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Biogenesis of pyrethrum: A review

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Abstract
Pyrethrum is the generic name given to a plant-based insecticide derived from the powdered, dried flower heads of the pyrethrum daisy, chiefly *Chrysanthemum cinerariae folium.* This paper discussed briefly Pyrethrins which are the six insecticidal active compounds in pyrethrum that occur in Chrysanthemum species. These pyrethrins are esters formed by a combination of two acids and three alcohols. The two acids are chrysanthemic acid and pyrethric acid. The three alcohols are pyrethrolone, cineralone and jasmololone. The paper also looked at Pyrethrins, the most economically important natural insecticides that have been used for about 150 years and have survived frequent challenges to their economic relevance. Extraction and Analytical procedures such as bioconversion as well as the progress achieved in methods for the identification and quantification of insecticidal compounds were briefly reviewed. The reviewed indicated that an industrial production of pyrethrins based on bioconversion of readily available precursors may be much more attractive for industrial development than the process based on plant cell/tissue cultures. The paper established that Pyrethrum has a very good toxicity profile and that some symptoms of pyrethrum poisoning in people include headaches and dizziness, these are related to disruptions of the nervous system. The paper concludes by reviewing some toxicology properties of Pyrethrins, it uses and its effect on the environment and animals.

Keywords: biogenesis, environment, pyrethrins, pyrethrum, *Chrysanthemum cinerariae folium*

Introduction

Biogenesis is the development of living things with particularly reference to plants and its occurrences. Pyretthrum originated in the Transcaucasus province of Asia at about 1800. It was introduced to Asia in an unidentified date and its manufacture began at about 1828 (Robbert L. M.2019). Pyrethrum is the generic name given to a plant based insecticide derived from the powdered, dried flower heads of the pyrethrum daisy, chiefly *Chrysanthemum cinerariae folium* this species is the emphasis for this study. Other plant based insecticidal species include *Chrysanthemum coccineum* and *Chrysanthemum marshalli*. Pyrethrins are the six constituent compounds with insecticidal properties that occur in these Chrysanthemum species. We should note not to confuse pyrethrum with pyrethrin. Pyrethrin refers to a more refined extract of pyrethrum (Antip and Zumyil 2022) [4]. According to Mccord *et al* (1921), Pyrethrins are the six insecticidal active compounds in pyrethrum. Pyrethrins are distributed in the different parts of the Pyrethrum plant. The ovaries of the disc and ray florets of the capitulum, however, contain by far the highest and largest while petals have the lowest amount. You will often find pyrethrum mixed with a synergist such as piperonyl butoxide (PBO). PBO gives pyrethrum an added "kick" that makes it more effective against insects. Although the absolute percentage of these pyrethrins in extracts from diverse plants is uneven, the insecticidal composition of the commercial pyrethrum extracts is relatively stable. The pyrethrins are esters formed by a combination of two acids and three alcohols. The two acids are chrysanthemic acid and pyrethric acid. The three alcohols are pyrethrolone, cineralone and jasmololone. These are shown in figure 1 below:

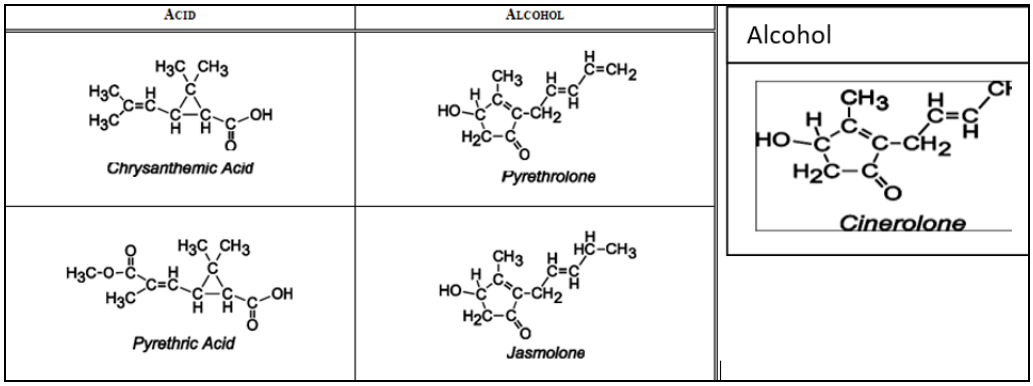

Fig 1

The esters of chrysanthemic acid are pyrethrin 1, cinerin 1 and jasmolin 1, respectively, and are jointly recognized as the pyrethrins 1 fraction (fig. 2-4). The esters of pyrethric acid, on the other hand, are pyrethrin II, cinerin II and jasmolin II, which signify the pyrethrin II fraction (fig. 5-7) (Rose, W. and Haller, H. (1937) [47] and Barton, D and de Mayo, P. (1957).
These workings are shown below:

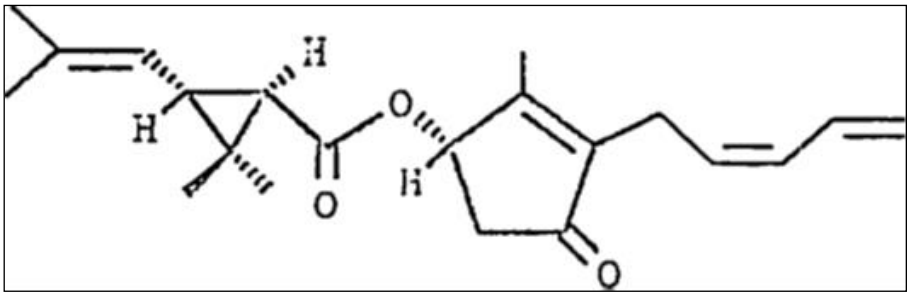

Fig 2: Pyrethrin I

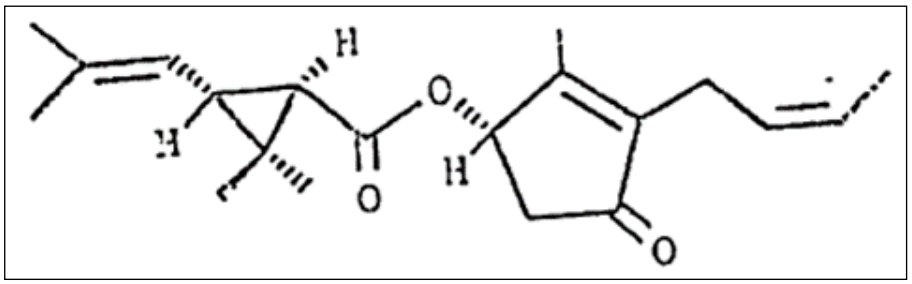

Fig 3: Cinerin I

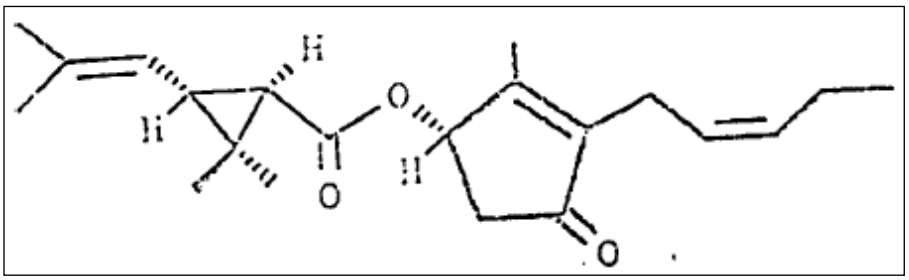

Fig 4: Jasmolin I

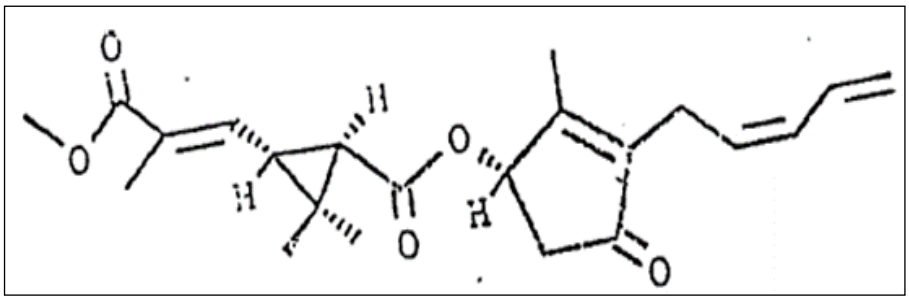

Fig 5: Pyrethrin II

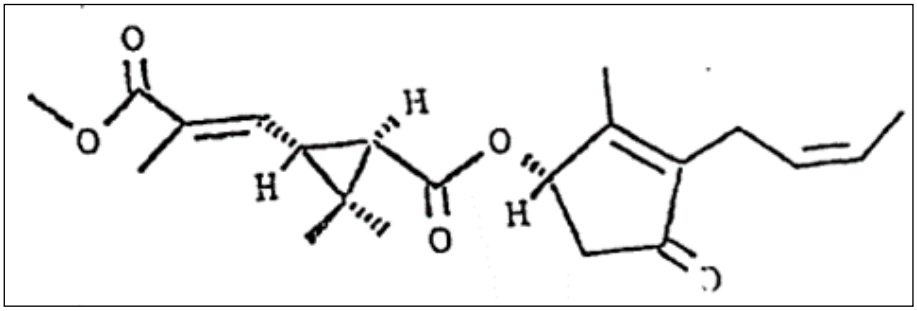

Fig 6: Cinerin II

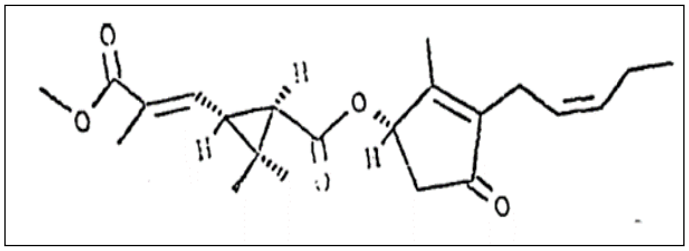

Fig 7: Jasmolin II

From toxicity data currently available, there is no proof that pyrethrins are carcinogenic, teratogenic or mutagenic in test animals and by extrapolation, to man (Barton, D. *et al*. I960). The alleged allergenic properties of pyrethrins and other pyrethrum extracts have been tentatively shown to be caused by impurities in the pyrethrum flower extracts. The main allergy causing agent has now been shown to be pyrethrosin (Tamura, T. and Matsubara, H. 1955).

Furthermore, Pyrethrins are located in all the over ground plant parts, but the achenes of the flower heads have approximately 94% of the total pyrethrins (Brewer, 1973) [14] in the inner secretory ducts (Head, 1973). The flower head accrues pyrethrins to the extent of 0.8 to 2% of the flower dry weight (Davies, 1985) [26]. Clones able to synthesize more than 3% pyrethrins are now used by companies such as SANOFI Chimie (France). The content in pyrethrins depends on genotype, picking interval, flower maturity, climate, and drying methods. In parallel,the yield of fresh flower is determined by the genotype of the selected clone, soil, climate, plant diseases, and pests (Jovetic and De Gooijer, 1995). Pyrethrin yields and quality of plants extracts are determined by pyrethrin content, flower yield, and the pyrethrins I/pyrethrins II ratio. Pyrethrins I are known to have a good knock-down action, while pyrethrins II have a better kill effect (Elliott, 1995). Pyrethrin I and II are highly insecticidal, and cinerin I, II and jasmolin I, II, are much less bioactive (Zong-Mao and Yun-Hao, 1996). Usually, a typical commercial extract can have equal amounts of pyrethrins I and II (Crombie, 1995) [24], but ratios ranging from 0.47 to 3.5 have been observed in different breeding lines (Head, 1973; Bhat, 1995) [11].

Mode of action

The natural pyrethrins have all the character of an ideal pest control agent. They are efficient against a broad range of insects with little development of resistant strains (Ley *et al* 1993) [43]. *Chrysanthemum cinerariaefolium* extracts have been demonstrated to be effective on *Lygus* spp., *Leptinotarsa decemnileata*, *Pieris rapae*, *Aspodydia* spp., *Empoasca devastans*, *Leucinodes orbonalis*, *Ophiomyia reticulata*, *anthonomous rubi*, *Earias fabia*, aphids, flies, beetles, cockroaches, ants, mosquitoes, grasshoppers, and numerous caterpillars, mites, thrips, and moths (Van Latum and Gerrits, 1991). They act rapidly in two ways, knock-down and kill. 'Knock-down' occurs within a few minutes affording early paralysis of insects, whereas 'kill' occurs several hours after the treatment. The action spot of pyrethrins has been found at the neuronal voltage-sensitive sodium channel (Kueh *et al*., 1985) [42]. They pose little danger to humans and other mammals as determined by toxicological tests (Environmental Protection Agency, 1989; Shcoenig, 1995) [32], and their repellency may be more important than the killing effect when protecting food (Crombie, 1995). Pyrethrins, being unstable in air and light, rapidly lose their insecticide activity (Allan and Miller, 1990) [3]. Thus, the non-persistence of pyrethrins makes them widely acceptable as safe and environmentally risk-free alternatives to other "hard pesticides" (Otieno, 1983).

Extraction and Analytical Procedures

From 1800 to this present day (21st century), Pyrethrum flowers are harvested and dried in the open air to avoid fermentation and pyrethrin losses. The dried flowers are ground and extracted with hexane or another suitable solvent (e.g., petroleum ether). More recently (21st century), supercritical CO2 has also been tested for the extraction of pyrethrins for pharmaceutical purposes. Undissolved plant matter is filtered out and the solvent is flashed off to leave a crude oleoresin that typically have about 30% pyrethrins. Several analytical methods have been used to identify and estimate the content in pyrethrins. The present reference quantification method is the AOAC/titrimetric procedure. This quantifies pyrethrins I and pyrethrins II groups after saponification and quantitation of chrysanthemic and pyrethric acid with the mercury-reduction procedure. This method has numerous drawbacks. It requires long saponification steps, it is unsuitable for the analysis of residues, and it does not quantify the six pyrethrins independently (Carlson, 1995). However, it is the reference method used to quantify commercial products and serve as a standard for other analytical methods. Gas liquid chromatography (GLC) of the 21st century offers the advantages of speed and reduced handling, but suffers from the drawback of pyrethrins II degradation by the high temperature. Usually, quantification by GLC is based only on pyrethrins I (Carlson, 1995).

Numerous methods for quantification of pyrethrins by GLC in various samples were developed (Nakamura *et al*., 1994; Nguyen *et al*., 1998). At present, the breeding programs of *Chrysanthemum cinerariaefolium* include the multiplication of high-productive cell lines selected on the basis of both chemical and agricultural characteristics. Valuable chemical characteristics included the yield in pyrethrins and the insecticide activity of the selected clones. This last parameter is related not only to the pyrethrins I/pyrethrins II ratio (as

conventionally estimated) but also to the relative proportions of the different esters inside the same group. Thus, it is important to have an analytical method that will assay each pyrethrin independently. According to McEldowney and Menary, (1988); Bushway, (1985) [16] and reversed Kamau, (1990); Wang *et al*., (1997 to 1999) at normal phase HPLC has proved a valuable method for pyrethrins analyses. The technique offers the advantages of high resolution and reduced handling without risk of pyrethrin degradation. UV is the most often used detector, although refractive index and fluorescence have also been employed. A recent technique is an adaptation of chromatography using supercritical fluids (SCF) as the carrier phase (Wieboldt *et al*., 1989; Lubke, 1991).

For the qualitative determination of pyrethrins, the coupling of chromatography procedures (GLC or HPLC) with mass spectrometric detection has now been used (Nikiforov and Kohlmann, 1983; Rajasekaran *et al*., 1993). With view to detection by GLC, electron-capture detection is most frequently selected in the pyrethrin analysis. With this detection method the detection boundary is ranged in nanogram-to-picogram level (Zao-Mao and Yun-Hao, 1996; Berger-Preib *et al*.,1997) [10]. A new identification and quantitation method has been developed recently by us using direct infusion of extract in the mass spectrometer, a tandem mass spectrometry method (MS/MS) was used to determine and to quantify the individual components of pyrethrins in the plant extracts **(**Barthomeuf *et al*., 2019) [9]. The method has the advantage to being simple and accurate and not requiring extensive clean up procedures. The detection is highly specific, and the six pyrethrins are assayed without prior separation. The limit of detection is 0.3 ppb (instead of 0.3 ppm with classic HPLC methods). The proposed procedure is a valuable tool for routine analyses of residues and rapid monitoring of each pyrethrin content during selection of high-productive clones or cell lines and could replace the AOAC method for quantitation of standards used for routine analyses of flower extracts by HPLC.

In 1976, a Japanese patent described the detection by gas chromatography and mosquito larva bioassay of pyrethrins in extracts of callus and redifferentiated plants (Aoki *et al*., 1976, 1978) [5,6]. The relationship between production rate of pyrethrins in parental clone, explant, and in cell cultures was analyzed (Zito *et al*., 1991; Barthomeuf *et al*., 1996) [9]. Most of the initiated calli were able to synthesize and accumulate low pyrethrin content regardless of the explant source. The authors concluded that there was a close correlation between pyrethrins content in *Chrysanthemum* callus cultures and that in original plants. The plant part used to initiate the cultures has little influence on pyrethrin production. Ravishankar *et al*. (1989) reported that maximal yield was reached at the end of the lag phase; however, in agreement with the results of Dhar and Pal (1993) [30], we obtained a higher accumulation at the beginning of the stationary phase. These results suggest that the production of pyrethrins is associated with a period of slow growth. Rajasekaran *et al*. (1991) compared the bioefficiency of the pyrethrins from the two sources; pyrethrins extracted from 45-day old callus tissue and standard extract from the Pyrethrum Board of Kenya. The comparative value of LC50 indicated that the toxicity to *Drosophila melanogaster* of the callus extract was almost 80% of that of standard pyrethrins. These authors suggested that further enhancement of the bioefficacy might be possible by the selection of cell lines that show higher levels of pyrethrins in cell cultures. The repellency and knockdown properties of pyrethrins obtained from callus of *Chrysanthemum cinerariaefolium* and naturally derived standard pyrethrins were compared by Rajasekaran *et al*. (1996). With *Culex quinquefasciatus* (mosquito), the knockdown insects did not recover within the 24-h post-exposure period, and standard extract was slightly superior in achieving 95% repellency. With *Tribolium castaneum* (beetle), there was no significant difference exerted by the extracts.

Bioconversion

The utilization of plant enzymes or genetically engineered microorganisms for bioconversion of pyrethrin precursors might afford an alternative to conventional pyrethrin production. McLaughlin Gromley Company (Minnesota) patented an enzymatic synthesis of pyrethrins in 1984. The production process comprised a preparation of cell-free homogenate containing enzymes and cofactors necessary for the pyrethrin synthesis pathway of *Chrysanthemum cinerariaefolium* and *Tagetes* spp., and an incubation of the homogenate with radio labeled mevalonic acid or isopentenyl pyrophosphate. In addition to pyrethrin production, this procedure can be used to produce chrysanthemyl alcohol by hydrolyzing chrysanthemyl alcohol phosphate.

For genetic engineering, it is essential to recognize and characterize the enzyme(s) catalyzing the pyrethrin synthesis and the gene(s) responsible for the synthesis of these enzyme(s). It is interesting to note that different stages of the pyrethrin biosynthesis pathway have been observed in the biochemical machinery of other plants and microorganisms. Chrysanthemyl alcohol can be oxidized by *Aspergillus ochraceus* into chrysanthemic acid (Rajasekaran *et al*., 1991; Nimala *et al*., 1992), and cinerone is converted into cinerolone by *Aspergillus niger* (LeMathieu *et al*., 1968; Davis and Miski, 1988) [43, 28]. The fungus *Botryo diplodra* is able to produce pyrethrolone (Miersch *et al*., 1989). These findings interested the American company, AgriDyne Technologies Inc. (Utah), which decided to use genetic engineering to develop a precursor of pyrethrins (also important in the chemical production of synthetic pyrethroids (Shand, 1992). They isolated the gene coding for chrysanthemyl diphosphate synthase and are testing its activity and production levels in microorganisms (Jovetic and De Gooijer, 1995). In parallel, The Advanced Technology Program (ATP) of the National Institute of Standards and Technology (NIST) planned production of the pyrethrin precursors using recombinant yeasts (Perrier, 1997).

Chrysanthemyl diphosphate synthase, the only enzyme to be expressed in a microorganism, is just one of the enzymes acting in the biosynthesis of pyrethrins. Because pyrethrins are a mixture of six esters the number of genes involved in their biosynthesis is unknown, even though the mechanism involved is polygenic inheritance.

Another setback is related to insufficient knowledge of the metabolic step involved in the monoterpene ester biosynthesis (Bhat, 1995) [11]. An industrial production of pyrethrins based on bioconversion of readily available precursors may be much more attractive for industrial development than the process based on plant cell/tissue cultures. This is owing to uncertainty concerning the look of the enzymatic activity of cell-free homogenate and the enzymes in microorganisms. To our knowledge, no hemisynthetic mode of production has been published so far, possibly because:

1. This production method is economically nonviable
2. Research is still in the development stage

Use of Pyrethrum

Pyrethrum is used widely throughout the world to manage many human and household pests such as mosquitoes and houseflies. While it was used widely in agriculture before World War II, cheaper and more effective synthetic products have mostly replaced it for farm use (Casida and Quistad 1995) [24, 26]. More recently, new pyrethrum products, often solvent-based and including PBO, have appeared on the agriculture market. Other than home and garden uses, pyrethrins are used on a variety of agricultural crops and for structural and public health pest control. Worldwide, about 200,000 kilograms (440,000 pounds) of pyrethrins are used each year (Crosby G, 1995) [26].

Hazard of Inert Ingredients

1. Propane is used as an inert propellant in pyrethrin products. It can cause dizziness when inhaled. It is also "extremely flammable" and easily ignited by heat, sparks, or flame (Crosby G, 1995) [26].
2. Isobutene is also used as an inert propellant in pyrethrin products. It depresses the central nervous system and can cause dizziness when inhaled. Like propane, it is extremely flammable and easily ignited (Casida and Quistad 1995) [24, 26].
3. Hydro treated light petroleum distillates (hydro treated kerosene) are used as an inert solvent in pyrethrin products. The Chemical Abstract Services number for this solvent is 64742-47-8. This solvent has caused skin tumors when applied to the skin of laboratory mice (Calif S, 2000)
4. Hydro treated heavy naphtha (white spirits) is also used as an inert solvent in pyrethrin products. The Chemical Abstract Services number for this solvent is 64742-48-9. It is damaging to kidneys and the nervous system. In a recent laboratory study, the offspring of animals exposed to white spirits developed "long-lasting and possibly irreversible changes" in brain cells. This damage to the brain was caused by an inability to maintain normal calcium concentrations (Federal Insecticide Act, 2008). This result is however contrary to what Barton, D. *et al*. I960 obtained which thy alledge that pyrethrum has no significant effect/harm on animals. However, Tamura, T. and Matsubara, H. 1955 are of the view that pyrethrosin causes allergy to animals.

Toxicological Information according to Vishal S and Amruta A (20014)

Pyrethrum (as 100%)
Acute Oral Toxicity LD50 (rat) = 3500 mg/kg
Acute Skin Toxicity LD50 (rabbit) = >19000 mg/kg

Piperonyl Butoxide (as 100%)

Acute Oral Toxicity LD50 (rat) = 6150 mg/kg
Acute Skin Toxicity LD50 (rabbit) = 1880 mg/k

How safe is Pyrethrum?

Pyrethrum has been widely studied for its effects on people and the environment. Like all insecticides, pyrethrum is used to have a toxic effect on insects. Thus it is not correct to say that pyrethrum is "safe." At the same time, we are in no doubt that pyrethrum has a very good
toxicity profile (Ware G, 2000). For mammals, doses that elicit toxic reactions are extensively larger than the exposures people typically experience in using pyrethrum-based products.

Effect on the Environment

1. **Fate in water:** Pyrethrum compounds are broken down in water to nontoxic products (40 code of Federal Regulations 200).
2. **Soil persistence:** Soil application studies of pyrethrum showed a half-life of only 1-2 hours. When used indoors, pyrethrum can persist much longer; up to two months or more in carpet dust (Shafey O., *et al* 2000).
3. **Wild life:** Pyrethrum is extremely toxic to fish such as bluegill and lake trout, while it is slightly or moderately toxic to bird species, such as mallards and bobwhite quail. Natural pyrethrins are highly fat soluble, but are easily metabolized and thus do not accumulate in the body. Because pyrethrin-I and pyrethrin-II have multiple sites in their structures that can be readily attacked in biological systems, it is unlikely that they will concentrate in the food chain (Shafey O., *et al* 2000).

Effect on beneficial arthropods

Synthetic pyrethroids are broad spectrum insecticides and are notorious for killing and repelling beneficial arthropods. However, since pyrethrum residues on the plant break down quickly, the effect on natural enemies is reduced. Pyrethrum is highly toxic to bees. The average lethal dose (LD50) for honeybees was measured at. 022 micrograms per bee (Ware G, 2000). Direct hits on honeybees and beneficial wasps are likely to be lethal (Ramadan A., *et al* 1988).

Effect on Human Health

1. Acute Toxicity

On broken skin, pyrethrum produces irritation and sensitization, which is further aggravated by sun exposure (Kakko I., *et al*. 2000). Absorption of pyrethrum through the stomach and intestines and through the skin is slow (Prasda K, 1984). However; humans can absorb pyrethrum more quickly through the lungs during respiration. Response appears to depend on the pyrethrum compound used. Inhaling high levels of pyrethrum may bring about asthmatic breathing, sneezing, nasal stuffiness, headache, nausea, lack of coordination, tremors, convulsions, facial flushing and swelling, and burning and itching sensations (Shafey O., *et al* 2000). The lowest lethal oral dose of pyrethrum is 750 mg/kg for children and 1,000 mg/kg for adults. Oral LD50 values of pyrethrins in rats range from 200 mg/kg to greater than 2,600 mg/kg. Some of this variability is due to the diversity of constituents in the formulation. Pyrethrins are a regular cause of insecticide poisonings (Zucker A. 1965) [51]. Wieboldt *et al*., (1989) found that pyrethrins, with the synergist piperonyl butoxide, caused over 9,000 incidents. Only the organophosphate insecticides (fig.8) caused more insecticide poisoning incidents (Ramadan A., *et al* 1988). Some symptoms of pyrethrin poisoning in people, headaches and dizziness, are related to disruptions of the nervous system. Laboratory tests have demonstrated that pyrethrins cause several neurological disruptions in mammals (WHO, 1999). These may be the reason of the sodium channel disruption that results in their toxic effects in insects, or an additional effect. Researchers from the University of Alexandria (Egypt) showed that pyrethrins inhibited calcium uptake in rat brain cells. Calcium plays a "vital role" (Ramadan A., *et al* 1988). In the nervous system, promoting the normal release of transmitter chemicals from junctions between nerves and stabilizing the membrane surrounding nerve cells (Kakko I., 2000). Two groups of researchers, from the University of Mississippi Medical Center and the University of Tampere Medical School (Finland) showed that pyrethrins disrupt energy production in brain cells (Yamanao T., *et al* 1983 and Adams R., 1983). Pyrethrins also affect physiological processes that are not related to the nervous system. For example, researchers at the Osaka City Institute of Public Health and Environmental Sciences (Japan) showed that in rat livers pyrethrins inhibit mitochondria; the cellular bodies that convert food to usable energy (Wax P and Hoffman R 1994, Adama R 1983). Pyrethrins can trigger allergic responses (Ramadan A., *et al* 1988, Kakko I., 2000) that range from unpleasant to life-threatening. Skin rashes, asthma, and hives caused by contact to pyrethrins or pyrethrum have been reported in medical text since the 1920s and 1930s.

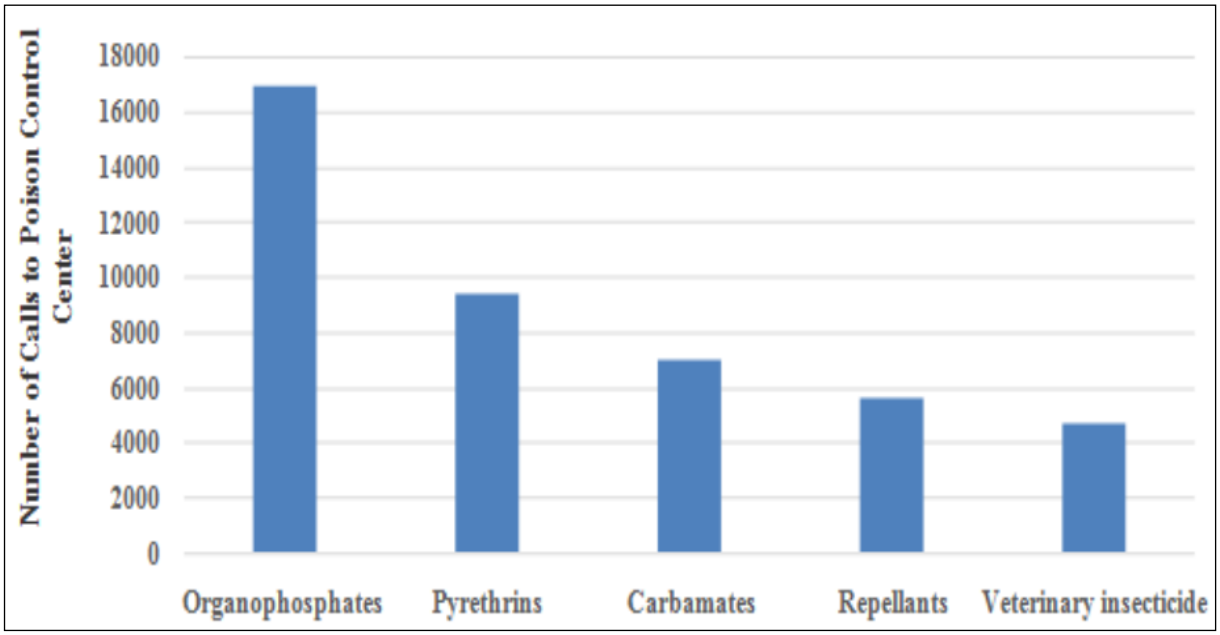

Fig 8: Frequency of Pyrethrins Poisoning

2. Organ Toxicity

In mammals, tissue accumulation has not been recorded. At high doses, pyrethrum can be damaging to the central nervous system and the immune system. Schoenig G. (1995) observed that when the immune system is attacked by pyrethrum, allergies can be worsened. Animals fed large doses of pyrethrins may experience liver

damage. Rats fed with pyrethrins at high levels for two years showed no major effect on survival, but slight, specific damage to the livers was observed (Saxena S. and Karel A 1974).

3. Fate in Humans and Animals

Pyrethrins and their metabolites are not known to be stored in the body nor excreted in the milk. The urine and feces of people given oral doses of pyrethrum contain chrysan the mumic acid and other metabolites. These metabolites are less toxic to mammals than are the parent compounds. Pyrethrins I and II are excreted unchanged in the feces. Other pyrethrum components undergo quick destruction and detoxification in the liver and gastrointestinal tract (Saxena S. and Karel A 1974).

Effects on the Circulatory System

Pyrethrins affect both sugar levels and oxygen-carrying ability of blood. Researchers from the University in Rajasthan (India) showed that an injection of pyrethrins caused gerbil blood sugar levels to rise between 30 and 70 percent (depending on dose). Blood sugar peaked an hour after treatment, but the increase persisted for several days (Prasda K, 1984). The same researchers (Saxena S.and Karel A 1974) showed that an injection of pyrethrins caused a decrease in the amount of hemoglobin (oxygen carrying molecules) in the blood according to WHO 2000 as well as a decrease in the number of red blood cells. Hemoglobin concentration remained low for 2–3 weeks (Saxena S. and Karel A 1974). Other types of exposures with a longer duration caused similar effects. A three-month feeding study with rats found pyrethrins caused a decrease in the amount of hemoglobin in females at doses at or above 170 milligrams of pyrethrins per kilogram of body weight (mg/kg) per day (the middle dose in this experiment). Similar effects were found in males at higher exposures. A three-month inhalation study found that pyrethrins caused anemia (fig.9) at doses at or above 0.07 milligrams per liter of air in males (all but the lowest dose in this experiment). They also caused anemia in females, although at higher exposures.

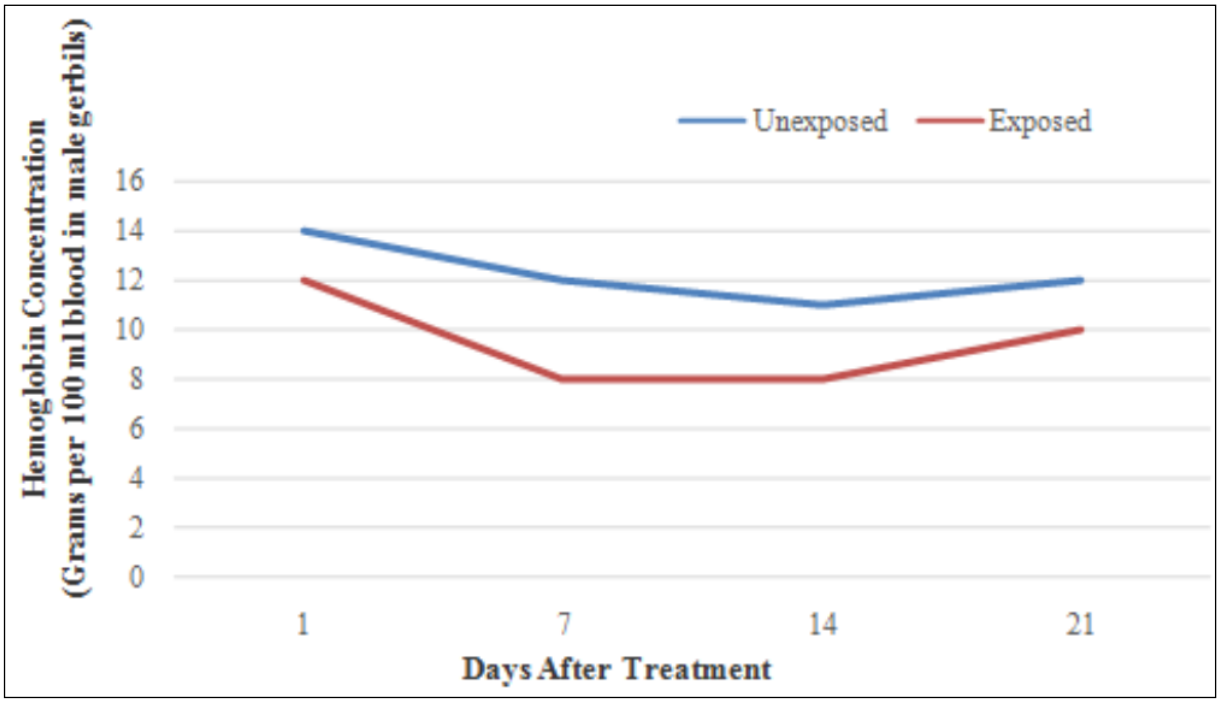

Fig 9: Exposure to Pyrethrin cause Anemia

Disruption of Hormone Systems

The impact that environmental pollutants can have on the normal function of human and animal hormone systems has been a significant concern in the last decade (Saxena S. and Karel A 1974). Hormones are biologically active molecules that control all responses and functions of frequency of several cancers in rats. The incidence of liver tumors was higher in exposed female rats than in unexposed ones (fig. 10). Also, in both sexes, the occurrence of thyroid tumors was greater in exposed rats than in unexposed ones (Prasda K, 1984). Other carcinogenicity studies showed that the occurrence of lung cancers in exposed male mice was greater than in unexposed ones according to Beasley V and Trammel H (1989) and that the occurrence of parathyroid tumors was greater in exposed rats than in unexposed ones (Hudson R. *et al* (1984).

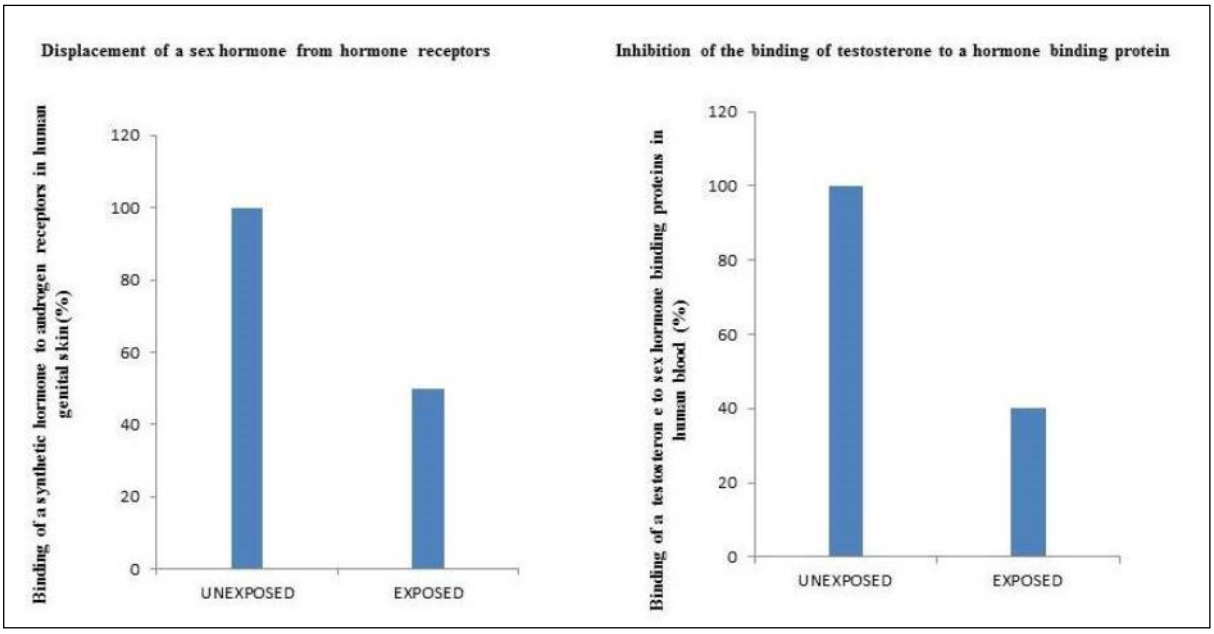

Fig 10: Exposure to Pyrethriins Disrupts Normal Hormone Function

Chronic Toxicity

Overall, pyrethrins have low chronic toxicity to humans and the most common problems in humans have resulted from the allergenic properties of pyrethrum. Patch tests for allergic reaction are a significant tool in determining an individual's sensitivity to compounds Hudson R. *et al* (1984) opined that Pyrethrum can produce skin irritation, itching, pricking sensations and local burning sensations. These symptoms may last for about two days according to Saxena P and Saxena S (1973) reported more serious chronic effects, including circulatory and hormonal effects.

Reproductive Effects

Rabbits that received pyrethrins orally at high doses during the sensitive period of pregnancy had normal litters. A group of rats fed very high levels of pyrethrins daily for three weeks before first mating had litters with weanling weights much lower than normal (Saxena P and Saxena S 1973., Ramadan A., *et al*). Overall pyrethrins appear to have low reproductive toxicity (Hurley *et al* 1998).

Carcinogenic Effects

Pyrethrins are associated with increased cancer risks among farmers and have also caused cancer in laboratory tests (Brown, L. *et al*. 1990) [15]. Researchers from the National Cancer Institute studying risk factors for leukemia found that farmers exposed to pyrethrins used for pest control on livestock had an increased risk of developing leukemia. According to WHO 200 and Eubank 1997, exposure to pyrethrins was associated with a 3.7-fold increase in risk. The agency concluded that pyrethrins should be classified as "likely to be a human carcinogen by the oral route." This evaluation was based on tests which demonstrated increases in the frequency of several cancers in rats. The occurrence of liver tumors was higher in exposed female rats than in unexposed ones. Also, in both sexes, the occurrence of thyroid tumors was greater in exposed rats than in unexposed ones (Campbell and Chapman 2000., Saxena S and Bakre 1978). Other carcinogenicity studies showed that the incidence of lung cancers in exposed male mice was greater than in unexposed ones and that the incidence of parathyroid tumors was greater in exposed rats than in unexposed ones (Brown L. *et al*. 1990) [15].

Effects on Soil Fertility

Insecticides are generally not expected to have impacts on plants. However, they can indirectly affect plant growth if they change the growth or abundance of soil microorganisms that are important in the maintenance of soil fertility (Brown, L. *et al*. 1990) [15]. Scientists at the University of Ibadan (Nigeria) showed that treatment of agricultural soils with pyrethrin caused an increase in the abundance of soil bacteria and a decrease in the abundance of soil fungi. In addition, the number of these species was less in treated soil than in untreated soil (Berger P. *et al* 2019) [10]. The end result was a reduction in the amount of the important soil nutrient nitrogen. Another study, from the Central Rice Institute (India), showed that pyrethrin treatment of rice fields reduced the nitrogen- fixing ability of the soils as much as 80 percent. Nitrogen fixation is the conversion (mostly by bacteria) of atmospheric nitrogen into a form that is usable by plants (Beasleh V and Trammel H 1989).

1. Persistence

Bakre, T. (1978) Opined that outdoors, pyrethrins persist only for a short time for example, after application of pyrethrins to bare soil, the half-life (the time required for half of the applied pyrethrin to break down or move

away from the application site) was two hours or less. Pyrethrins persist much longer indoors than they do outdoors. Studies conducted at the University of Ulm and the Fraunhofer Institute of Toxicology and Aerosol Research (Germany) found that pyrethrins persisted 60 hours after treatment on horizontal surfaces, two weeks after treatment on airborne particles, and over two months in carpet dust (fig 11).

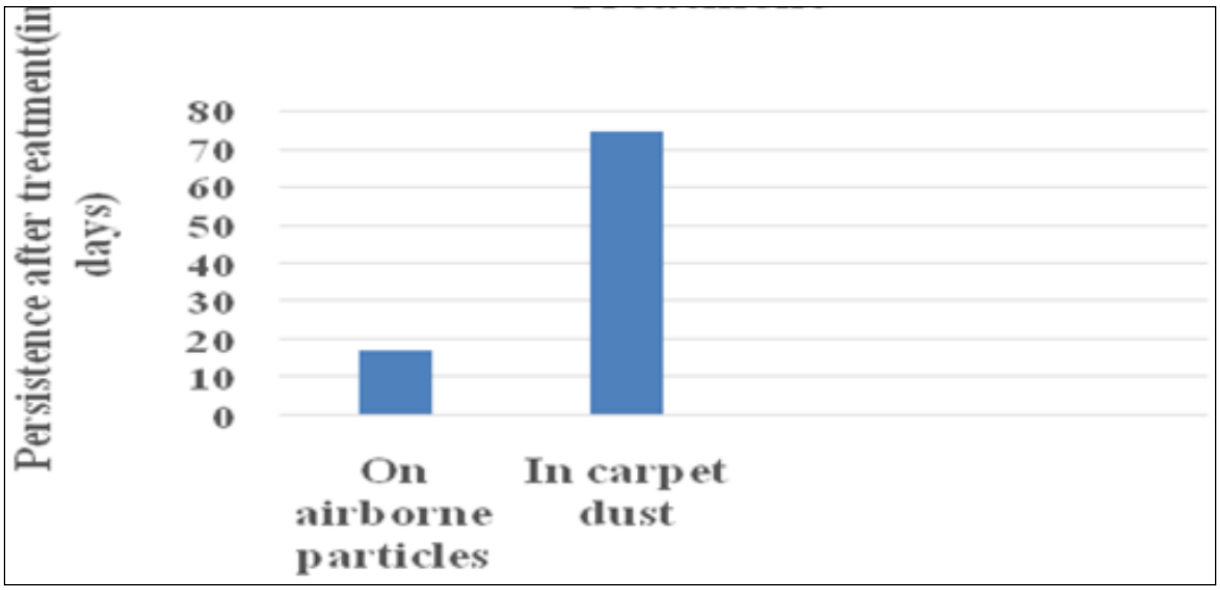

Fig 11: Persistence of Pyrethrins after Treatment

Conclusion

The present investigation revealed that Pyrethrum, the most economically important natural insecticides, have been used for about 150 years and have survived frequent challenges to their economic relevance to this present day. Accordingly, the development of efficient biotechnological processes able to improve the production of pyrethrins and their use as an alternative to the traditional extraction procedures is a current challenge. Effect of Pyrethrum on animals and the environment is ongoing and the identification of biochemical and/or genetic markers for secondary metabolites production is regarded as essential. The common view of authors is that the identification of the specific key enzymes in the biosynthetic pathway of pyrethrins is obviously a prerequisite for any bioconversion or genetic engineering programs.

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