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Review on Organophosphorus acaricides, their problems and potential alleviation strategies

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Review Article

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Abstract

In Egypt, ticks are a major arthropod vectors that transmit various infections including blood parasites, viruses, and bacteria to livestock and humans. Ticks are found in all geographic extents of Egypt. There are different species of ticks in Egypt, with the majority being Hyalomma and Rhipicephalus species. Tick control strategies in Egypt mainly involve the use of acaricides. One of these is Organophosphorus acaricides (OPS). Later, these acaricides persist in the environment causing severe pollution problems such as impairing soil fertility, water quality, plants genetic variations, the development of tick resistance and harmful residues in all food channel. Thus developing of other environmentally safe bioacaricides become fundamental. This review aims to explore OPS used on domestic animals and suggest new environmentally friend tick control techniques, such as, tick endosymbionts, medicinal plants and green pesticides.

Keywords: *Ticks, Control, Organophosphorus acaricides, Bioacaricides.*

Introduction

Ticks are blood sucking arthropods that parasitize humans and animals, worldwide **Parola (2004)**, and are graded second to mosquitoes as vector-borne arthropods. Ticks transmit various pathogens to humans and animals, during their bites, including viruses, bacteria and parasites **Jongejan and Uilenberg (2004)**. Additionally, ticks can cause anemia, reduce milk and meat production, allergies and potentially lead to paralysis **Ghosh *et al.* (2007); De La Fuente *et al.* (2008) and Dantas-Torres *et al.* (2012).** The geographic distribution of tick species is rapidly expanding, probably motivated by climatic changes, world animal trade and increased human movement leading to the emergence and spreading of zoonotic diseases **Kilpatrick *et al.* (2017)**. Egypt located on the migration route for birds migrating between their breeding grounds in Eurasia and their wintering grounds in Africa, providing opportunities for the spread of ticks and their pathogens **Hoogstraal *et al.* (1964)**. Of these dispersed tick species are: Argas spp. **Hoogstraal *et al.* (1964)**. Egypt's climate offers an encouraging environment for the growth of various tick species and tick-borne pathogens **CBD (2016); Abdelbaset *et al.* (2020); Abdelbaset *et al.* (2021)**. Besides, the importation of live animals increases the risk of the emergence of new tick species **Napp *et al.* (2008)**. The main species of ticks in Egypt are Hyalomma spp. and Rhipicephalus spp. Amongst TBDs that recorded in Egypt: theileriosis; babesiosis; anaplasmosis, ehrlichiosis and rickettsiosis **Abdelbaset *et al.* (2022)**. It has been estimated that global financial losses caused by tick infestation is US$22-30 billion/annum **FAO (2024)**.

Several control policies are applied to control ticks on domestic animals. Chemical control using acaricides have ascertained the best attitude in controlling tick populations **Rahman *et al.* (2022)**. There are several formulations of acaricides including: Arsenical preparations, Chlorinated hydrocarbons (DDT), Organophosphorus componds, Carbamates, Pyrethroids, macrocyclic lactones (Ivermectin) and Phenylpyrazoles (Fipronil) **William *et al.* (2019)**. Some of these acaricides, has been withdrawn, such as organochlorines. Certain compounds of organophosphates (OP), Pyrethroids and Macrocyclic lactones are the main acaricides that are currently used in Egypt **Githaka *et al.* (2022).** Organophosphates (OPs) are chemical insecticides that used over past 7 decades. OPs involve 40% of total insecticides **Payra *et al.* (2023)**.OPs encompass several highly toxic compounds that inhibit the Acetyl cholinesterase enzyme consequently, it disturb the central nervous system leading to neurological disorders **Gupta (2001)**. Moreover OPs causes seizure, respiratory complaints that may lead to death of animal or human. Parathion and chlorpyrifos, have been withdrawn from any use **Payra *et al.* (2023).** Nevertheless, Organophosphates kill ticks, it have stark side effects on all ecological food channel, including human, animals, birds and fish **Ortiz-Hernández *et al.* (2014)**. Organophosphate acaricides interact with the earth microbiota so change the biomolecules of the environment **Ghorab and Khalil (2015)**, and persist in the environment for many years **Ragnarsdottir (2000)**. The improper usage of OPs during transport, storage, application and disposal may cause lethal effects on non-target organisms, for instance aquatic organisms, animals, and humans **Fernández *et al.* (2010)**. As result of disadvantages associated with OPs so novel tick control strategies like green pesticides come into picture. Green pesticides are costless, biodegradable, safe and have no tick resistance.

Organophosphorus acaricides

Organophosphates (OPs) are a class of insecticides which comprise several highly poisonous chemicals. Nearly100 organophosphorus compounds have been reviewed by WHO as agents for the control of disease vectors. OPs were among the most commonly used insecticides in veterinary practices, until the 21st century, where several famous Ops have been withdrawn form veterinary use; comprising parathion and chlorpyrifos **Henk van den Berg (2009)**.

Classification

There are several structurally and toxicologically different groups of organophosphorus compounds (OPs).

Structurally OPs are classified to phosphates, phosphinates, phosphonates and phosphorothioates **Worek *et al.* (2016).** Different structures of organophosphorus insecticides are explained in Table 1. Generally these are esters, amides, or thiol derivatives of phosphoric or phosphonic acid:

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R1     O (or S)
   ||  \
        P -- X
R2/
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R are usually simple alkyl group, that may be fused directly to phosphorus (in phosphinates), or connected via O (oxygen), or S (sulfur) (in phosphates), or R^1 may be fused directly and R^2 bonded to one of the above groups (phosphonates). Carbon may connect to phosphorus via an -NH group (phosphoramidates). X is referred to as the leaving group that can be an aromatic, aliphatic, or heterocyclic group that attached to phosphorus through -O- or -S-. If the double-bonded atom was oxygen so the OP would be phosphates, but if it was sulfur the OP would be phosphorothioates. The P=O form is referred to oxon, and the P=S form is thion. P=S form is more stable so most manufactured OPs are in this form. **EHC 63 (1986).**

Table (1). Chemical structure of organophosphorus insecticides

Phosphorus group	Structure	Common name
Phosphate	O ‖ $(R\text{-}O)_2$-P-O-X	Chlorfenvinphos, Crotoxyph dicrotophos, Heptenphos, Dichlorvos Mevinphos Monocrotophos Tetrachlorvinphos
O -alkyl phosphorothioate	O ‖ $(R\text{-}O)_2$-P-S-X S ‖ $(R\text{-}O)_2$-P-O-X	Phoxim, Amiton, Demeton- S-methyl methyl. Azothoate, Bromophos, Brom pyriphos, Chlorpyriphos-mezinon, Chlorpyrifos, Diazinon, Dichlofenthion, Fenthion, Io-dofenphthion-methyl, Pyrazophos, Pyrimi-phos-methyl.
Phosphorodithioate	S ‖ $(R\text{-}O)_2$-P-S-X	Amidithion, Azinophos-ethy dimethoate, Dioxathion, di-formothion, Malathion, Me-cidathion, Morphothion, Phephosalone, Phos-met
S- alkyl phosphorothioate	R O \ ‖ S ‖ \ ‖ P-O-X / O / R	Profenofos, Trifenofos
S- alkyl phosphorodithioate	S R-S ‖ \ ‖ P-O-X / R-O	Prothiofos, sulprofos
Phosphoramidate	O ‖ $(R\text{-}O)_2$-P-NR_2	Cruformate, Fenamiphos
Phosphorotriamidate	O ‖ R_2N-P-N | NR_2	Triamiphos
Phosphorothioamidate	O ‖ R-O-P-NR2 | S-alkyl S ‖ (R-O)2-P-NR2	Methamidophos Isofenphos
Phosphonothioate	S R-O ‖ \‖ P-O-X / R	EPN, Trichlornat
Phosphonate	O RO ‖ \ ‖ P-O-X / R	Butonate, Trichlorfon

According to their degree of toxicity OPs classified to: highly toxic OPs as coumaphos (Co-Ral, Asuntol) ® and moderately toxic OPs as diazinon (Spectracide) ®, fenthion (mercaptophos, Entex, Baytex, Tiguvon) ®, dichlorvos (DDVP, Vapona) ® phoxim (Baythion) ® malathion (Cythion) ® **Eddleston *et al.* (2008)**.

Mode of action

All OPs work by inhibition of the affected tick acetylcholinesterase enzyme (AChE) resulting in loss of available AChE so accumulation of acetylcholine peripherally at cholinergic neuro-effector junctions so Muscarinic effect and centrally at the autonomic ganglia so nicotinic effects **Karaboga *et al.* (2024)**.

Toxicity

In human and animal:

Excessive ACh causes muscle contraction and may cause muscle twitching. Respiratory failure may occur due to impairment of the diaphragm muscles. In the CNS, elevated Ach concentrations cause behavioral disturbances like: incoordination, increased pulmonary secretions and respiratory failure so death from organophosphate poisoning. Despite, Organophosphates are efficiently absorbed by inhalation and ingestion, the absorption of OPs varies between both routes. For example, the oral LD50 of parathion in rats (3-8 mg/kg) is equivalent to dermal LD50 (8 mg/kg), **DuBois (1971); Pasquet *et al.* (1976)**. On the other hand, LD50 of phosalone in dermal route (1,500 mg/kg) is lower than that by the oral route (120 mg/kg), **Pasquet *et al.* (1976)**. OPs are biotransformed (through the replacement of sulfur bond by phosphorus and the addition of an oxygen atom (oxidative desulfurization)) by the metabolic activation of cytochrome P450, in the body, to highly toxic metabolites (oxon), **Abbas *et al.* (2012)**. Lipophilic organophosphates such as diazinon, fenthion and methyl parathion, have delayed toxicity as it permit fat storage so late release **Garcia-Repetto (1995); Roberts (2007)**.

Symptoms of toxicity in human and animal

- **Acute toxicity**:
  Symptoms of acute organophosphate toxicity appear during or shortly after exposure, depending on method of exposure. The most common symptoms to acute OPs toxicity are diarrhea, vomiting, hypersecretion, nausea, muscle twitching, respiratory depression, bronchospasm/ bronchorrhea, tachycardia/bradycardia, seizures and loss of consciousness **WHO (2006)**.
- **Chronic toxicity**:
  Certain organophosphates may be stored in fat tissue, so these need prolonged antidote regimen till extermination of all acaricide from the body **Roberts and Aaron (2007)**; this syndrome is called organophosphorus induced delayed neuropathy (OPIDN) and is characterized mainly by weakness or paralysis of the extremities **Jamal (1997)**.

Intermediate syndrome occurs within 24–96 hours after exposure. Respiratory paresis and muscular fatigue of the facial, neck and proximal limb muscles are prevailing in this syndrome. Moreover, depressed tendon reflexes may occur. Atropine and oximes fail to provoke these symptoms; therefore, cure is mainly supportive. The most common OPs encountered in this syndrome are dimethoate, methyl parathion and fenthion **De Bleecker *et al.* (1992; 1993)**.

Organophosphate toxicity medication

As organophosphate reach to the effector junction, aging process occur, AChE-phosphoryl bond is strengthened by loss of one alkyl group. Time required for aging process varies from minutes to days. According to the aging time, some phosphorylated AChE can be dephosphorylated (revitalized) by a compound known as an oxime. Now, the only FDA-approved oxime in the United States is pralidoxime **Antonijevic and Stojiljkovic (2007)**. Though medical therapy in organophosphate (OP) poisoning include pralidoxime (2-PAM), atropine and benzodiazepines (eg, diazepam) **Gummin *et al.* (2022)**.

Effect of Organophosphate acaricides on animal and human health:

Some OPs have shown carcinogenic effect on laboratory animals, in the form of non-Hodkin's lymphoma (NHL), leukemia, brain cancer and mammary gland carcinoma **WHO (2006)**. Despite the low toxicity of many OPs, it can disrupt the immune responses, and diminish the animal resistance to infectious diseases. Malathion is a very low toxic OP but even in small doses, it intrude the immune system, especially disturbing non-specific immune mechanisms **Camacho-Pérez (2022)**. Some OPs have been found to have endocrine disrupting properties **Kavlock (2001)**. OPs exposure cause reproductive disorders by affecting the gonads **Peiris-John and Wickremasinghe**

(2008). OPs are able to alter pituitary–adrenal, pituitary–thyroid functions and disturb the serum prolactin levels **Kokka *et al.* (1987)**. Parathion and methyl parathion have similar structure of hormones, comprising estrogens, so it can attach to the estrogen receptor protein and affect the gene transcription **Korach *et al.* (1988)**. Diazinon and malathion proven to cause toxicity to embryos **Ducolomb *et al.* (2009)**. Experimental studies on the effect of diazinon on male mice showed significant reduction in spermatogenesis, sperm counts and serum testosterone concentration **Fattahi *et al.* (2009)**. Chlorpyrifos reported to have genopoisonous and teratogenic effects in human beings **Sandal and Yilmaz (2011)**. Numerous OPs compounds cause reproductive noxiousness in both human and animals, as fenthion, dichlorvos, malathion, parathion, diazinon, chlorpyrifos **Payra *et al.* (2023)**.

Effect of Organophosphate acaricides on Environment

Organophosphate persist in the environment and cause stark pollution problems such as:

- **Soil contamination:** The OPs residues become pollutant to the soil, leading to soil aridity, intrude the earthworm leading to the plant root unviability and nitrate leakage **Verma and Sagar (2013)**. Chlorpyrifos is degraded slowly so it persist for long periods in soil and affect the soil biomass **Yadav *et al.* (2016)**.
- **Foodstuff contamination:** Lipophilic OPs accumulate in milk fatty matrix **Juhler (1997).** 1% of Quinalphos interacted with target tick spp., and the rest of it persist in the crops and soil **Gangireddygari *et al.* (2017).**
- **Air contamination**: organophosphates degrade in higher air layers then return to the earth's surface through dry and wet deposition **Muir *et al.* (2004)**.
- **Water contamination:** Methyl parathion was identified in many water samples **Diagne *et al.* (2007)**. Furthermore, the accumulation of methyl parathion residues in various elements of aquatic life has been recorded **Diagne *et al.* (2007); Huang *et al.* (2011)**. OPs pollute the ground water and surface water and affect the water quality **Wang and Lamely (2001)**.
- **Bionetwork problems:** Methyl parathion cause potential risk to the aquatic organisms and hamper with their reproductive, and developmental processes **Rico *et al.* (2010)**. Methyl parathion residues accumulate in water and danger all aquatic beings **Huang *et al.* (2011)**. photolysis of chlorpyrifos by the ultra-violet rays sunlight, leads to Sulfotep release, a poisonous pollutant that persist in the environment **Ali and Lamia (2018)**.

Evaluation of organophosphorus acaricides

Several studies were conducted in Egypt, on OPs efficacy; **Abdel-Fattah and El-Kholany (2005)** found that diazinon at dilution of 1:500 case 90% inhibition to oviposition and hatching of laid eggs of *B. annulatus*. **El-Bahy *et al.* (2015)** recorded that the highest effect of diazinon against *Boophilus annulatus*, invitro, was 100 % after 3h of exposure.

Many researchers from different countries had evaluated the efficacy of Ops: **Eshetu *et al.* (2013)** recorded mean Diazinon efficacy against ticks of about 80.1%, in Borena, Ethiopia. **Asha and Eshetu (2015)** reported Diazinon tickicidal efficacy of 65.3%. **Feyera *et al.* (2015)** estimated 85.2% maximum efficacy for diazinon, 72 h post-application, against *Hyalomma dromedarii* and *Rhipicephalus pulchellus* collected from camels in Ethiopia. **Gashaw *et al.* (2018)** reported that the in vitro efficacy of Diazinon 60% against *B. decoloratus*, in Ethiopia, was 100%.

Organophosphorus acaricides resistance

Tick resistance is defined as "the capability of tick strain to grow and/or to survive even with administration of a given acaricide in a recommended doses" **Rao *et al.* (2014)**.

Villarino *et al.* (2001) proposed that organophosphates interact with cuticle layer esterases of *R. microplus*, causing the high expression of esterases in larvae as well as in *adult R. microplus*, and subsequent resistance to OPs. **Yilma *et al.* (2001) and Sileshi *et al.* (2004)** in Ethiopia, found that ticks develop resistance with the most extensive, under or over concentration and frequent use of organophosphates compounds. **Fragoso *et al.* (2004)** explained that resistance to organophosphates compounds develops in almost 7-8 years of their use. **Natala *et al.* (2005); Kirby (2010)** and **Alanr (2011**) reported that incorrect concentration of an acaricide will affect its efficacy and cause failure of tick control. **De Oliveira *et al.* (2015)** in Brazil, stated that Organophosphates were one of the first resistant acaricides. **Hernandez *et al.* (2002)** and **CMPV (2018)** observed that tick resistance to an acaricide caused as a result of metabolic detoxification and point mutations at target sites. **Kumar (2019**) illustrated that before the application of acaricides on ticks, there were minute levels of natural resistance genes for acaricides and upon frequent use of acaricide these genes usually increases leading to declining the acaricide efficacy. **Kumar *et al.* (2020)** in India, mentioned that poor infrastructure and management practices may provide favorable sites for the easy propagation, survival and reproduction of ticks throughout the year; furthermore, the easily accessible acaricides to farmers and lack of intensive efforts by veterinarians to monitor the efficacy of acaricides have also contributed to the development of resistance. **Githaka *et al.* (2022)** expected that climate change may alter tick distribution, especially cattle tick which have higher susceptibility for accumulating acaricide resistance.

Identification of six mutations in the AChE3 gene of an OP resistant *R. microplus* strain was not sufficient to discuss OP resistance at the whole organism level, so extra mutations are possible to exist **Tameyer *et al.* (2013)**. Meanwhile 1950, ticks have established resistance to more than 30 OPs in 40 countries **Abbas *et al.* (2014)**. The resistance of *R. microplus* to organophosphorus acaricides is owing to a single autosomal gene partially dominant with respect to its susceptible allele **(Stone, 1968)**. Resistance of *Boophilus microplus* to organophosphate has been reported in several studies **Kuntz and Kemp (1994); Beugnet and Chardonnet (1995); Romero *et al.* (1997); Davey and George (1998); Baxter and Barker (1999); Crampton *et al.* (1999); Miller-Robert *et al.* (1999); Jamroz *et al.* (2000); Benavides and Romero (2000); Guerrero *et al.* (2001); Bianchi *et al.* (2003); Foil *et al.* (2004); Rosario-Cruz *et al.* (2009)**. **Li *et al.* (2003)** studied the resistance to two organophosphate acaricides, diazinon and coumaphos, in B. microplus. They detected cross-resistance between those two acaricides. **Sileshi *et al.* (2003)** in South Africa, detected relatively greater level of resistance to diazinon than amitraz. **Miller *et al.* (2008)** observed that *B. microplus* at Nuevo Leon, Mexico, was highly resistant to diazinon but not to coumaphos. **Turkson and Botchey (2010)** in Ghana, described that some tick species are resistant to organophosphates like diazinon. **Kumar *et al.* (2011)** found that the constant use of diazinon leads to *B. microplus* resistance to diazinon in 20 locations located at India. **Fernández-Salas *et al.* (2012)** reported that *R. microplus* exhibited resistance and mortalities to diazinon (24.2%). **Shyma et *al.* (2012)** found that *H. anatolicum* showed low-grade of resistance to diazinon at six areas in india. **Alonso-Díaz *et al.* (2013)** stated that Amblyomma cajennense were 91.7, 100 and 12.5% resistant to coumaphos, diazinon and chlorpyriphos, respectively. **El Hachimi *et al.* (2022)** in Morocco, stated that the cattle tick *Hyalomma marginatum* has resistance to diazinon.

Foil *et al.* (2004) described that *B. microplus* from Mexico has established resistance to many acaricides including organophosphates and chlorinated hydrocarbons (DDT). **Mendes *et al.* (2007)** in São Paulo, Brazil, recorded an emerging resistance of *B. microplus* to chlorpyriphos (58.3% sensitive, 33.3% resistant level I and 8.4% resistant level II) using the larval packet test (LPT) technique. **Nagagi *et al.* (2020)** in Tanzania found resistance of *Rhipicephalus evertsi* and *R. microplus* and ticks to chlorfenviphos.

Resistance of tick against most existing acaricides rose the development of alternative attitudes to mitigate tick resistance, such as development of novel stable, cheaper, easily accessible, environment-friendly acaricides **Obaid *et al.* (2022)**. The use of combination of tick vaccines in some countries; TickGARD and Gavac® vaccines; reduce the resistance of *R. microplus* to chemical acaricides **Willadsen (2004); de la Fuente & Contreras (2015)**.

Conclusions

From all previous studies it is clear that intensive application of OPs acaricides led to tick resistance that threatened nutritional security through economic losses in animal production sector. This review evidently shows the worrying threat from OPs use to human and animal health, besides, its environmental impact. Annually, a lot of people in developing countries, dies due to pesticide toxicity together with very high percentage of chronic disease cases. Though, alternative safer policies are in demand for tick control.

Recommendations

This review revealed that ticks pose significant health problem for both humans and animals in Egypt. We should consider alternative novel control methods such as genetically engineered subunit vaccines, endosymbionts of ticks, plant extracts like Azadirachta indica, Gynandropsis gynandra, Pelargonium roseum and their derivative compounds (azadirachtin, citronellal, and geraniol) in Egypt. These are environmentally friendly and have demonstrated 90–100% efficacy against tick in various studies Compared to organophosphorus acaricides. The biological agents such as bacteria (Bacillus thuringiensis), fungi (Metarhizium anisopliae and Beauvaria bassiana), nematodes and parasitoids wasps (Ixodiphagus hookeri) require further studies for use and be promoted against ticks.

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