Chemistry Research Journal, 2016, 1(3):21-26

Available online www.chemrj.org

ISSN: 2455-8990
CODEN(USA): CRJHA5

Review Article

Potential Uses of Synergists in Insecticides Resistance Management Accompanied by Their Contributions as Control Agents and Research Tools

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Abstract Insecticides form a major proportion of the agricultural products and their importance and impact on the farm cannot be denied. In this context, new molecules and strategies are urgently needed to preserve the efficacy of insecticide-treated materials used in public health. The purpose of this paper is to consider the best possible roles of synergists in insecticide resistance management by highlighting the types of formulations which are available. Among the different strategies proposed, the combination of a repellent with a carbamate or an organophosphate is an effective approach to manage pesticide resistance by the addition of synergists to counteract metabolic resistance. Synergists are also useful for laboratory investigation of resistance mechanisms through their ability to inhibit specific metabolic pathways. These natural or synthetic chemicals are by themselves considered nontoxic, which increase the lethality and effectiveness of currently available insecticides. The mode of action of the majority of synergists is to block the metabolic systems that would otherwise break down insecticide molecules. These interfere with the detoxication of insecticides through their action on polysubstrate monooxygenases and other enzyme systems. The role of synergists in resistance management is related directly to an enzyme-inhibiting action, restoring the susceptibility of insects to the chemical, which would otherwise require higher levels of the toxicant for their control. Synergists are among the most straightforward tools for overcoming of metabolic resistance because they can directly inhibit the resistance mechanism itself. Their effective application against agricultural pests has offered tremendous promise, but achieved little utility. Synergism is the application of a mixture in which one component when used alone is inactive at the rate of treatment and insecticide combinations can also give a greater than additive effect. Their contributions as research tools and as control agents are quite different, these can be less active on predators than pests, and at times these approaches have vital implications in integrated pest management.

Keywords Synergist, Insecticide, Resistance, Metabolic Inhibitor, Formulation

1. Introduction

An increase in global population and area under cultivation has brought the problem of maintaining a sustainable agricultural system, with the constraints on land-use and environmental protection. One acute problem in agriculture production is that of arthropod pests, for which chemical control remains the foundation of device for growers today and for the foreseeable future. Insecticides form a major proportion of the agricultural products being produced in the country and imported from abroad. The product available is of mixed quality from highest standards of the multinational and local companies to the lesser quality products of some of the small manufacturers. Thus, products related to the insecticides available in the market belong both from well reputed and slighter quality products pesticide companies. The importance and impact of the insecticides on the farm cannot be denied both in terms of the useful and residual effects. Similarly, they form a major part of the agriculture industry and there is an excess of availability of the insecticides in the agriculture markets [1-9].

Synergists have been used commercially for about fifty years and have contributed significantly to improve the efficacy of insecticides, particularly when problems of resistance have arisen. These natural or synthetic chemicals, which increase the lethality and effectiveness of currently available insecticides, are by themselves considered nontoxic. The mode of action of the majority of synergists is to block the metabolic systems that would otherwise break down insecticide molecules. They interfere with the detoxication of insecticides through their action on polysubstrate monooxygenases and other enzyme systems. The role of synergists in resistance management is related directly to an enzyme-inhibiting action, restoring the susceptibility of insects to the chemical, which would otherwise require higher levels of the toxicant for their control. For this reason synergists are considered straightforward tools for overcoming metabolic resistance and can also delay the manifestation of resistance. However, the full potential of these compounds may not have been realized in resistance management. Synergists have an important role to play in the ongoing investigation of insecticide toxicity, and mode of action and the nature of resistance mechanism. They also can be used in understanding the effects of other xenobiotics in non-target organisms. The search for and the need of new molecules capable of synergizing existing or new pesticides has reactivated the identification and characterization of secondary plant compounds possessing such activity. Plants do possess and utilize synergists to overcome the damage produced by phytophages. In this perspective, some prime synergists include bucarpolate, dietholate, jiajizengxiaolin, octachlorodipropyl ether, piperonylbutoxide, piperonyl, cyclonene, piprotal, propyl isome, sesamex, sesamolin, sulfoxide, tribufos and zengxiaoan [10-13].

As research tools, synergists can help to boost the potential toxicity of a compound and they can also aid in determining the particular mechanisms of insecticide resistance encountered. A major contribution of this approach may be in bridging the gap between biochemical studies and population genetics. As control agents, synergists can potentially render to resistant populations into susceptible and prevent the development of resistance. The reports also show that synergists can be less active on predators than on pests and have the implications in integrated pest management. A number of practical usage problems, however remain, and these represent major hurdles to their widespread application. To overcome these hurdles, synergists will have to be viewed in a broader sense than previously and integrated into a complex array of interactions between the insect and its environment [14-19]. These have to be exploited in pest management programs for intention of resistance management in insects. In the current article, the potential role of synergists in insecticide resistance management, mode of action, natural occurrence and significance in research in insecticide synergists are examined. This information is to be exploited in pest management program, and hopefully, it will lead to a new perspective on the nature and significance of synergism.

2. Practical Usage of Insecticide Synergists

Synergists have varying degrees of potential in each of four broad areas of insecticide resistance management in insects like analytical tools, control of resistant populations, prevention of resistance and preservation of natural enemies. Perhaps the most promising use of synergists is as research tools. Synergists have been used analytically to delineate the relative importance of penetration or detoxification in insect-insecticide activity relationships. They have also been used to quantify the potential activity of a compound solely on the basis of its toxicity at the active site by removing interfering oxidative processes. Several synergist classifications are available, including those based on the insecticide category affected, structural class of the synergist, spectrophotometric behavior and enzyme system affected. From an applied viewpoint, the classification based on insecticide categories affected is the most important, but from a physiological standpoint, the most useful approach is to consider synergist types based on the detoxification mechanism they inhibit. The foremost among these detoxification mechanisms are mixed function oxidases. Consequently, most insecticide synergists are inhibitors of this group [20-22].

Synergists are commonly used in combination with pesticides to suppress metabolism-based resistance and increase the efficacy of the agents. They are also useful as tools for laboratory investigation of specific resistance mechanisms based on their ability to inhibit specific metabolic pathways. To determine the role of metabolic degradation as a mechanism for acaricide resistance in human scabies, piperonylbutoxide, S,S,S-tributylphosphorotrithioate and diethyl maleate are used with permethrin as synergists in a bioassay of mite killing. A statistically significant difference in survival time of permethrin-resistant *Sarcoptesscabiei* variety *canis* is noted when any of the three synergists are used in combination with permethrin compared to survival time of mites exposed to permethrin alone ($p<0.0001$). These results indicate the potential utility of synergists in reversing tolerance to pyrethroid-based acaricides (the addition of synergists to permethrin-containing topical acaricide cream commonly used to treat scabies). To further verify specific metabolic pathways being inhibited by these synergists, enzyme assays are developed to measure esterase, glutathione S-transferase and cytochrome P450 monooxygenase activity in scabies mites. Results of *in vitro* enzyme inhibition experiments show lower levels of esterase activity with S,S,S-tributylphosphorotrithioate; lower levels of glutathione S-transferase activity with diethyl maleate and lower levels of cytochrome monooxygenase activity with piperonylbutoxide. These findings indicate the potential utility of synergists in reversing resistance to pyrethroid-based acaricides and suggest a significant role of metabolic mechanisms in mediating pyrethroid resistance in scabies mites [23].

The continued use of permethrin isthreatened by pyrethroid resistance and resistance in head lice *Pediculus capitis* (De Geer) has been reported from various global localities. Most of permethrin-resistant head lice show resistance to other pyrethroid insecticides. The resistance to permethrin in head lice is accompanied by cross-resistance to d-phenothrin and bioallethrin, and the lice are also resistant to d-phenothrin. In previous study, it is reported that all field-collected lice that are resistant to permethrin also show resistance to d-phenothrin and deltamethrin. The development and spread of pyrethroid resistance in head lice occur relatively soon after their introduction. The lack of safe and effective alternative compounds suggests an urgent need for the development of a resistance management strategy. Basic rules of this management plan include the absence of cross-resistance and lack of similarity in biochemical mechanisms in head lice. In addition, the uses of synergists for the inhibition of detoxifying enzymes represent not only an alternative to improve control, but a tool for elucidating resistance mechanisms. The data concerning the cross-resistance profile and synergism by enzyme inhibitors, when permethrin resistance head lice are concerned, demonstrate that enhanced metabolism is involved in pyrethroid resistance. However, the substantial degree of resistance remaining after synergism suggests the presence of other resistance mechanisms. Cross-resistance to pyrethroids and the susceptibility to carbaryl suggest that a common site of pyrethroid action exist. Further investigations in the physiological mechanisms are necessary to develop a proper resistance management strategy in *P. capitis* [24-25].

Permethrin-resistant colonies of *P. capitis* areused to establish a resistance profile and to examine resistance mechanisms. All permethrin-resistanthead lice (resistance ratio from 52.8 to 88.7) are also resistant to d-phenothrin (resistance ratiofrom 40.86 to .48.39) and deltamethrin (resistance ratio from 16.24 to 38.06). No cross-resistance to carbaryl is found in any of the pyrethroid-resistant *P. capitis* tested. Otherwise, all resistant colonies show low to high levels of resistance to b-cypermethrin. This pyrethroid has never been applied as a pediculicide; however, the high levels of resistance found in these permethrin-resistant colonies (resistance ratio from 9.74 to 50.97) demonstrate that pyrethroid cross-resistance occur to this novel insecticide. Treatments with piperonylbutoxideortriphenylphosphate significantly decrease the toxicity of permethrin in the four coloniestested. The esterase inhibitor triphenylphosphate produces lower enhancement of toxicity than the multifunction oxidase inhibitor piperonylbutoxide in the colonies having the highest resistance levels. Results present hereconcerning the cross-resistance profile and synergism by enzyme inhibitors in permethrin-resistant head lice demonstrate that enhanced metabolism is involved in the pyrethroid resistance. However, the substantial degree of resistance that remained after synergism suggests the presence of another resistance mechanism. Cross-resistance to pyrethroid and susceptibility to the carbamate carbaryl suggest a common action mechanism [26].

Insecticide resistance continues both to increase and broaden; a situation that will be exacerbated by the withdrawal of some older insecticidal actives. One possible solution that has been advocated is the use of synergists, especially if coupled with 'temporal synergism', a concept reported previously whereby a synergist contacts a pest some hours before the insecticide component of the treatment. For example, when crop pests are exposed to piperonylbutoxide several hours before pyrethroid, carbamate or neonicotinoid insecticides, inhibition of the metabolic enzymes (P450s and esterases) that would normally degrade these insecticides occur, leaving the insect pests in a hypersensitive state before exposure to the insecticide. However, it may be that not just the target insects would be exposed to both synergists and insecticides, but beneficial insects such as bees would potentially also be at risk. The honey bee (*Apismellifera*) (Hymenoptera: Apidae) is a global pollinator of many crop plants, encountering various challenges such as disease, parasites and both intended and unintended insecticide exposure. Although, chemical control is currently an indispensable input for global agriculture, pesticides have been suspected to be involved in the disappearance of honey bees since the report of colony collapse disorder. As with other insects, honey bees use their metabolic enzymes to detoxify insecticides and although their genome contains a smaller number of genes encoding detoxification enzymes (as judged by comparison with the published genomes of other insects), the literature indicates that a lower number of detoxification genes does not necessarily correspond to a lower detoxification activity. So, there will a regime to control insect pests by inhibition of their detoxifying enzymes also penalize honey bees in the same way. Before advocating widespread use of synergists such as piperonylbutoxide, it is essential that studies are performed to characterize their effects against the defense enzymes of the honey bee; both in terms of potency and to identify which defense enzymes (P450s and/or esterases) are inhibited. The synthetic pyrethroid, tau-fluvalinate, is used widely as an acaricide treatment against the bee parasite *Varroa destructor* in apiculture. It has been reported that the reason for tau-fluvalinate's lower toxicity to the bees themselves is due to rapid metabolism by their P450s. If this is correct, and piperonylbutoxideinhibits this honey bee defense system, it could be expected that exposure to this pyrethroid would result in high mortality, rendering this insecticide of no value impotent for parasite control [27-33].

Phytochemicals have been considered as alternatives for conventional pesticides because of their low mammalian toxicity and environmental safety. They usually display less potent insecticidal effects than synthetic compounds, but may express as yet unknown modes of action. In the study, 14 plant essential oils are evaluated for their toxicities and synergistic effects with carbaryl and permethrin against fourth instars of *Aedes aegypti* (L.), as well as 5-7-d-old adults. Six essential oils show significant synergistic effects with carbaryl at 10-50 mg/liter, but paradoxically all of them decreased the toxicity of permethrin against *Ae. aegypti* larvae. None show toxicity or synergistic effects on *Ae. aegypti* adults, at doses up to 2,000 ng/insect. The six essential oils displaying synergistic effects in *Ae.aegypti* larvae, inhibit the *in vitro* activities of cytochrome P450 monooxygenases and carboxylesterases in the low milligram per liter range. The data indicate that cytochrome P450 monooxygenases and carboxylesterase are probably targets for these natural synergists. Thus, the mechanism of synergism is most likely inhibition of metabolism and not interacting target site effects [34].

To better understand the mechanisms involved and assess the impact of detoxifying enzymes (oxidases and esterases) in these interactions, bioassays are carried out in the laboratory against the main dengue vector *Ae.aegypti*. Topical applications of DEET (chemical name, N,N-diethyl-meta-toluamide) and propoxur (carbamate), used alone or as a mixture, are carried out on female mosquitoes, using inhibitors of the two main detoxification pathways in the insect. Piperonylbutoxide, an inhibitor of multi-function oxidases, and S,S,S-tributylphosphorotrithioate, an inhibitor of esterases, are applied one hour prior to the main treatment. Results show that synergism between DEET and propoxur disappears in the presence of piperonylbutoxide,but not with S,S,S-tributylphosphorotrithioate. This suggests that oxidases, contrary to esterases, play a key role in the interactions occurring between DEET and cholinesterase inhibitors in mosquitoes [35].

Consequently, the first step in resistance mechanism is to determine the insecticide classes for which resistance is present in an insect population. For each appropriate insecticide category, there is a corresponding group of synergists. The value of this approach is that it greatly reduces the time, expense, equipment and expertise needed to determine the cause of resistance. The development and spread of resistance to insecticides occur relatively soon after their introduction into body. The lack of safe and effective alternative compounds suggests an urgent need for the development of a resistance management strategy. Basic rules of this management plan include the absence of cross-resistance and lack of similarity in biochemical mechanisms in insect. In addition, the use of synergists for the inhibition of detoxifying enzymes represents not only an alternative to improve control, but a tool for elucidating resistance mechanisms [36-37].

3. Conclusion

In conclusion, with the spread of insecticides resistance in insects, the combination of an insecticide (carbamate or organophosphate) with a repellent is considered as a promising alternative strategy for the treatment of plants and other relevant materials. Synergists can play an important role in agriculture and insecticide resistance management, but probably not in the simplistic fashion once envisioned. Their value as research tools is well established, but the obstacles to field utility are formidable. At times, these approaches are even in conflict, and it is that synergists that will have to be integrated into a complex array of interactions between the insect and its environment. There include in this environment, the natural enemies, secondary pests, host plants, insecticides and nontraditional control agents. These outcomes are of great interest for the implementation of combination nets in the field. They support the need to combine insecticide with repellent to overcome insecticide resistance in mosquitoes of public health importance. In areas where resistance to insecticides can no longer be controlled, the use of carbamate (or organophosphate) combined to repellents appears as an effective alternative to pyrethroids, as they show efficacy equivalent to these insecticides in simulated field situations. In other situations, such combinations might also be used as a supplement to pyrethroids to retard the spread of resistance. Further investigations in live situations are certainly necessary prior to the use of insecticide and repellent combinations for vector control. The efficacy of these mixtures against mosquitoes has to be assessed in the field on a significant period of time, as well as its cost and safety to human. Using such combinations may also be of great interest in areas where mosquito populations show resistance based on oxidase metabolism. As observed in the laboratory, metabolic-based resistance may facilitate synergism between carbamate and repellent when using ‘two in one’ treated materials. In this perspective, these mixtures should be evaluated in areas where mosquitoes show a high and broad range of metabolic-based resistance. Hopefully, this information would lead to a new perspective on the nature and significance of synergism.

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