657-2665.

114 Roth C.W., Holm I., Graille M., Dehoux P., Rzhetsky A., Wincker P., Weissenbach J. & Brey P.T. 2003. Identification of the *Anopheles gambiae* ATP-binding cassette transporter superfamily genes. *Molecules and Cells*. 15(2): 150-158.

115 Sarli M., Torrents J., Morel N. & Nava S. 2022. Analysis of sequence variations in the GABA gated chloride gene associated with resistance to fipronil in *Rhipicephalus* (*Boophilus*) *microplus* ticks from Argentina. *Ticks and Tick-Borne Diseases*. 13(6): 102030. DOI: 10.1016/j.ttbdis.2022.102030

116 Scharf M.E., Neal J.J., Marcus C.B. & Bennett G.W. 1998. Cytochrome p450 purification and immunological detection in an insecticide resistant strain of german cockroach (*Blattella germanica*, l.). *Insect Biochemistry and Molecular Biology*. 28(1): 1-9.

117 Schnitzerling H.J., Nolan J. & Hughes S. 1983. Toxicology and metabolism of some synthetic pyrethroids in larvae of susceptible and resistant strains of the cattle tick *Boophilus microplus* (Can.). *Pesticide Science*. 14(1): 64-72.

118 Selles S.M.A., Kouidri M., González M.G., González J., Sánchez M., González-Coloma A., Sanchis J., Elhachimi L., Olmeda A.S., Tercero J.M. & Valcárcel F. 2021. Acaricidal and Repellent Effects of Essential Oils against Ticks: A Review. *Pathogens*. 10(11): 1379. DOI: 10.3390/pathogens10111379

119 Shahein Y., Abouelella A. & Hamed R. 2013. Glutathione S-Transferase Genes from Ticks. In: Baptista G.R. (Ed). In: *An Integrated View of the Molecular Recognition and Toxinology - From Analytical Procedures to Biomedical Applications* [Internet]. London: IntechOpen. Available from: https://www.intechopen.com/chapters/45105. DOI: 10.5772/52482

120 Sheehan D., Meade G., Foley V.M. & Dowd C.A. 2001. Structure, function and evolution of glutathione transferases: implications for classification of non-mammalian members of an ancient enzyme superfamily. *Biochemical Journal*. 360(1): 1-16.

121 Shi H., Pei L., Gu S., Zhu S., Wang Y., Zhang Y. & Li B. 2012. Glutathione S-transferase (GST) genes in the red flour beetle, *Tribolium castaneum*, and comparative analysis with five additional insects. *Genomics*. 100(5): 327-335.

122 Silva Vaz Jr. I., Torino Lermen T., Michelon A., Sanchez Ferreira C.A., Joaquim de Freitas D.R., Termignoni C. & Masuda A. 2004. Effect of acaricides on the activity of a *Boophilus microplus* glutathione S-transferase. *Veterinary Parasitology*. 119(2-3): 237-245.

123 Silva Vaz Jr. I., Imamura S., Ohashi K. & Onuma M. 2004. Cloning, expression and partial characterization of a *Haemaphysalis longicornis* and a *Rhipicephalus appendiculatus* glutathione S-transferase. *Insect Molecular Biology*. 13(3): 329-335.

124 Smelt C.L.C., Sanders V.R., Puinean A.M., Lansdell S.J., Goodchild J. & Millar N.S. 2021. Agonist and antagonist properties of an insect GABA-gated chloride channel (RDL) are influenced by heterologous expression conditions. *PLOS ONE*. 16(7): e0254251. DOI: 10.1371/journal.pone.0254251

125 Soderlund D.M. 2012. Molecular mechanisms of pyrethroid insecticide neurotoxicity: recent advances. *Archives of Toxicology*. 86(2): 165-181.

126 Sonenshine D.E. & Roe R.M. 2013. *Biology of Ticks*. vol. 1. 2nd edn. Oxford: Oxford University Press, 560p.

127 Stone N.E., Olafson P.U., Davey R.B., Buckmeier G., Bodine D., Sidak-Loftis L.C., Giles J.R., Duhaime R., Miller R.J., Mosqueda J., Scoles G.A., Wagner D.M. & Busch J.D. 2014. Multiple mutations in the para-sodium channel gene are associated with pyrethroid resistance in *Rhipicephalus microplus* from the United States and Mexico. *Parasites & Vectors*. 7(1): 456. DOI: 10.1186/s13071-014-0456-z

128 Sturm A., Cunningham P. & Dean M. 2009. The ABC transporter gene family of *Daphnia pulex*. *BMC Genomics*. 10(1): 170. DOI: 10.1186/1471-2164-10-170

129 Sungirai M., Baron S., Moyo D.Z., De Clercq P., Maritz-Olivier C. & Madder M. 2018. Genotyping acaricide resistance profiles of *Rhipicephalus microplus* tick populations from communal land areas of Zimbabwe. *Ticks and Tick-Borne Diseases*. 9(1): 2-9.

130 Takata M., Misato S., Ozoe F. & Ozoe Y. 2020. A point mutation in the β-adrenergic-like octopamine receptor: possible association with amitraz resistance. *Pest Management Science*. 76(11): 3720-3728.

131 Tavares C.P., Sabadin G.A., Sousa I.C., Gomes M.N., Soares A.M.S., Monteiro C.M.O., Vaz Jr. I.S. & Costa-Junior L.M. 2022. Effects of carvacrol and thymol on the antioxidant and detoxifying enzymes of *Rhipicephalus microplus* (Acari: Ixodidae). *Ticks and Tick-Borne Diseases*. 13(3): 101929. DOI: 10.1016/j.ttbdis.2022.101929

132 Temeyer K.B., Olafson P.U. & Miller R.J. 2009. Genotyping Mutations in BmAChE3: A Survey of Organophosphate-Resistant and -Susceptible Strains of *Rhipicephalus* (*Boophilus*) *microplus*. *Journal of Medical Entomology*. 46(6): 1355-1360.

133 Temeyer K.B., Pruett J.H. & Olafson P.U. 2010. Baculovirus expression, biochemical characterization and organophosphate sensitivity of rBmAChE1, rBmAChE2, and rBmAChE3 of *Rhipicephalus* (*Boophilus*) *microplus*. *Veterinary Parasitology*. 172(1-2): 114-121.

134 Torrents J., Sarli M., Rossner M.V., Toffaletti J.R., Morel N., Martínez N.C., Webster A., Mangold A.J., Guglielmone A.A. & Nava S. 2020. Resistance of the cattle tick *Rhipicephalus* (*Boophilus*) *microplus* to ivermectin in Argentina. *Research in Veterinary Science*. 132: 332-337.

135 Villarino M.A., Waghela S.D. & Wagner G.G. 2003. Biochemical Detection of Esterases in the Adult Female Integument of Organophosphate-Resistant *Boophilus Microplus* (Acari: Ixodidae). *Journal of Medical Entomology*. 40(1): 52-57.

136 Wang K., Liu M., Wang Y., Song W. & Tang P. 2020. Identification and functional analysis of cytochrome P450 CYP346 family genes associated with phosphine resistance in *Tribolium castaneum*. *Pesticide Biochemistry and Physiology*. 168: 104622. DOI: 0.1016/j.pestbp.2020.104622

137 Wang X., Wang R., Yang Y., Wu S., O'Reilly A.O. & Wu Y. 2016. A point mutation in the glutamate-gated chloride channel of *Plutella xylostella* is associated with resistance to abamectin: A mutated PxGluCl confers abamectin resistance. *Insect Molecular Biology*. 25(2): 116-125.

138 Wolstenholme A.J. 2012. Glutamate-gated Chloride Channels. *Journal of Biological Chemistry*. 287(48): 40232-40238.

139 Yawa M., Nyangiwe N., Jaja I., Marufu M. & Kadzere C. 2022. Acaricide resistance of *Rhipicephalus decoloratus* ticks collected from communal grazing cattle in South Africa. *Journal of Advanced Veterinary and Animal Research*. 9(1): 33. DOI: 10.5455/javar.2022.i566

140 Yu F.H. & Catterall W.A. 2003. Overview of the voltage-gated sodium channel family. *Genome Biology*. 4(3): 207. DOI: 10.1186/gb-2003-4-3-207

141 Yu Q., Lu C., Li B., Fang S., Zuo W., Dai F., Zhang Z. & Xiang Z. 2008. Identification, genomic organization and expression pattern of glutathione S-transferase in the silkworm, *Bombyx mori*. *Insect Biochemistry and Molecular Biology*. 38(12): 1158-1164.

142 Zhao X., Salgado V.L., Yeh J.Z. & Narahashi T. 2003. Differential Actions of Fipronil and Dieldrin Insecticides on GABA-Gated Chloride Channels in Cockroach Neurons. *Journal of Pharmacology and Experimental Therapeutics*. 306(3): 914-924.

143 Zhao X., Yeh J.Z., Salgado V.L. & Narahashi T. 2004. Fipronil Is a Potent Open Channel Blocker of Glutamate-Activated Chloride Channels in Cockroach Neurons. *Journal of Pharmacology and Experimental Therapeutics*. 310(1): 192-201.

144 Zhao X., Yeh J.Z., Salgado V.L. & Narahashi T. 2005. Sulfone Metabolite of Fipronil Blocks γ-Aminobutyric Acid- and Glutamate-Activated Chloride Channels in Mammalian and Insect Neurons. *Journal of Pharmacology and Experimental Therapeutics*. 314(1): 363-373.

145 Zheng Y., Priest B., Cully D.F. & Ludmerer S.W. 2003. RdlDv, a novel GABA-gated chloride channel gene from the American dog tick *Dermacentor variabilis*. *Insect Biochemistry and Molecular Biology*. 33(6): 595-599.

146 Zhou X., Hohman A.E. & Hsu W.H. 2022. Current review of isoxazoline ectoparasiticides used in veterinary medicine. *Journal of Veterinary Pharmacology and Therapeutics*. 45(1): 1-15. DOI: 10.1111/jvp.12959