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Synthetic Acaricides As A Promising Tool in Tick Control Program-The Present Scenario

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ABSTRACT

Ticks constitute a widely distributed group of exclusively hematophagous arthropods, vectoring and transmitting an array of pathogens of medical and veterinary importance. From time immemorial, tick control programs in the world were primarily dependent upon synthetic acaricides. Therefore, it becomes mandatory to develop strategies that can conserve the efficiency of existing acaricides. The present paper gives a brief account of the synthetic acaricides that were used during early times, and the ones which are available in the market presently. The mode of action of each class of acaricides, their impact on the environment, problems related to resistance developed by the tick species against these chemicals and their causes, measures adopted to promote the efficacy of available acaricides, etc. are also discussed in the paper.

Keywords: *Synthetic acaricides, mode of action, acaricide resistance, resistance management*

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INTRODUCTION

Ticks are highly specialized obligate, blood-sucking arthropods [1, 2] that feed on a wide range of vertebrates all around the globe [3]. They are well known to science [4, 5] because of the tremendous role they play as vectors of many life-threatening diseases, and as distressing pests of humans and their domestic wealth [6]. Domestic animals play an important role as a source of income, energy, food, raw materials, and manure for rural farmers, especially in developing countries [7]. The heavy parasitization of these animals by ticks is estimated to cause a global loss, between US$ 13.9 and 18.7 billion annually [8] and thus, tick control has become a global priority of public and animal health systems.

The control of ticks chiefly depends on the use of synthetic acaricides to offer a relatively quick and cost-effective suppression of tick populations during vast and immediate outbreaks. However, the long-term use of these chemicals has resulted in the evolution of resistance in many tick species [9, 10], thereby reducing its ability to control them. Therefore, regular monitoring of ticks for the development of resistance against the commonly used acaricides is highly critical for economic livestock production. This paper hence discusses the different aspects of synthetic acaricides in the ensuing sections for the better understanding and development of an effective control strategy against resistant tick species.

SYNTHETIC ACARICIDES

The use of chemical agents to control ticks was a common practice of animal health authorities in the United States, Australia, and Southern Africa, even before the discovery of the role of ticks as

vectors transmitting *Babesia bigemina* in cattle by Smith and Kilborne [11]. The early panacea adopted by the United States included smearing the legs, and sides of the body of cattle with a lard and sulfur mixture, a combination of lard and kerosene, fish oil, or cotton-seed oil. A fusion of kerosene, cotton-seed oil and sulfur, an emulsion of 10% Kerosene, a combination of crude petroleum and cotton-seed oil, or Beaumont crude oil alone allegedly proved efficacious when applied on cattle two to three times a week with syringes, brushes, sponges, brooms, or mops [12, 13]. On the other side, dipping vats containing mineral oil and 'carbolics' was practiced by Australian investigators for immersing cattle during early 1895 [14].

Arsenicals

Arsenic was the first widely used acaricide in controlling tick and tick-borne diseases. The application of arsenical solutions in controlling parasites of sheep started even before the first report of their use as an acaricide to control ticks on cattle in the years 1893 and 1895 in Southern Africa and Australia [15]. It was considered as inexpensive, stable, water-soluble [16] and was cheapest and more efficacious [17]. Arsenical solutions were used especially in the control of ticks of the genus *Boophilus* in different countries like South Africa, Australia, Brazil, Argentina, Colombia, Kenya, Zambia, etc. [17].

However, a few years later field failures began to occur; the first indication of field failure in Australia against *B. microplus* was noted in 1937. Similar cases of arsenic resistance were reported from South Africa in species of *B. decoloratus Amblyomma hebraeum, Hyalomma rufipes, H. truncatum, Rhipicephalus appendiculatus, R. evertsi* etc. Due to the lack of an alternate acaricide, tick infestations on cattle in different parts of the world increased in enormous proportion [18]. The evolution of resistance in ticks to arsenicals, the narrow limits between the effective concentration for tick control, and the toxic concentration for cattle and concern about toxic residues in animal tissues were the major factors that contributed to the replacement of arsenic with synthetic organic insecticides after the end of World War II [19].

Organochlorines

The first synthetic class of organic insecticides to be marketed for the control of ticks on cattle were organochlorines. This class of chemicals had a broad spectrum of action with higher efficiency and long residual activity. In comparison to arsenic, they also had the benefit of being less toxic and less expensive [20]. Of particular interest among this group, were benzene hexachloride [16] and DDT [21-23]. Other chemicals of this class that were widely used for the control of ticks on cattle included dieldrin, aldrin, cyclodiene compounds, and toxaphene, a polychloroterpene product [18]. These compounds were thought to bind at the picrotoxinin site in the $^{\gamma}$-aminobutyric acid (GABA) chloride ionophore complex [24, 25] that inhibited Cl^- flux into the neuron [26, 27]. As the function of the GABA-ergic inhibitory neuron got impaired, it resulted in the hyper-excitation of neurons, which ultimately led to the death of ticks.

In 1952, the first case of resistance to organochlorines by *B. microplus* was observed in Brazil [28]. Development of cross-resistance among different populations of tick species including *B. microplus, B. decoloratus, R. appendiculatus* against organochlorines led to a reduction in the use of these chemicals [18], in areas such as Australia [29, 30], Equatorial, and Southern Africa [31, 32]. A decade later, in 1962 the use of all organochlorines was literally banned against ticks, due to their residual effect in meat, milk, and the environment resulting from the poor biodegradability and affinity for lipids [33]. A recent study on the in vitro efficacy of lindane on engorged female *R. (B.) annulatus* and *Haemaphysalis bispinosa* revealed its efficiency as an effective acaricide. Its use is currently banned in India even though it was proved to cause heavy mortality, inhibition of fecundity, and blocking of egg hatching in engorged females [34].

Organophosphates and carbamates

Considering the resistance of tick species against organochlorines a new class of organic insecticides namely the organophosphates was formulated. Based on their effect on the nervous system, these compounds were tested for their pesticidal activity during the 1930s. In the 1940s, the first organophosphate, parathion was

developed. In the mid-1950s, organochlorines were gradually replaced by organophosphates in South America, as many tick species became resistant against these compounds [33, 35]. Unlike the highly persistent organochlorines, the organophosphates were chemically unstable and non-persistent. However, the risk of causing acute toxicity to livestock was greater [16]. The formulation of organophosphate acaricides was solely intended for the control of organochlorine resistant *Boophilus* ticks which were very common throughout the cattle prevalent areas of the tropics and subtropics [36]. This class of acaricides dominated in controlling ticks in Australia from the 1950s until the late 1960s and early 1970s. Similarly, the national tick eradication program in Mexico between 1974 and 1984 witnessed the heavy use of organophosphates [37]. The organophosphates which were used during the above period mainly included coumaphos, chlorpyriphos, chlorfenvinphos, diazinon, and ethion.

Another group of chemicals called carbamates were also introduced during the mid-1950s along with organophosphates. These were esters of carbamic acids, and closely resembled the organophosphates [38]. Both organophosphates and carbamates (e.g., carbaryl and promacyl) exerted their toxic effects by inhibiting the targets' AChE, a key enzyme vital for the functioning of the nervous system [18, 39-41]. When ticks were poisoned with a cholinesterase inhibitor, the enzyme would become unavailable for the breakdown of acetylcholine, thereby resulting in the continuous firing of neurons, which in turn would cause over-stimulation of the nervous system, and leading to their death [42]. However, when compared to organophosphate, carbamate was a little more toxic for mammals and was much more expensive [17].

Unfortunately, the importance of organophosphate-carbamate groups of acaricides for the control of ticks got reduced as tick species started to develop resistance against these chemicals. Organophosphate-carbamate resistant *B. microplus* strains were first reported from Australia during the mid-1960s [43]. In addition, organophosphate-carbamate resistance was also reported in several tick species viz., *B. microplus, B. decoloratus, A. hebraeum, R. appendiculatus,* and *R. evertsi* from South Africa during this period. Resistant strains of *B. microplus* were also reported from other countries like Brazil, South America, Mexico, Colombia, Uruguay, Argentina, Venezuela, etc. [18]. Thus, the 1970s witnessed a reduced use of organophosphate among the European Union member nations and North America [44]. Similarly, the use of organophosphate-carbamate groups was also minimized in Australia, much of Africaو and parts of Latin America [45]. However, some organophosphates are still commercialized as acaricides for veterinary and public health uses in several parts of the world, based on their very specific acaricidal use, in certain instances. For example, Coumaphos was an active ingredient in the acaricide that was officially approved by the U.S. Cattle Fever Tick Eradication Program to treat livestock [46].

Formamidines

During the mid-1970s when organophosphate-carbamate groups were proven ineffective in controlling ticks, they were substituted by amidines [47]. Members of this class of chemicals were chlordimeform, clenpyrin, chloromethiuron, amitraz, and cymiazole [48]. Chlordimeform was introduced in Australia as an additive to organophosphates in dipping vats of cattle to restore their efficacy against an organophosphate resistant tick strain [47], but was removed from the market in 1976 because of its carcinogenic nature [49]. Amitraz, a triazapentadiene compound, remained to be the main active ingredient in this class of acaricides, and was commonly used to control ticks infesting livestock and dogs [44]. Amitraz served to function as an octopamine agonist, thus exerting its toxic effects on arachnids [50]. Commercial formulations of amitraz offered the ability to control organophosphate resistant *B. microplus* and were used extensively in Australia to treat cattle during the mid-1970s [18, 51]. A series of trials executed in South Africa over a period of five years proved the effectiveness of amitraz in controlling *B. decoloratus, R. appendiculatus, R. evertsi*, and *A. hebraeum* [52].

Four to ten years after its first use, reports on the development of resistance against amitraz came from different parts of the world. The first evidence of resistance was reported from Australia during the early 1980s [47]. Since

then, there were scientific reports of acaricide resistance against these groups of chemicals from Mexico, South America, South Africa, New Caledonia, Brazil, and Colombia [18]. However, as correctly pointed out by Jonsson and Hope [53], amitraz remained in use as one of the most popular acaricides in controlling cattle infesting ticks in Australia, Latin America, and Southern Africa [54].

Pyrethroids

The late 1970s witnessed the introduction of pyrethroids against the cattle ticks that were resistant to amidines. Natural pyrethrum that was unstable in sunlight was the predecessor to a series of synthetic pyrethrin-like materials. Even though the history of the evolution of pyrethroids dates back to 1949, the third generation chemicals, permethrin, and fenvalerate were the first of these materials to be made available for the control of ticks on cattle. It was in the 1970s, that the US Environmental Protection Agency (EPA) described and registered the use of permethrin and deltamethrin as acaricides. Other pyrethroids commonly employed in the control of ticks include cypermethrin, flumethrin, cyhalothrin, and cyfluthrin [55, 56]. These compounds exerted a knock-down effect against arachnids [42]. Their action upon the sodium ion channels caused changes in the nerve membrane permeabilities to sodium and potassium ions, and thereby induced nerve excitation [57, 58]. At the beginning of the 21st century, pyrethroids could account for about 17% of the world insecticide market [59]. Flumethrin was found to be effective at a relatively low concentration in controlling both one-host and multi-host tick species infesting cattle when compared to other pyrethroids [60]. Similarly, Schnitzerling et al. [61] revealed that trans-flumethrin isomer was approximately fifty times more toxic to *B. microplus* than the other most-toxic pyrethroids, cis-cypermethrin, and deltamethrin. Although pyrethroids were considered safer in terms of acute avian and mammalian toxicity, their widespread use raised some issues such as urban runoff, which potentially exposed aquatic organisms to a harmful level of toxins in water and sediments.

Macrocyclic lactones

Macrocyclic lactones were introduced to the market in 1981 [62]. These compounds were systematically active against ticks and had a longer residual activity when compared to synthetic pyrethroids and were active against a wide range of arthropods and nematodes [55]. There were two classes of macrocyclic lactones with acaricidal activity; one was avermectins, derivatives of the actinomycete *Streptomyces avermitilis* and the other was milbemycin derived from the fermentation of *S. hygroscopicus aureolacrimosus* [63]. Ivermectin, eprinomectin, and doramectin were found related to avermectins; whereas moxidectin was the only milbemycin-derived macrocyclic lactones marketed for the control of ticks. Macrocyclic lactones exerted its toxic effect on ticks by stimulating the release and binding of gamma-aminobutyric acid (GABA) at nerve endings which eventually blocked the transmittance of electrical activity in nerves and muscle cells [64-66]. Ivermectin, doramectin, and moxidectin treatments administered as subcutaneous injections are found to efficiently control the infestation on cattle by *B. microplus*. Formulations of ivermectin, eprinomectin, doramectin, and moxidectin were found to bring satisfactory control of *B. microplus* on cattle [67, 68]. Even though macrocyclic lactone acaricides were highly effective in controlling ticks, the high cost of these chemicals limited their use [69]. The first macrocyclic lactone-resistant strain of *B. microplus* was recorded from Brazil, at the beginning of the 21st century [18].

Phenylpyrazoles

Fipronil, the prototype of the phenylpyrazole class of acaricides was discovered during the 1980s and was developed initially as a pesticide for crop protection. Later, it was applied as a pour-on to cattle infected with *B. microplus* in an open-sided barn, and was found to have a therapeutic efficacy greater than 99% and a similar degree of persistent protection against larval re-infestation for eight weeks after the application [70]. However, the high degree of persistent efficacy of a single pour-on treatment of fipronil on cattle was reduced by two or three weeks under field conditions with exposure to sunlight and other weather conditions [71]. Fipronil, though available in several countries in Latin America for the control of ticks, but it has

not been registered in the United States and some other countries for use on food animals.

Benzoylphenylurea

The first benzoyl phenyl urea was diflubenzuron that was approved as an oral formulation in Brazil to control *R. (B.) microplus* infestations. Most of the benzoyl phenyl ureas including diflubenzuron, lufenuron, and flufenoxuron were reported to be effective against a wide variety of insects, but fluazuron a member of this group was a mere exception as it was efficacious against ticks, and some mite species [55]. Fluazuron was marketed as a tick-development inhibitor in various regions of the world and pour-on formulation, providing long-term protection against *R. microplus* [72]. Fluazuron treatment caused a reduction in the fecundity and fertility of engorged females to nearly zero. It also increased the mortality of immature ticks by interfering with their molting to the next instar. Effects of fluazuron would persist for approximately twelve weeks and because of its binding nature to fat, fluazuron would be excreted in milk and hence, was found unnecessary to treat suckling calves. Due to the persistent nature of this acaricide in fat, it was required to withhold treated cattle from human consumption for six weeks [72].

Spinosad

Spinosad represents a new class of pesticides, the spinosyns. These are tetracyclic-macrolide compounds produced from the fermentation of soil-dwelling bacteria in the genus *Saccharopolyspora* [73, 74] and has a unique mode of action that involves disruption of the binding of acetylcholine in nicotine acetylcholine receptors at the postsynaptic cell [49]. The utility of spinosad as a systemic acaricide was documented in association with its use as oral treatment in dogs to control *R. sanguineus* infestations [75]. Studies on its efficacy in controlling hard and soft ticks revealed its potential as an alternative to other acaricides used commonly to control vectors and pests of public health importance [76]. Spinosad provided about 90% control of *B. microplus* on cattle infected with all three parasitic stages at the time of treatment. The nymphal and larval stages of ticks were more prone to spinosads when compared to mature stages [77]. Its unique mode of action validates it as an alternative acaricide to be considered for the control of *B. microplus*, which are resistant to other chemicals [18].

RESISTANCE MANAGEMENT STRATEGIES

The most effective way to control ticks is by using chemicals, but these are becoming less efficient, in the present days [78]. The indiscriminate use of acaricides without any restrictions, errors in solution preparation, mistakes in the manner, stage and frequency of application, and inadequate management of parasite control, all have favored the selection of ticks resistant to the chemical agents most often used by the cattle producers [79]. It is unlikely that it will be possible to prevent the evolution of resistance in tick control programs, which features the use of acaricides. However, some options can be adopted in slowing the rate of selection for resistant individuals, and also there are a few options that may be used when resistance renders an acaricide ineffective [80].

Application practices

The selection of an acaricide should always be done after obtaining a clear knowledge about the tick species present on the affected area, and its resistance status over various chemicals. The frequency and the dosage of acaricides used, the method of application [81], the timing of treatments [82] etc., should also be taken care while planning for delaying the development of resistance. High frequency of acaricide application contributes to the emergence of resistant tick strains. Earlier studies conducted by Jonsson et al. [81] and Thullner et al. [83] strictly recommended that application should not exceed for more than five times in a season. Sun et al. [84] suggested that cases of field resistance should be confirmed in the laboratory and complemented against known management practices.

Rotation of acaricides

Alternation of acaricides having different modes of action can reduce the emergence of resistance to any particular acaricide group [42]. The continuous application of a single acaricide for prolonged duration results in the fixation of a resistant allele within the tick population, which

finally results in complete product failure [44]. According to a laboratory study conducted by Thullner et al. [83], *R. microplus* stain that showed very high resistance to deltamethrin, showed less resistance to deltamethrin after its application in rotation with coumaphos. Similarly, a study by Jonsson et al. [85] revealed an apparent decrease of amitraz resistance in groups of cattle where rotation in between spinosad and amitraz was done. However, further field studies are required to elucidate the efficiency of such practices.

Using combinations of acaricide

The likelihood that one will not have resistant alleles to two chemicals with different modes of action enhanced the use of a combination of acaricides to delay the emergence of resistance in ticks [86]. This strategy has been deployed in different countries around the globe. For example, Australia has witnessed the use of organophosphate-synthetic pyrethroid combinations, and combination products of deltamethrin + ethion and cypermethrin + chlorfenvinphos remained on the market [18]. Likewise, Furlong [87] stated the use of acaricides *containing* mixtures of cypermethrin + chlorfenvinphos and permethrin + dichlorvos in Brazil. Cymiazole + cypermethrin remains the most commonly used mixtures of acaricides in Mexico [88]. A recent study by Santana [89] revealed that the combination of cypermethrin (15%) + chlorpyrifos (25%) + citronellal (1%) was efficient in combatting the *R. (B.) microplus* strain, than the isolated use of pyrethroids and organophosphate associations in Brazil.

Use of synergist

Synergist relationships have also been demonstrated among several groups of acaricides. Piperonyl butoxide is a synergist that has been used along with pyrethroid acaricides to control ticks that are resistant to pyrethroids. Synergism in a combination of permethrin and amitraz was observed by Li et al. [90]. Fernandez-Salas et al. [91] successfully evaluated the synergistic effect of amitraz and permethrin against an *R. microplus* strain that showed pyrethroid resistance in Mexico. However, utmost care should be taken in this strategy regarding the compatibility and the persistence of these combination products on the animal, and they must be applied at recommended concentrations [42].

Use of tick pheromones in combination with acaricides

The behavior of ticks could be extensively arbitrated by employing semiochemicals, and various novel approaches to tick control exploit the effect of these chemicals on tick behavior. Discovery of various pheromones which mediate the behavior of ticks, such as their assembly/aggregation/attachment/mating, etc. sheds light on the candidacy of these chemicals in future tick control programs, as promising tools to attract ticks [92, 93]. However, successful tick control cannot be achieved by the use of pheromones and it would be preferable, to use these in association with an acaricide. Similarly, for productive use, these compounds must be incorporated into a slow-release delivery device. Henceforth, diverse technologies are made available to delay the release of pheromone compounds, e.g., incorporation into plastic, adhesive materials, paraffin, or gelatin microcapsules.

A field trial with assembly pheromone + toxaphene was found to be effective in controlling *A. hebraeum* [94]. Sonenshine *et al.* [95] reported high mortality of *D. variabilis* when a pesticide, propoxur was applied in combination with the sex pheromone 2,6-dichlorophenol on dogs rather than the chemical alone was applied. Likewise, Sonenshine et al. [96] used an arrestant pheromone of *Ixodes scapularis* in oily droplets along with permethrin in laboratory trials and observed 95% mortality in adult ticks. The combinational use of pheromones and acaricides would increase the efficiency of acaricidal applications and thus could be practiced to wield tick distribution so that acaricides could be applied more effectively while minimizing their effects on non-target species.

CONCLUSION

Tick and tick-borne diseases have become a threat to the welfare of human and animal populations throughout the world. Tick control has become a global priority of public and animal health systems and acaricides would play a pivotal role as an ingredient in the toolbox

available for effective control. During immediate outbreaks, the sole reliance will be on chemical acaricides, to bring out a fast and effective control. However, the aftermaths related to resistance, the requisition for much safer acaricidal products, and the environmental health concerns they cause, etc., are shaping the use of acaricides. As chronicle indicates, the evolution of resistance to acaricides is unstoppable and hence, the long-term prospects for tick control require a prolonged basic and applied research efforts to identify and develop novel acaricides with reduced-risk and to deploy integrated control management approaches.

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Conflict of interest

The authors declare that there aren't any competing financial interests in relation to the work described.

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