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Review Paper

Insecticidal Activity, Toxicity, Resistance and Metabolism of Pyrethroids: a Review

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Abstract
Pyrethroids are synthetic or man-made versions of natural pyrethrins discovered in the flowers of a plant species of the Compositae family called "*Chrysanthemum cinerariaefolium*". The plant was transported into Europe and America after it was discovered in the Near East. Commercial insecticides such as pyrethrin and synthetic pyrethroid are available. These are used to control agricultural pests as well as non-agricultural insects. They are also commercially used in personal care items such as shampoo and as a scent in insect repellent to boost efficacy and persistence in the environment, these insecticides are frequently combined with additional chemicals in diverse formulations, known as synergists. Nerve toxins, known as pyrethroids, although their chemical mechanism of action is unknown. Pyrethroids are neurotoxins, which interfere with the messages sent along nerves by maintaining sodium and chloride channels in an open position. This review presents perspectives, commercial uses and other useful characteristics features of pyrethroids based on human benefits and environmental friendly.

Keywords
Pyrethroids, Pyrethrins, Neurotoxicity and Environmental Friendly

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1. INTRODUCTION

Pyrethroids are synthetic or man-made versions of natural pyrethrins discovered in the flowers of a plant species of the Compositae family called "*Chrysanthemum cinerariaefolium*" (often referred to as pyrethrum). The plant, which is native to the Near East, was first imported to Europe and America in the nineteenth century, then to Japan and Africa afterwards. Kenya and other African countries, Equador, and Japan are its key cultural regions. Pyrethrin's insecticidal capabilities come from the ketoalcoholic ester of chrysanthemic acid and the pyrethronic acids. These acids are very lipophilic, allowing them to easily permeate and pyralize the neural systems of many insects.

Natural chemicals contained in *Chrysanthemum cinerariaefolium* (Figure 1) extracts decompose rapidly when exposed to light, thus they've been replaced with synthetic derivatives that were once thought to be safe for humans and higher animals (Bradberry et al., 2005; Costa, 2015; Soderlund, 2012). Since the 1980s, they've been used as insecticides all over the world due to their high efficacy and low toxic effects when contrasted towards other insecticides like organophosphates and carbamic ester chemicals (Cárcamo et al., 2017). Pyrethrum was discovered to have valuable insecticidal characteristics in the 19^{th} century. In the first part of the twentieth century, these properties motivated a detailed research of the chemical composition of active esters. Commercial insecticides such as pyrethrin and synthetic pyrethroid are available. These are used to control agricultural pests as well as non-agricultural insects. To boost efficacy and persistence in the environment, these insecticides are frequently combined with additional chemicals in diverse formulations, known as synergists.

Pyrethroids are also used in personal care items including shampoo and insect repellent scent. In recent years, the pesti-

cides 'cypermethrin', 'deltamethrin', 'fenpropathrin', 'fenvalerate', 'bifenthrin', 'permethrin', 'l-cyhalothrin', and 'cyfluthrin' have all been extensively utilized (Gong, 2013). Pyrethroid pesticides are less prone to pollute the environment than other synthetic pesticides. It can get into your body via the food chain. They are particularly toxic to aquatic life and may have unfavorable effects on the aquatic environment (Zhao, 2014). Vulnerability to even minimal dose pyrethroid over a period can increase serious illnesses and damaging effects on an organism's neurological, immunological, circulatory, and hereditary systems, resulting in teratogenic effects, mutagenicity, and carcinogenicity (Xin, 2009). Pyrethroid exposure has been linked to problems with the male reproductive system (Koureas et al., 2012). Urinary pyrethroid metabolite levels have been reported to be linked to sperm aneuploidy (Radwan et al., 2015).

Figure 1. *Chrysanthemum cinerariaefolium* Flower

2. DEVELOPMENT OF COMMERCIAL PYRETHROIDS

The evolution of commercial pyrethroids is depicted in the form of a tree with different architectures (Figure 2). The discovery of "3-phenoxybenzyl alcohol ($C_6H_5OC_6H_4CH_2OH$)" and, "α-cyano-3-phenoxybenzyl alcohol ($C_{14}H_{11}NO_2$)" moieties as agricultural insecticides was significant at the main trunk A. A few branches from the main stem have been marketed for agricultural use, as have numerous diphenyl ether-type pyrethroids. At trunk B, N-hydroxymethyl type pyrethroids are used, which have significant knockdown activity against a variety of insect pests. Pyrethroids of the allethrin class are used at trunk C. Prallethrin is found towards the end of trunk C and has a structure that is quite similar to pyrethrin I. Tetrafluorobenzyl type pyrethroids are found in the fourth trunk D. Sumitomo chemical chemists created the pyrethroids shown in yellow in Figure 2. The author contributed significantly to the development of the pyrethroids shown in pink by Matsuo (2019).

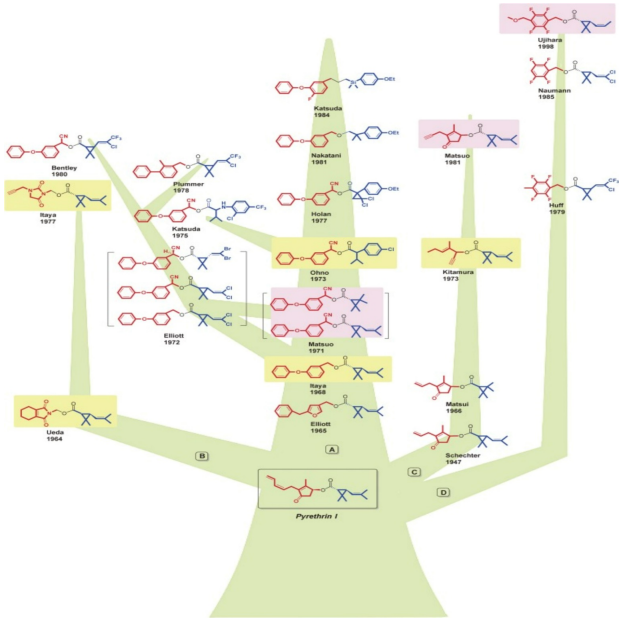

Figure 2. Tree Depicts The Evolution of Pyrethroids

3. CLASSIFICATION OF PYRETHROIDS (TYPE I AND TYPE II)

Pyrethroids are classified into two groups depending on their chemical and physical properties: type I and type II are its two different types. Pyrethroid derivatives without a cyano (-CN) group are classified as type I pyrethroids, that cause tumors syndrome (T), which is characterized by whole-body tumours, aggressive behaviour, hypersensitivity, and ataxia. In mammals, type II pyrethroids produce chloreoathetosis and salivation, choreoathetosis-salivation syndrome (CS), and motor impairment (Motomura and Narahashi, 2001; Williamson et al., 1989). These chemicals have been shown to influence chloride channels, particularly GABA-dependent ones, in addition to sodium channels (Chen et al., 2018). Classification of pyrethroids is shown as pictorial form in Figure 3.

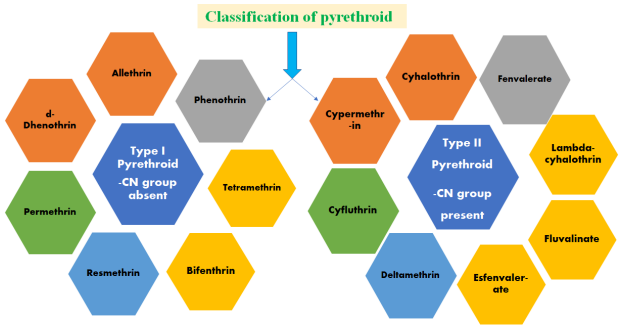

Figure 3. Classification of Pyrethroids

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4. MOLECULAR CHEMISTRY OF PYRETHROID

Pyrethrum extract is made up of six insecticidal esters known as pyrethrins, which are almost identical save for the terminal substituents on the acid and alcohol side chains (Chen et al., 2018). Pyrethrum is a genus of old category *Chrysanthemum* or *Tanacetum* plants species. Its Molecular chemistry is represented in the form of the chemical structure of chrysanthemic acid in both *cis* and *trans* form Matsui et al. (2020) is shown in Figure 4. The alcohol is a substituted cyclopentenolone, and the acid is a substituted cyclopropanecarboxylic acid. Pyrethrolone (Figure 5), cinerolone (Figure 6(a)), and jasmolone (Figure 6(b)) are the three alcohols involved in the "pyrethrins", "cinerins", and "jasmolins", respectively.

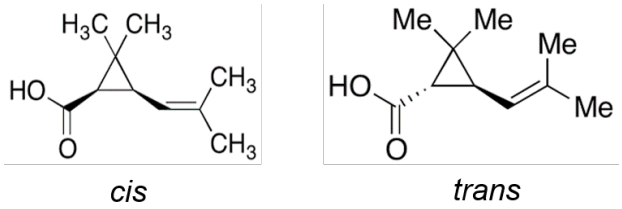

Figure 4. Chemical Structural Representation of Chrysanthemic Acid

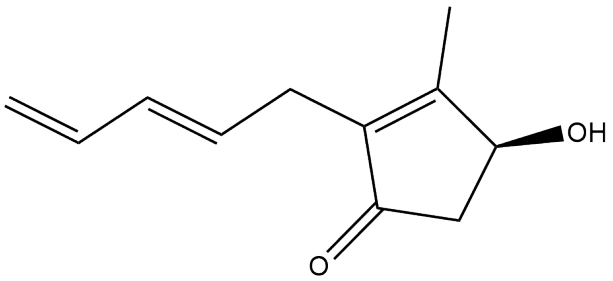

Figure 5. Chemical Structural Representation of Pyrethrolone

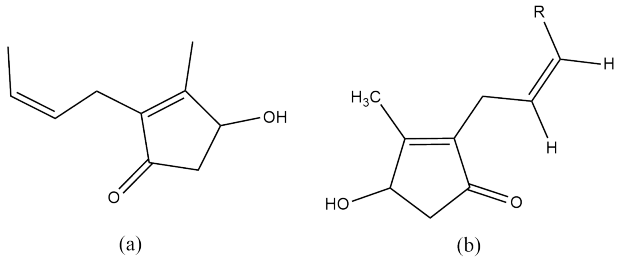

Figure 6. Cinerolone (a) and Jasmolone (b)

Pyrethrin I, a "3-penta-1,3-dienyl-2-methyl-4-oxocyclopent-2,1-en-1-ylester" of chrysanthemic acid, (4S)-4-hydroxy-3-methyl-2-[(2Z)-penta-2,4-dien-1-yl]cyclopent-2-en-1-one is the active ingredient in pyrethrum (rethrins). Pyrethrin II is a pyrethric acid ester composed of 3-penta-1,3-dieny-1-2-methyl-4-oxocyclopent-2-en-1-yels. The chemical names Todd et al. (2003a) of the pyrethrins are listed in Table 1.

Cinerin I, cinerin II, the "3-but-2-enyl" analogues, as well as 'jasmolin I' and 'jasmolin II', the 3-pent-2-enyl analogues of pyrethrin I and pyrethrin II, correspondingly. Table 2 presents the chemical identity and features of pyrethrins (Todd et al., 2003a).

Pyrethroids that are commercially accessible include. Commercially available pyrethroids include 'allethrin', 'bifenthrin', 'bioresmethrin', 'cyfluthrin', 'cyhalothrin', 'cypermethrin', 'deltamethrin', 'esfenvalerate' (fenvalerate), 'flucythrinate', 'flumethrin', 'fluvalinate', 'fenpropathrin', 'permethrin', 'phenothrin', 'resmethrin', 'tefluthrin', 'tetramethrin', and 'tralomethrin'. Tables 3, 4, 5, and 6 provide information on the chemical identification Todd et al. (2003a) of pyrethroids.

The structures and stereochemical properties of both the acid and alcohol components influence the biological activities of the pyrethrum constituents. Pyrethrins I and II have a much higher potency than cinerins and jasmolins. The chrysanthemates (I) are more lethal, whereas the pyrethrates (II) are more successful in knocking down. As a result, pyrethrum has both an effective knockdown agent (pyrethrin II) and a powerful insecticidal component (pyrethrin I). Because pyrethrins contain three chiral centres, they can take on eight distinct optically active forms (Figure 7). There is additionally geometrical isomerism (E or Z) in the side chain of the alcohol (chrysanthemates) or the acid and alcohol (pyrethrates), resulting in a total of 16 stereoisomers for chrysanthemates and 32 stereoisomers for pyrethrates. Despite the fact that not all of these isomers have been created and tested, the existing information clearly suggests that the naturally occurring configuration is the most powerful (Huang et al., 2005).

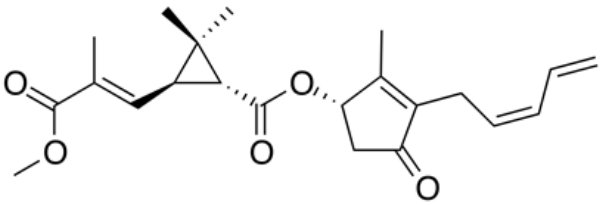

Figure 7. Pyrethrin II (*Trans*)

Unlike single molecules, pyrethroids are complex mixtures of isomers other than deltamethrin. Isomerism around the cyclopropane ring has a significant impact on the toxicity of pyrethroids with the cyclopropane moiety. Two pairs of diastereomers result from the existence of two chiral centres in the ring. Diastereomers and their non-super-imposable mirror duplicates (enantiomers) are depicted in Figure 8. The carbon atom linked to the ester moiety is given to the C-1 position of the ring in this diagram. Instead of giving an absolute configuration to the stereochemistry at the C-3 location, it is more common to simply label it as '*cis* or *trans*' in relation to the

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Table 1. Chemical Features of The Pyrethrins

Characteristic	Pyrethrin I	Cinerin I	Jasmolin I
Chemical Name	(1S)-2-Methyl-4-oxo-3-[(2Z)-penta-2,4-dien-1-yl]cyclopent-2-en-1-yl (1R,3R)-2,2-dimethyl-3-(2-methylprop-1-en-1-yl)cyclopropane-1-carboxylate	[(1S)-3-[(Z)-but-2-enyl]-2-methyl-4-oxocyclopent-2-en-1-yl] (1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropane-1-carboxylate	[(1S)-2-methyl-4-oxo-3-[(Z)-pent-2-enyl]cyclopent-2-en-1-yl] (1R,3R)-2,2-dimethyl-3-(2-methylprop-1-enyl)cyclopropane-1-carboxylate
Trade Name	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl
Chemical Formula	$C_{21}H_{28}O_3$	$C_{20}H_{28}O_3$	$C_{21}H_{30}O_3$
Molecular Structure	328.5	316.4	330.5

Table 2. Chemical Features of The Pyrethrins

Characteristic	Pyrethrin II	Cinerin II	Jasmolin II
Chemical Name	[(1S)-2-methyl-4-oxo-3-[(2Z)-penta-2,4-dienyl]cyclopent-2-en-1-yl] 3-[(E)-3-methoxy-2-methyl-3-oxoprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate	[(1S)-3-[(Z)-but-2-enyl]-2-methyl-4-oxocyclopent-2-en-1-yl] (1R,3R)-3-[(E)-3-methoxy-2-methyl-3-oxoprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate	[(1S)-2-methyl-4-oxo-3-[(Z)-pent-2-enyl]cyclopent-2-en-1-yl] (1R,3R)-3-[(E)-3-methoxy-2-methyl-3-oxoprop-1-enyl]-2,2-dimethylcyclopropane-1-carboxylate
Trade Name	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl	Alfadex, Evergreen, ExciteR, Milon, Pycon, Pyrocide, Pyronyl
Chemical Formula	$C_{22}H_{28}O_5$	$C_{21}H_{28}O_5$	$C_{22}H_{30}O_5$

ester group attached to C-1. The 1R isomers are significantly more poisonous than the 1S isomers around the cyclopropane ring. Both the '*cis* and *trans*' isomers have insecticidal activity, although the *cis*-isomers are more effective in mammalian toxicology (Huang et al., 2005). The toxicity of pyrethroids with a cyano substituent at the alcohol moiety is determined by the optical isomerism of the α-carbon (type II pyrethroids). The S conformation around the α-carbon has been demonstrated to be substantially more dangerous to insects than the R-conformation (Bradberry et al., 2005). The S-conformation of the 'type II' pyrethroid cyhalothrin around the alpha carbon is shown in Figures 8-9. Pyrethroids with three chiral centres, such as 'cyfluthrin', 'cypermethrin', and 'cyhalothrin', have eight potential isomers. One reason for the vast range of reported toxicity of pyrethroids is the production of these compounds with varied isomeric ratios. For example, cypermethrin is divided into 4 distinct insecticides depending on the ratio of various isomers (α-, β-, θ-, and ζ-cypermethrin), each with its own toxicological effects.

5. INGREDIENTS AND SYNERGISTS OF PYRETHROIDS

Pyrethroid that is chemically pure (technical grade) is frequently prepared (combined with carriers, solvents, and other ingredients) for commercial pest control. When determining the toxicity of a created product, the toxicity of these other constituents must be taken into account. Fenvalerate, for example, is far less hazardous to mice than the manufactured drug pyridine (Gosselin et al., 1984). In rare circumstances, it's possible that formulations containing the same active substance with various carriers. have a ten-fold difference in toxicity. Pyrethroid and pyrethrin are frequently combined with synergists like piperonyl butoxide (PBO) and n-octylbicycloheptane dicarboximide and packed with oil or petroleum distillates. Synergists are used to boost the pesticide's toxicity. Synergists are included in a variety of goods, including foggers, repellents, and garden sprays. Many formulations of permethrin, resmethrin, and sumithrin, such as Scourge and Anvil, are used to control and battle mosquitoes and contain the synergist PBO. PBO has been demonstrated to inhibit hepatic microsomal oxidase enzyme in laboratory rodents and interfere in humans, making it a crucial liver enzyme responsible for several poisons,

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Table 3. Chemical Features of Selected Pyrethrins

Characteristic	Allethrin	Bifenthrin	Bioresmethrin
Chemical Name	2-methyl-4-oxo-3-(2-propenyl)-2-cyclopenten 1-yl-2,2-dimethyl-3-(2-methyl-1-propenyl)cycloprane carboxylate	(2-methyl[1,1'-biphenyl]-3-yl)methyl-3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropane-carboxylate	(1R-*trans*)-[(5-phenylmethyl)-3-furanyl]mehtyl 2,2-dimethyl-3-(2-methyl-1-propenyl)cyclopropane-carboxylate
Trade Name	Pyresin, Pynamin Forte	Talstar	Exthrin
Chemical Formula	$C_{19}H_{26}O_3$	$C_{23}H_{22}ClF_3O_2$	$C_{22}H_{26}O_3$

Table 4. Chemical Features of Selected Pyrethrins

Characteristic	Cyfluthrin	Cyhalothrin	Cypermethrin
Chemical Name	Cyano(4-fluoro-3-phenoxyphenyl)methyl 3-(2,2-dichloroethenyl)-2,2-dimethylcyclopropanecarboxylate	[1α,3α(Z)]-(±)-Cyano-(3-phenoxyphenyl)methyl 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylate	Cyano(3-phenoxyphenyl)methyl-3-(2,2-dichloro ethenyl)-2,2-dimethylcyclopropanecarboxylate
Trade Name	Baythroid, Baygon aerosol, Solfac	Cyhalon, Grenade	Arrivo, Cymbush, Cymperator, Cynoff, Ripcord, Basathrin, Demar, Grand, Starcyp
Chemical Formula	$C_{22}H_{18}NO_3Cl_2F$	$C_{23}H_{19}ClF_3NO_3$	$C_{22}H_{19}Br_2NO_3$

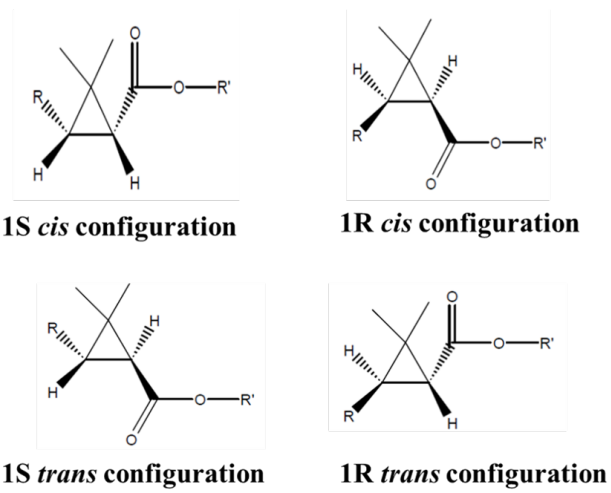

Figure 8. Diastereomers and their Non-Superimposable Mirror Images of Pyrethroid

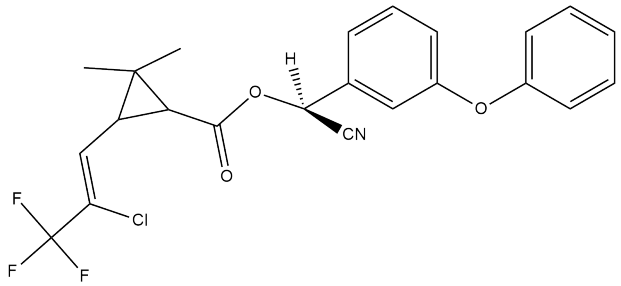

Figure 9. (S) Conformer at Alpha Carbon of Cyhalothrin Pyrethroid

including the active ingredients in pesticides. Because these enzymes are involved in the detoxification of many medications and chemicals, prolonged exposure to an insecticidal synergist may make a person sensitive to a variety of harmful insults that would otherwise be tolerated. Anorexia, vomiting, diarrhoea, intestinal inflammation, lung bleeding, and maybe mild central nervous system depression are all symptoms of PBO poisoning. Contact with the skin on a regular basis may produce minor irritation. Increased liver weight has been shown in chronic toxicity trials, even up to 30 mg/kg/day. Animal studies have showed hepatocellular carcinomas, even with dosing as low as 1.2 percent (Takahashi et al., 1994; FMC Agricultural Chemicals Group, 1989), despite the fact that it is not deemed a carcinogen by the EPA.

Inert (secret) components and pollutants can further alter the toxicity of pyrethroid formulations, especially because designed products frequently include more "inert" constituents than pyrethroid formulations used in America. Are compounds

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Table 5. Chemical Features of Selected Pyrethrins

Characteristic	Deltamethrin	Esfenvalerate	Fenpropathrin
Chemical Name	[1R-[1α(S),3α]-Cyano (3-phenoxyphenyl)methyl]3-(2,2-dibromo ethenyl)-2,2-dimethylcyclopropanecarboxylate	[S-R,R]-Cyano(3-phenoxyphenyl)methyl 4-chloro-2-(1-methylethyl)benzeneacetate, fenvalerate	Cyano(3-phenoxyphenyl)methyl 2,2,3,3-tetramethylcyclopropanecarbo-xylate(racemate) fenpropanate
Trade Name	Butox, Decis, K-Othrin, Kordon, Sadethrin	Sumi-alfa, Sumi-alpha, Asana Pydrin, Ectrin, Sumicidin Arfen, Dufen, Fenval (fenvalerate)	Danitol, Herald, Meothrin, Rody, Digital
Chemical Formula	$C_{22}H_{19}NO_3Br_2$	$C_{25}H_{22}NO_3Cl$	$C_{22}H_{23}NO_3$

Table 6. Chemical Features of Selected Pyrethrins

Characteristic	Flucythrinate	Flumethrin	Fluvalinate
Chemical Name	Cyano(3-phenoxyphenyl)methyl-4-(difluoromethoxy)(1-methylethyl)benzeneacetate	2-Cyano-4-fluoro-3phenoxybenzyl -3-(β,4-dichlorostyryl)-2,2-dimethylcyclopropanecarboxylate	Cyano(3-phenoxyphenyl)methyl N-N-[2-chloro-4-(trifluoromethyphenyl)-DL-valinate
Trade Name	Cybolt, Cythrin, Pay-off, Fluent	Bayticol, Bayvarol	Klartan, Mavrik
Chemical Formula	$C_{26}H_{23}NO_4F_2$	$C_{28}H_{22}NO_3Cl_2F$	$C_{26}H_{22}N_2O_3ClF_3$

that depress the central nervous system (CNS) such as benzene or are recognized or probable carcinogens (such as silica, trimethylbenzenes, and ethyl benzene) (such as xylenes). Toxic contaminants including ethylene oxide, benzene, and arsenic can be found in pyrethroid compositions (ICI Americas, 1989; FMC Corporation, 1989; FMC Corporation, 1988; Walters et al., 2009).

6. MAINLY USED PATTERNS OF PYRETHROID

There isn't a lot of information regarding how pyrethroids are used. According to data gathered from various sources. In non-agricultural contexts across the world, the amount of pyrethroids professionally administered was higher than in agricultural regions.

Pyrethroids are commonly used in houses to control cockroaches, wasps, ants, and spiders, as well as animal parasites such as fleas and ticks, and lice on humans (Figure 10). They are also used to control mosquitoes in areas where they may be carrying infectious diseases such as West Nile Virus. Pyrethroids can be delivered in many different forms: in powders, gels, traps, spray solutions, combustible spirals, and in aerosols delivered from spray can sand bombs (Thatheyus and Selvam, 2013a).

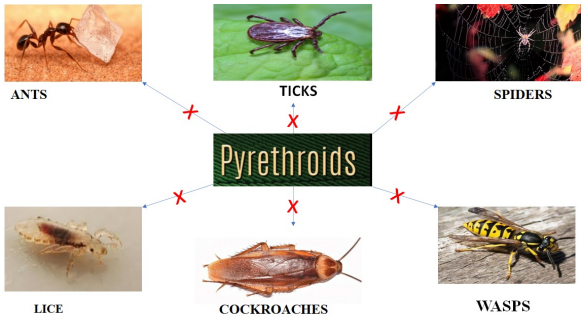

Figure 10. Common uses of Pyrethroids in Home to Kill Cockroaches, Wasps, Ants, and Spiders, as well as Animal Parasites like Fleas and Ticks, and Lice

7. PYRETHROID IN THE PRESENT ENVIRONMENT

Pyrethroid is not persistent, but omnipresent. Natural pyrethrins are rapidly degraded in the presence of humidity by sunlight or microorganisms (Berger-preieß et al., 1997). Synthetic pyrethroids, however, are more stable inside homes (Weston and Lydy, 2010). Protected from the elements, pyrethroids may be even more persistent. In domestic use, they may be disposed of through sewers and water treatment plants which are ineffective at removing the chemicals (Giroux and Fortin, 2010). In outdoor applications, pyrethroids can enter surface waters when washed off surfaces by rain (Oros and Werner,

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Table 7. Applications of Pyrethroids

Pyrethroid	Insects	Crops	Additional applications and regions
Allethrin	Flies, mosquitoes, ants	N/A	Public health places, residential place, animal houses, topi cal application in pet sprays and shampoos
Bifenthrin	Beetles, weevil, houseflies, mosquitoes, lice, bedbugs, aphids, moths, cockroaches, locust	Alfalfa hay, beans, cantaloupes, cereals, corn, cotton, field and grass seed, hops, melons, oilseed rape, potatoes, peas, raspberries, watermelons, squash	N/A
Bioresmethrin	Houseflies, mosquitoes, cockroaches	N/A	Household, public health, animal houses
Cyfluthrin	Aphids, cabbage stem flea beetle, cockroaches, house flies, mosquitoes, rape winter stem weevil	Alfalfa, cereals, cotton, citrus, deciduous fruit, ground nuts, maize, oilseed rape, pears, potatoes, rice, sugar beet, sugar cane, tobacco, vegetables	Green houses
Cyhalothrin	Bedbugs, beetles, house flies, ked, lice, mosquitoes, moths, weevils	N/A	Public health, animal houses, inert surfaces
Cypermethrin	Cockroaches, flies, moths	Cotton, lettuce, onions, pears, peaches, pecans, sugar beets	Residential and commercial buildings, animals houses
Deltamethrin	Aphids, beetles, bollworm, bud-worm, caterpillars, cicadas, coding moths, totrix moths, weevils, whitefly, winter moths	Alfalfa,beet,cereals, coffee, cotton, figs, fruits, hops, maize, oilseed rape, olives, oil palms, potatoes, rice, soybeans, sunflowers, tea, tobacco, vegetables.	Forests, households, animal houses, stored products
Esfenvalerate	Beetles, moths	Cabbage, corn, cotton, fruit trees, grains, groundnuts, maize, pecan, potatoes, sorghum, soybeans, sugar cane, sunflowers, sweet corn, tomatoes, vegetables, wheat	Ornamentals, non-crop land
Fenvalerate	Beetles, cockroaches, flies, locusts, mosquitoes, moths	Alfalfa hay, apples, beet, cere als, cottonorn, nuts, cucurbita, fruit, greenbeans, grounnuts, hops, maize, oilseed rape, olives, potatoes, sorghum, soybeans, squash, sugarcane, sunflower, vegetabes, vines, tobacco.	Ornamentals, forestry, non-crop land
Fluvalinate	Aphids, leafhoppers, moths, spider mites, thrips, white-flies	Apples, vegetables, vines, tobacco, cereals, peaches, cotton, pears	Outdoor and indoor ornamentals, turf
Permethrin	Ants, beetle, bollworm, bud-worm, fleas, flies, lice, moths, mosquitoes, termites, weevils	Alfalfa hay, corn, cotton, grains, lettuce, onion, peaches, potatoes, sweet corn, tomatoes, wheat.	Home gardens, green houses, pet sprays and shampoos

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2005; Kuivila et al., 2012a) particularly in urban areas where they are used near to, or on, impervious surfaces that facilitate runoff (Giroux, 2014).

Surface water of certain agricultural regions has detectable levels of pyrethroids (i.e., permethrin, cypermethrin, lambda-cyhalothrin) in concentrations which may surpass the criteria established to protect aquatic life (Kuivila et al., 2012b). According to an American study, urban surface waters may be even more contaminated by pyrethroids than agricultural waters (Larocque et al., 2015). Permethrin and piperonyl butoxide, common pyrethroids formulation ingredients, have also been found in Québec aquifers (Ray, 2003). Although 20% of Québec residents-scattered over 90% of the inhabited territory-drinking groundwater, our knowledge of pyrethroid concentrations in ground water remains fragmentary (Hodgson and Levi, 1999). Several Application of pyrethrin are shown in Table 7 (Berger-preieß et al., 1997; Weston and Lydy, 2010; Giroux and Fortin, 2010; Oros and Werner, 2005; Kuivila et al., 2012a; Giroux, 2014; Kuivila et al., 2012b; Larocque et al., 2015; Ray, 2003; Hodgson and Levi, 1999).

8. PYRETHROIDS MODE OF ACTION

Pyrethroids are nerve toxins, although their chemical path of action is unknown. Pyrethroids are neurotoxins, which interfere with the messages sent along nerves by maintaining sodium and chloride channels in an open position. It's unclear if symptoms in insects and other animals are caused by central nervous system impacts, peripheral nervous system effects, or both (Hutson, 1979). They allow repetitive nervous influx, or a depolarization, which leads to different symptoms such as tremors, involuntary movements and enhanced salivation in animals. As a consequence, pyrethroid poisoning mostly affects excitable cells (nerve and muscle), resulting in dysfunctional function rather than structural damage. In addition to their active ingredients, formulations sold on the market may also contain one of two common co-formulants that enhance the toxicity of pyrethroids (Abou-Donia, 1996). These synergists, piperonyl butoxide and MGK-264, inhibit enzymes that break down pyrethroids, making them last longer ; they are all toxic themselves (Abou-Donia, 1996). By blocking pyrethroid hepatic metabolism, piperonyl butoxide increases pyrethroid toxicity. These pesticides are degraded by the cytochrome P450 (CYP) monooxygenases using piperonyl butoxide as an alternate substrate. When CYP hydroxylates piperonylbutoxide, an intermediary (a carbene) creates a long-lasting molecule with the cytochrome's haem iron, effectively preventing CYP function in the future. Certain CYP isozymes are predicted to produce the inhibitory complex preferentially, although these have yet to be identified with certainty (He et al., 1990). As a result, using 'piperonyl butoxide' with most formulations will not only improve the 'knock down' effect on insects, but also increase poisonous effects in people. When a substantial amount of pyrethroid and piperonyl butoxide is consumed, huge amounts of circulating insecticide and piperonyl butoxide can be generated. The latter may then interfere with the metabolism of the pyrethroid, resulting in increased toxicity. Organophosphorus pesticides obstruct pyrethroid metabolism if a sufficient amount of the two insecticides is consumed, hence co-formulation might greatly enhance human toxicity of the two insecticides (Ray, 1991; Kaneko, 2010; Leahey, 1985).

9. METABOLISM OF PYRETHROID

Pyrethroids are metabolized in liver by oxidation of aromatic ring and methyl group as well as hydrolysis of ester linkage by conjugate reaction (Cárcamo et al., 2017; Kinsler et al., 1990). These processes produce a variety of metabolites, which are mostly eliminated in urine (Dalvi and Dalvi, 1991). *Trans*-isomers are hydrolyzed faster than *cis*-isomers, whose principal metabolic pathway is oxidation (Conney et al., 1972).

Piperonyl butoxide inhibits CYP mono-oxygenase enzymes by up to 50% within three hours of treatment (Conney et al., 1972; Zhang et al., 1991). The activity of CYP is then gradually boosted, but it takes another 36 hours for it to revert to normal. With typical use, inclusion of 'piperonyl butoxide' in commercial pyrethroid formulations appeared unlikely to be clinically relevant (Narahashi, 1989; Eells et al., 1992). In animals, organophosphorus insecticides have been reported to prevent pyrethroid hydrolysis (Ray, 1991; Kaneko, 2010; Leahey, 1985), and sprayers using a methamidophos/deltamethrin or methamidophos/fenvalerate mixture excreted more unmodified pyrethroid than sprayers using pyrethroid alone (Vijverberg and Bercken, 1982). Carboxyesterae responsible for pyrethroid hydrolysis is inhibited by organophosphorous insecticide (Soderlund and Casida, 1977).

10. NEURO-TOXIC IMPACTS OF PYRETHROIDS

10.1 Effects on Sodium (Na) Channels

Most excitable cells rely on sodium ion channels, which are voltage-gated channels with their opening controlled by voltage. They produce an action potential by generating an inward sodium current, which is closed at standard resting potentials. Depending on the species and the location of the anatomical structure, they come in a variety of isoforms. All of these are extremely ion selective, with sodium ions having a 30:1 ratio over potassium ions. Pyrethroids alter the gating properties of voltage-sensitive sodium channels in mammalian and invertebrate neural membranes, causing the channels to delay closing (Soderlund and Bloomquist, 1989; Miyamoto et al., 1995). This allows for a prolonged sodium inflow, often known as sodium 'tail current' (Clark and Brooks, 1989; Forshaw and Ray, 1990; Forshaw and Ray, 1993). The proportion of sodium channels that have been altered, which is determined by the pyrethroid concentration, dictates the amplitude of the tail current. The tail current's duration, on the other hand, is determined by the pyrethroid's structure, which is independent of its concentration. Permethrin and deltamethrin are type I pyrethroids that maintain the channel open for a shorter duration than type II pyrethroids. If a sodium tail current is sufficient to keep the cell membrane potential over thresh-

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old, a second action potential will occur extremely early, and a repeating strain of action potentials will be formed. This mechanism is hypothesised to be responsible for pyrethroid-induced paraesthesiae. Despite the existence of tail currents, cells may continue to function, although at a very high level of excitation. However, they may reach a point when they can no longer operate at this level, a circumstance known as "conduction block". Type II pyrethroids (when the sodium channel is maintained open for an excessive amount of time) Ray et al. (1997) or type I pyrethroids (when the sodium channel is kept open for an excessive amount of time) can induce conduction block (when a large amplitude tail current is produced).

10.2 Effects on Chloride Channels

Type II pyrethroids impact on voltage-dependent ion chloride channels inside the brain, neurons, muscles, and salivary glands (Forshaw et al., 2000). Their role is to regulate inversely proportional cell excitability, chloride conductance, and sodium conductance. Those vulnerable to pyrethroids had the most chloride channels (Hutson, 1979). They haven't been described at the molecular level, although depolarization activates them. They are calcium-independent and have a high conductivity. Protein kinase C phosphorylation renders them inactive (Bloomquist et al., 1986). In vitro Bradbury et al. (1983) and in vivo Forshaw et al. (2000), chloride channel currents are reduced by type II pyrethroids. Pyrethroid-induced salivation, choreoathetosis and tiresome firing in skeletal muscle are prevented by ivermectin and pentobarbital, which activate chloride ions channels Joy and Albertson (1991), the most important component in the symptoms of type II pyrethroid poisoning, such as salivation and myotonia, is probably chloride channel actions.

10.3 Effect on GABA Ionophrone Complex

Pyrethroids may also act on 'GABA'-gated chloride channels, which may explain why severe type II poisoning leads to seizures (Cremer et al., 1980). Some more studies have shown that the GABA receptor-ionophore complex is involved in type II pyrethroid toxicity components. In deltamethrin-poisoned rats, however, baclofen had no therapeutic impact (Hutson, 1979; Cutkomp et al., 1982). GABA antagonists had no effect on deltamethrin-induced hippocampal inhibition or deltamethrin choreoathetosis in rats (Rao et al., 1984; Clark and Matsumura, 1982). The apparent potential of type II pyrethroids to act on the GABA receptor appears to be of restricted clinical significance outside of acute poisoning.

10.4 Calcium Regulation and ATP-Hydrolyzing Enzymes

The ion pumps that maintain ionic gradients across cell and organelle membranes are powered by adenosine triphosphate (ATP), a fundamental component of cell energy metabolism. Pyrethroid neurotoxicity may be mediated by ATP-using enzymes and ion pumps, which are classified as ion dependent ATP hydrolyzing enzymes (ATPases) Clark and Matsumura (1987) type I and type II pyrethroids have been demonstrated to block oligomycin-sensitive Mg^{2+}-ATPases in recent investigations (Ray, 1982). In addition to the numerous Ca^{2+} ATPases involved in the homeostatic regulation of intracellular calcium levels, pyrethroids also act through a second type of ATPases. In squid and cockroach nerve preparations, pyrethroids decreased the activity of two Ca^{2+}ATPases: type I pyrethroids, such as allethrin, inhibited the Na^{+}+Ca^{2+} ATPases, which were assumed to represent an ATP-modulated sodium-calcium exchange transporter. Type II pyrethroids, such as cypermethrin, inhibited the Ca^{2+}+Mg^{2+} ATPases, an energy-dependent calcium extrusion mechanism (Brodie and Aldridge, 1982; Bradberry et al., 2005).

10.5 In Mammals

Pyrethroids are systemically toxic in mammals; cismethrin, a type I pyrethroid, causes the T syndrome (tremor) in rats. Additional symptoms include social arousal, continuous muscular tremor with poor coordination, heightened scary reaction, back muscle twitching, and respiratory failure (Müller-Mohnssen, 1999). The CS (choreoathetosis/psalivation) syndrome (also known as type II poisoning) causes significant chewing, noising, and overstated jaw opening in rats, as well as mucus secretion, coarse whole-body vibration, steadily increasing muscles tone in the hind limbs, choreiform body movement of the forelimbs and trunk, and hetotic spasms encompassing the limbs (Zhang et al., 2007; Todd et al., 2003b).

Many pyrethroids can irritate the skin and eyes, ranging from mild to severe. Some pyrethroids have been shown to cause reversible skin sensitivity on the face (Thatheyus and Selvam, 2013b). Some pyrethroid formulations have a higher skin toxicity than the technical grade.

10.6 Effects on Human

The major impact of pyrethroid on people in China was in the packaging of fenvalerate and deltamethrin. Burning sensations, numbness or stiffness in the mouth, runny noses, and cough or sneeze plague them. Abnormal face feelings, dizziness, weariness, and skin rashes were among the other complaints (Clark and Matsumura, 1982). The disorders include cerebro-organic disorders, sensomotor polyneuropathy of the lower limbs and mental illnesses such as paroxysmal tachycardia, heat sensitivity, and exercise intolerance all are the prolonged pyrethroid side effects (Van Engelsdorp et al., 2009).

In hamster and human cell lines, the pyrethroid permethrin has been found to cause mutations (Goulson et al., 2008). The US Agency for Toxic Substances and Disease Registry (ATSDR) has categorized the three pyrethroids, deltamethrin, fenvalerate and permethrin, as potential carcinogens for humans (Potts et al., 2010). Recently, the "International Agency for Research on Cancer" (IARC) considered an updated review of permethrin's carcinogenicity to be a high priority for the 2015-2019 periods.

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10.7 Effects on Non-Targeted Organisms

Certain beneficial insects such as bees can be killed or sublethally affected by pyrethroids (Stork and Eggleton, 1992; European Food Safety Authority, 2011) when exposed during the application process or when they visit treated plants (Smith and Stratton, 1986). Sublethal concentrations of insecticides, including pyrethroids are suspected of contributing to the worldwide decline of bee populations, in combination with other environmental factors (Kallaji, 1990; Moore and Waring, 2001). Other invertebrates, such as earthworms that play a crucial role in organic matter recycling can also die or suffer sublethal effects from long-term exposure to pyrethroids (EPA, 2009).

Pyrethroids are extremely harmful to the majority of fish. Deltamethrin is the most harmful, allethrin is the tiniest hazardous, and 'cypermethrin', 'permethrin', and 'fenvalerate' are in the middle. As a result of synergistic interactions, concentrated pyrethroid emulsions are up to nine times more toxic than technical grade pyrethroids (EPA, 2006). White sucker fish is substantially more poisonous to resmethrin combined with piperonyl butoxide than the technical grade product (Mddelcc, 2015; Shu, 2016).

Pyrethroids have sublethal effects on fish, such as gill damage and behavioural abnormalities. Because pyrethroids are strongly lipophilic, they are absorbed by the gills even from water having modest amounts of them. They are more risky for fish, frogs, and reptiles at lower temperatures. Toxicity assessments for estuarine fish, marine, crustaceans, mollusks and benthic species are, however, severely limited (Shu, 2016; Santé Canada, 2010).

11. ALTERNATIVES TO PYRETHROIDS

Several alternatives of pyrethroids exist. They include physical, biological or less toxic chemical treatments. For example heat can kill bed bugs and head lice; and cold can kill bed bugs, head lice and cockroaches (Olson et al., 2013; Choi et al., 2016; Buhagiar et al., 2017). Regular monitoring, early intervention, sometimes with the assistance of a professional exterminator or health practitioner, can increase the effectiveness of non-chemical alternatives to pyrethroids. Biological insects and biopesticide can be used for controlling the insect in agriculture. This involves using a pest insect predator or parasite to control pest populations (Buhagiar et al., 2017; Zhou et al., 2019; Zhu et al., 2020).

12. CONCLUSIONS

The focus of the review paper is on the insecticides known as "pyrethroids", because of their excellent efficacy and in comparison to other insecticides, it is low in toxicity (e.g. organophosphorus and carbamic ester compounds), they have been in use since the 1980s. They are synthetic or man-made versions of natural pyrethrins discovered in the flowers of a plant species of the Compositae family called "*Chrysanthemum cinerariaefolium*" Compositae family of plants. Commercial insecticides such as pyrethrin are often used to manage both agricultural and non-agricultural pests. To boost efficacy and persistence in the environment, these insecticides are frequently combined with additional chemicals in diverse formulations, known as synergists e.g n-octylbicycloheptane dicarboximide and piperonyl butoxide. Synergists remain used to boost the pesticide's toxicity. Synthetic pyrethroid are most stable inside homes as natural pyrethrins are not persistent and are rapidly degraded in the presence of humidity by sunlight or microorganisms. The development of pyrethroids and their classification as 'type I' and 'type II' without –CN group, molecular chemistry and its chemical structure is well discussed in the article. Pyrethroids mode of action as neurotoxins, which interfere with the messages sent along nerves by maintaining sodium, chloride channels, GABA ionophrone complex, ATP-Hydrolyzing Enzymes and Calcium Regulation as well in Mammal and their potential effects on Human body and some non-targeted organisms is presented.

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