Available online on www.ijtpr.com
International Journal of Toxicological and Pharmacological Research 2017; 9(4); 194-203

ISSN: 0975-5160

Review Article

Hepatotoxicity Under Stress of Type II Pyrethroids in Mammals: A Mechanistic Approach

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Available Online:25th September, 2017

ABSTRACT

Hazards and environmental contamination through abuse of vide variety of pesticides has been a matter of great attention worldwide. There has been a broad concern throughout the globe regarding the non target toxicity of pesticides and its assessment. Pyrethorids are greatly in use these days among commercially available pesticides therefore carry more chances of contaminating various ecosystems. Pyrethroids are considered a genuine substitute to organochlorine and organophosphate pesticides, by virtue of their high effectiveness, comparatively low non-target toxicity and easy biodegrability. Although, synthetic pyrethroids are considered comparatively safe synthetic pesticides, but their widespread use, non-selective potency and considerable stability in the environment, makes them potentially harmful at very many levels. They represent a considerable threat to various metabolic pathways going inside the cells belonging to various systems with in body of organisms surviving on this planet. A brief account of toxicological manifestations under stress of type II pyrethroid pesticides have been discussed *vide infra*.

Keywords: Pyrethroids, toxicity, liver, environment, contamination.

INTRODUCTION

Pyrethroids comprise a group of globally recognised multipurpose pesticides, used against broad categories of insect pests such as beetles, lice, cockroach, mosquitoes etc. Pyrethroids are named so, as chemically are synthetic analogues of pyrethrins contained in flowers of genus *Chrysanthemums.* Pyrethroids differ from basic pyrethrin as former are the commercial formulations of later, chemically boosted up with enhanced potency and photostability by modifying the basic pyrethrin structures. Key features behind great market success and promising effect of pyrethroids includes comparatively low photostability, non-target toxicity and high LD_{50} than other counterparts available (Morisseau *et al.*, 1999; Sakr and Azab, 2001; Assayed *et al.*, 2010; Bhushan *et al*., 2010; Bhushan *et al.*, 2013; Moustafa and Mohamed, 2016).

Pyrethroids, no doubt are in use for yonks, but their recent non-target toxicity evaluations have revealed heart-wrenching stories, as of causing byzantine effects to society which are yucky in the form of health related complications to various non-target organisms including humans. Such atrocious conditions mainly are a consequence of excessive and indiscriminate use of these chemicals by unskilled and unaware users, comparatively more in developing and underdeveloped nations because of mainstay role of agriculture in general economy maintenance. Uneven hygienic conditions, resistance development in insect pest species and favourable climatic conditions for growth, also in addition, add up for increase in pest populations and thus concomitant excessive use of these pesticides by same users. This great field application of these chemicals initially can disturb the soil ecosystems with possible repercussions in vegetation growing on such soil and mammalian consumers there in, and simultaneously can enter other ecosystems related, through various possible routes. Depending upon symptoms following acute intoxication and absence and presence of α-cyano group in their chemical structures, pyrethroids have been broadly divided into type-I and II respectively. Some of the type-II pyrethroids are fenvalerate, deltamethrin, cypermethrin, beta-cyfluthrin *etc.* (Yavasoglu *et al.*, 2006; Al-Sahhaf, 2007; Bhushan *et al*., 2013; Pande *et al*., 2014; Rajawat *et al*., 2015; Aouey *et al*., 2017).

Whenever, these chemicals enter inside the body of a living organism, they can undergo variety of consequences, potentially harmful to the organism. Within the body of mammals, liver is very susceptible towards pesticide induced damage as plays a central role in xenobiotic metabolism, detoxification and bioactivation due to presence of xenobiotic metabolizing enzymes. Hepatocytes are the main metabolic engines of the liver and pesticidal hepatotoxicity can result in disruption of normal hepatocellular structure as well as function (Sakr *et al*., 2002; Bhushan *et al*., 2010; Grewal *et al*., 2010; Gomaa *et al*., 2011; Waheed and Mohammed, 2012; Bhushan *et al*., 2013).

An effort has been made herein to record some work on pyrethroid induced hepatotoxicity and related mechanisms, focusing on respective changes in basic

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hepato-biochemistry, histochemistry of certain important macromolecules and histo-architecture.

A close review of LD_{50} of four type II pyrethroids namely, Fenvalerate, Deltamethrin, Cypermethrin and Beta-cyfluthrin has been considered which following 96 hours intoxication came out to be 1949, 622, 416.98 and 354.8 mg/kg b.wt. respectively, selecting these chemicals as per their great use and they are derived on a common pattern. Characteristic symptoms following intoxication of all these pyrethroids includes tremors, shivering, abnormal gait and salivation. Mortality has been found to follow a dose dependent pattern (Verma, 1996; Singh, 1998; Saxena and Tomar, 2003; Sharma, 2006; Singh *et al*., 2009; Bhushan *et al*., 2010; Bhushan *et al.,* 2013; Pande *et al*., 2014; Rajawat *et al*., 2015). A difference in the LD_{50} values calculated by various workers has been found, however, due to difference in various deciding factors such as environment, the strain of animal used, sex of animal, type of administration etc. But instead, among these four pyrethoids selected, the numeric values corresponding to LD_{50} can be different in various studies but the trend in ascending order generally remains the same as is written over. The difference in LD_{50} among the four selected pyrethroids may be due to structural differences (Saxena and Yadav, 2011; Bhushan *et al.,* 2013; Yadav *et al*., 2014).

Liver plays a central role in the detoxification of pyrethroids. Hence, there is a tendency for accumulation and subsequent toxicity of pyrethroids to the liver, disrupting the normal hepatic function. However, initial signs of pyrethroid induced hepatotoxicity have manifested itself in the form of alterations in the liver weight of treated animals in different studies. Liver weight has reached to a significant level following pyrethroid. Rapid cell proliferation as well as lipid accumulation under the stress of alpha-cyano derivatives seems to be the main responsible factors for such increase (Singh *et al*., 2005; Bhushan *et al*., 2010; Bhushan *et al*., 2013).

Evaluation of hepato-biochemical changes

ALP (Alkaline phosphatase) is an important hepatocellular enzyme principally situated in canalicular and sinusoidal membranes. This enzyme plays determinant role in vital cellular functions such as maintenance of cellular energetics, growth, transport, protein synthesis etc. by virtue of catalytic role in splitting of phosphoryl esters. ALP estimation is an important indicator of hepatocellular membrane damage as well as necrosis if any, under stress of a xenobiotic or disease (Bhushan *et al.,* 2013).

Pyrethroids, in general, have been found to cause reduction in the biochemical level of this enzyme within the liver, whereas increase in the levels of this enzyme within the serum of intoxicated rats.

The decline in activity of hepatic ALP in albino rats following intoxication of pyrthroids, initially may be due to interference of pyrethroids as well as their toxic intermediates with the hepatocellular membrane resulting in its damage and altered permeability, and further, the cyano derivative present in these type-II pyrethrois, do bring structural damage in the enzyme ALP. These two factors seems to be main responsible factors for leakage of the hepatic ALP from hepatocytes into the blood stream (Singh and Saxena, 2001; Singh and Saxena, 2002; Singh *et al.,* 2005; Prakash *et al.,* 2009; Rifat *et al.,* 2012; Bhushan *et al.,* 2013; Bhushan *et al.,* 2013; Ghassemi et al., 2015; Rajawat *et al.,* 2015).

Aminotransferases (ALT and AST) are also an important indicator of hepatocellular damage as are the enzymes that catalyze the transfer of amino acid and keto group into alpha-amino acid and alpha-keto acids of immense importance as precursors of energy yielding metabolic pathways. ALT (Alanine aminotransferase) is a cytosolic enzyme, whereas AST (Asparatate aminotransferase) a mitochondrial, and their estimation therefore is of immense importance to have an insight of generalized as well as metabolic alterations to the hepatocytes under pyrethroid stress (Bhushan, 2011)

Activity of the enzymes (vide supra) has been found to increase within the rat liver as well as in serum following pyrethroid intoxication. The probability of oxidative stress induced by cyano derivatives cannot be denied. The so induced oxidative stress induces alterations in the hepatocytic amino acids and interfere with hepatocellular functions besides altering metabolic pathways such as Kreb's cycle within the mitochondria of hepatocytes. The increase in activity of AST and ALT under pyrethroid stress can thus be attributed to tissue damage (Singh and Saxena, 2001; Arora et al., 2012; Raghuvanshi *et al*., 2012; Bhushan *et al.,* 2013: Bhushan *et al.,* 2013).

LDH (Lactate dehydrogenase), is an important catabolic oxidative enzyme, principally concerned with carbohydrate metabolism in mammalian liver. LDH catalyzes the irreversible interconversion of pyruvate to lactate in the process of glycolysis. An increase in hepatic LDH is an indication of altered carbohydrate metabolism in the liver of experimental animals under pyrethroid induced stress.

Hepatocytes under normal conditions are provided with adequate oxygen supply in order to undergo aerobic respiration, necessary for retrieving maximum energy from glucose molecule and to produce pyruvate which can participate in Kreb's cycle (Nelson and Cox, 2000; Hinton and Grasso, 2000).

Elevation in hepatic LDH leads to hypoxic condition in liver lobules under the stress of pyrethroids. Though, these compounds are capable enough to cause hypoxia, they also possesses strong mutagenic potential (Singh and Saxena, 2002; Bhushan *et al.,* 2009).

The increased hypoxic condition along with nuclear damages seen in the liver architecture following pyrethroids intoxication probably due to over expression of these enzymes at gene level.

Liver is a hub for protein synthesis and a wide variety of hepatic proteins are synthesized within the hepatocytes of mammals (Tortora and Grabowiski, 2003). Proteins are the working molecules of a cell and carry out the programme of activities encoded by genes. Proteins are designed to bind every conceivable molecule from simple ion to large complex molecules like fats, sugars, nucleic acids and are thus the basic structural unit of the cell. They are composed of amino acids and catalyze extraordinary range of

chemical reactions, provide structural rigidity to the cell and control flow of materials through membranes via channels and pumps (Lodish *et al.*, 2001).

Proteins are thus the most vulnerable molecules to any xenobiotic substances and the decrease in hepatic total proteins under stress of pyrethroids in the present study may be due to lysis of structural proteins as well as arrested hepatocytic metabolism. Proteolytic products so formed, include amino acids, might get utilized in energy yielding metabolic pathways to meet out the demand of enhanced energy requirement of cell under pyrethroid stress (Sakr et al., 2002; Saxena and Doneriya, 2004; Manna *et al*., 2005; Omotuyi *et al*., 2006; Bhushan *et al.*, 2013; Bhushan *et al.*, 2013) .

Glycogen is a highly branched polysaccharide composed of glucose units, excess of later are stored and thereafter released upon demand. This way glycogen acts as a depot whereby glucose is trapped intracellulary, reducing osmotic forces acting on the cell, and can also be easily metabolized without ATP requirement for initiation. Liver acts as largest reservoir of glycogen storage in mammalian body. Muscle glycogen act as a source of localized energy, hepatic glycogen whereas, plays a genuine role in balancing the glycogen level in entire mammalian body (Roach *et al.,* 2012).

The decrease in level of hepatic glycogen under pyrethroid stress may possibly be due to increased catabolism through enhanced glycogenolysis within hepatocytes of treated animals. The catabolic activity in turn might have increased due to enhanced energy demands, necessary to maintain normal neural and general body functions. Further, hypoxic conditions could have played a significant role in decreasing hepatic glycogen content due to shifting normal aerobic glycolysis into anaerobic, thereby reducing ATP output by altering pathways related to glycolysis viz. Kreb's cycle. Simultaneous reduction in synthesis of hepatic glycogen might be a contributing factor towards this demand (Sakr et al., 2002; Saxena and Doneriya, 2004; Manna *et al*., 2005; Omotuyi *et al*., 2006; Bhushan *et al.*, 2013; Bhushan *et al.*, 2013).

Lipids are hydrophobic molecules that are found enormously in the cellular membranes which in turn, maintain cellular integrity and allow the cytoplasm to be compartmentalized into specific organelles. Due to high caloric value and less water consumption, the storage of lipids as energy storage products is more effective in comparison to glycogen and proteins (Laguerre *et al*., 2017).

Liver is actively engaged in lipid metabolism and control level of lipoproteins in mammalian body. Enhanced level of hepatic total lipids in the present investigation therefore reflects altered lipid metabolism in the respective organ. Possible metabolic alteration may be at the level of lipogenesis, thus giving rise to excessive hepatic lipids. Further the process of lipolysis might get interrupted, since the process takes place mainly in hepatocytic mitochondria, however, pesticides and organic compounds are capable to alter normal hepatocytic mitochondrial structure and function (Gassner *et al.*1997; Kalender *et al.*, 2005). Further, hypoxic conditions are well capable of disturbing normal mitochondrial functions (Braguini *et al.*, 2004). In addition, metabolism of other components of hepatic lipid profile the cholesterol, phospholipids and lipoproteins might have contributed to this increase (Saxena and Doneriya, 2004; Bhushan *et al*., 2013; Bhushan *et al.*, 2013).

Cholesterol is a four ring hydrocarbon with eight ring side chain, critical component of cellular membranes, a precursor of steroid hormones (adrenal and gonadal) and bile acids. Liver of mammals is actively concerned with cholesterol homeostasis.

Increased hepatic cholesterol level in the present study may be consequence of excessive cholesterol accumulation in hepatocytes probably due to hepatobillary dysfunction, as evident by decreased hepatic ALP. In addition, cholesterol catabolism might have decreased under pyrethroid stress and result in such an increase (Saxena and Doneriya, 2004; Bhushan *et. al*., 2013)

Phospholipids are principal components of cellular membranes and are essential for all vital cell processes. They are most important membrane building blocks and are amphiphilic molecules with unique physiochemical properties having both hydrophobic and philic parts of molecules. Phospholipids also play critical role in intracellular signalling (Fricker *et al.,* 2010).

Possible explanation for such increase in hepatic phospholipid content may be attributed to increased hepatic total lipids as well as altered ALP values thereby suggestive of altered phosphorylatic mechanism. Pyrethroids as well as their toxic intermediates might also alter intracellular phospholipids production due to interaction with signaling pathways such as that of phospholipase-c-pathway of signalling.

Free fatty acids are ubiquitous minor components of all living tissues and their measurement is an important tool to assess metabolic status of any organ. They can interact with a wide range of enzyme systems in both specific and non specific ways. Therefore they must be readily sequestered in tissues by various means to ensure that their activities are closely regulated.

In animal, much of the dietary lipids is hydrolysed to free fatty acids before it is absorbed and utilized for lipid synthesis. FFA are transported from serum to tissues as they are bound to protein albumin and diffuse into the aqueous phase and are taken up by the outer leaflet of plasma membrane by non-enzymatic biophysical pathways such as flip- flop. Additionally certain membrane bound fatty acid transporter proteins are also activity engaged in their transportation as well as trafficking to particular destinations (Burdge and Calder, 2005; Thormar and Hilmarson, 2007).

Intact lipids in tissues can also by hydrolysed to free fatty acids by a variety of pathways catalyzed by enzymes (e.g. lipoprotein lipase, hormone sensitive lipase, phospholipase A), before being metabolized in various ways including oxidation, desaturation, as reesterification (Nakamura *et al*. 2004; Hamilton, 2007)

Apart from their obvious role as a source of energy and important intermediate of lipids synthesis, free fatty acids also act as second messengers required for translation of

Evaluation of dose response relationship of type ii pyrethroids

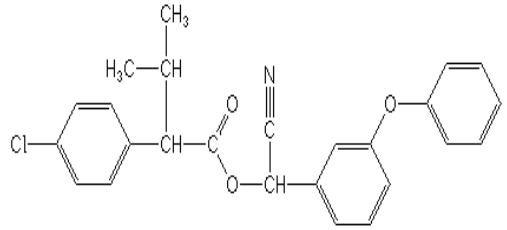


Figure 1: Structure of Fenvalerate

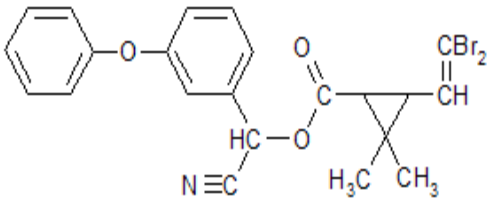


Figure 2: Structure of Deltamethrin

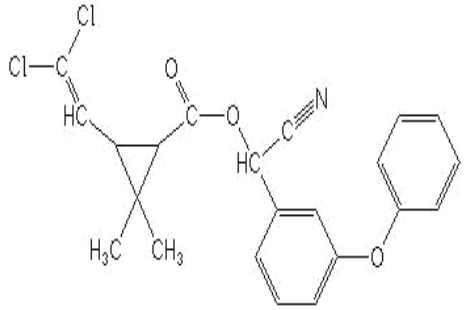


Figure 3: Structure of Cypermethrin

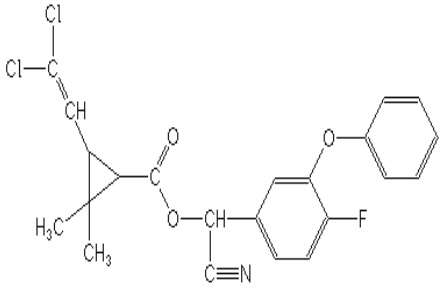


Figure 4: Structure of Beta-Cyfluthrin

various external signals. In addition, in mammalian tissues, free fatty acids are involved in regulating gene expression, mainly targeting genes that encode proteins with role in fatty acid transport or metabolism. However, it is believed that free fatty acids binding proteins are actively involved in this process and bind with free fatty acids in cytoplasm and transport them to nuclei through nuclear pores, where they are able to form complexes with nuclear receptors enabling them to regulate receptor activation.

The above explanation provides sufficient grounds to postulate a mechanism for increase in free fatty acids under stress of pyrethroids. The enhancement could have been due to absorption of FFA from peripheral blood circulation to act as instant energy source, formation of FFA from pyruvate under altered mitrochondrial functions under pyrethroids stress and also an outcome of reduced lipid catabolism inside hepatocytes (Saxena and Doneriya, 2004; Bhushan, 2011, Bhushan *et al.*, 2013). An overall summary of the mechanistic approach has been shown in Fig.5-6.

Evaluation of hepato-pathological changes

Hepatic lobule is the basic functional unit of the liver (Fig. 7). It is a cylindrical structure of several millimeters in length and 0.8 to 2 millimeters in diameter. A lobule is typically six-sized structure (hexagon) comprised of specialized cells called hepatocytes, arranged in irregular, branching, interconnected plates around a central vein. These plates radiate centrifugally from the central vein just like the spokes in a wheel. Each hepatic plate is one to two cells thick and between the adjacent cells lie small bile canaliculi that empty into bile ducts in the fibrous septa separating the adjacent liver lobules. Also in the septa are small portal venules that receive their blood mainly from the venous outflow of the gastrointestinal tract by the way of the portal veins. From the venules blood flows into flat, branched hepatic sinusoids that lie between the hepatic plates and thence into the central vein. Thus the hepatic cells are exposed continuously to the portal venous blood. In addition to portal venules, hepatic arterioles are also present in the interlobular septa. These arterioles supply arterial blood to the septal tissues and many of the small arterioles also empty directly into the hepatic sinusoids (Guyton, 1991; Tortora and Grabowski, 2003).

Liver from pyrethroid intoxicated rats revealed variety of pathological conditions including abnormal integrity of interalobular vein (ILV) and sinusoidal cords, movements of hepatocytes towards ILV, destruction of cellular membrane, vacuolization, pyknotic nuclei, necrosis, nuclear division. Karyorrehexis, giant cell formation and karyolysis (Doneriya and Saxena,

2004; Bhushan *et al.*, 2013; Al-Amoudi, 2015; Omonoma et al., 2015; Tomar *et al.*, 2015).

Basic components of hepatocytes are proteins, lipids and carbohydrates. Pyrethroids as well as their metabolic byproducts might interfere with hepatocytic membranes and probably causes the lysis the protein moiety of hepatocellular membranes, thereby altering normal membrane structure, histologically supported as disrupted hepatocellular membranes. Additionally, pyrethroids are lipophilic and must have easily entered the hepatocytes crossing lipid bilayer, causing oxidative stress, as a consequence of which abnormal degradation of amino acids gets evident biochemically in terms of enhanced activity of aminotransferases leading to cytoplasmic vacuolization (Tos-Luty *et al.*, 2001; Doneriya and Saxena, 2004; Issam *et al.*, 2012; Bhushan *et al.*, 2013).

The conditions like cellular pycnosis and necrosis might be due to release of lysosomal proteins within the damaged hepatocytes, whereas those like karyolysis, karyorrhexis and giant cell formation may be due to abnormal cellular cycle as well as mutagenesis within the hepatocytes of pyrethroid intoxicated rats. Further, abnormal lipid accumulation within the hepatocytes may be associated

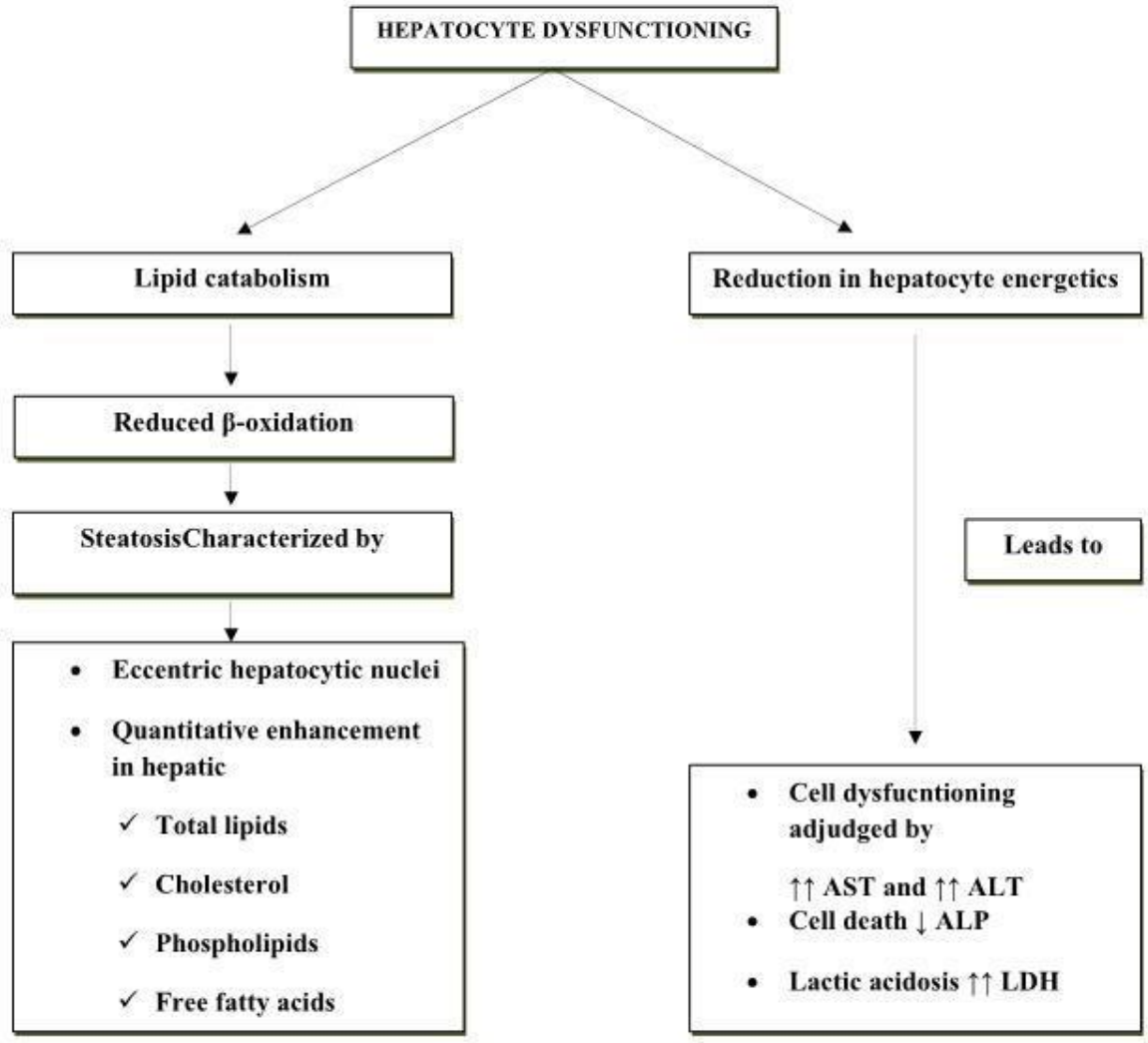


Figure 5: flow chart showing hepatocyte dysfunctioning under stress of pyrthroids in albino rat and enzymatic contents.

with abnormal positioning of the hepatocellular nuclei (Doneriya and Saxena, 2004; Bhushan *et al.*, 2013).

Evaluation of hepato-histochemical changes

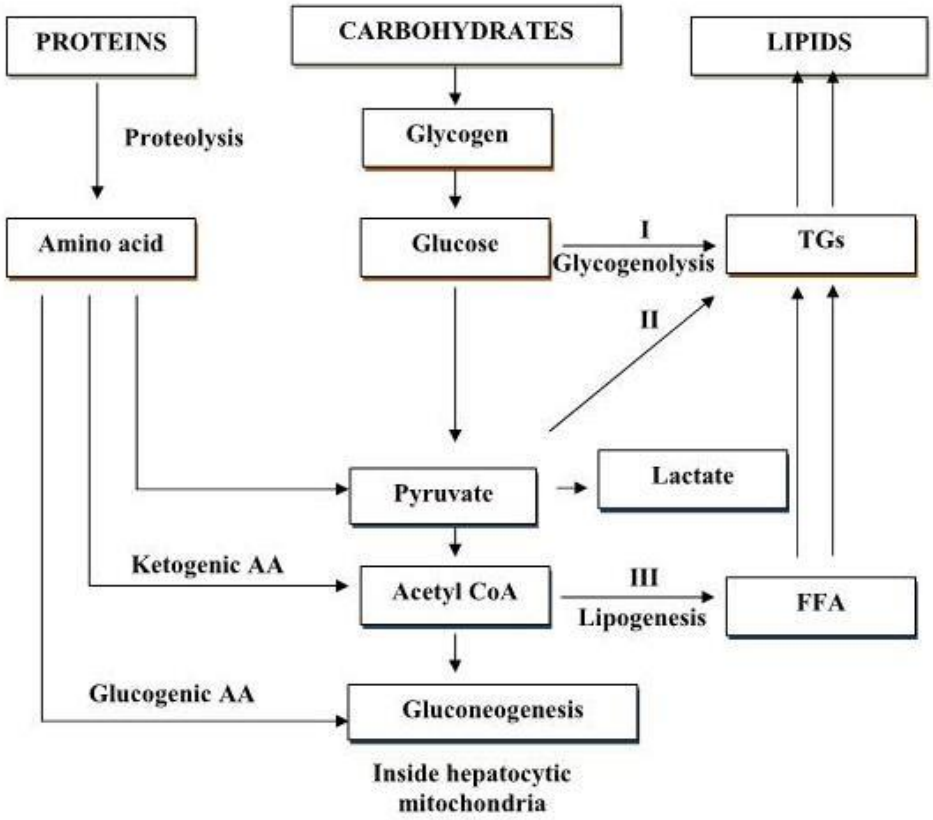
Hepatic glycogen has been found to decrease histochemically within the hepatocytes of pyrethroid intoxicated rats which seems to be due to many fold increase in the process of glycogenolysis following pyrethroid stress resulting in its reduced glycogen production as well as increased energy demands to maintain normal muscular, neural and general body functions under pesticidal stress. Additionally, hypoxic condition may be a contributing factor towards this decline.

However, very slight interzonal variations in the localization of hepatic glycogen content within the liver of treated animals, whereby periporatal zone is the zone of maximum difference. The interzonal difference in this zone may be due to the fact that maximum carbohydrate metabolizing enzymes are concentrated in this zone of hepatic lobule and the experimental compounds as well as their toxic intermediates might have increased the activity of these enzymes (Hinton and Grasso, 2000; Stolz, 2002; Sakr *et al.*, 2002; Bhushan, 2011; Bhushan *et al.*, 2010; Nagarjuna and Jacob, 2010; Bhushan *et. al.*, 2013; Bhushan *et al.*, 2013).

Lipids are important components of cellular components serving structural as well as vital cellular functioning such as cellular signaling and also are energy reserves. Histochemical studies have revealed an increase in hepatic total lipid level, with interzonal variations (Bhushan *et. al.*, 2013).

Qualitative increase in hepatic total lipids with simultaneous decrease in hepatic glycogen points towards alterations in their metabolism in hepatocytes possibly at the level of lipogenesis. Effect of pyrethroids on metabolism of other components of lipid profile viz. cholesterol and phospholipids can not be ruled out (Saxena and Doneriya, 2004: Manna *et al.*, 2004; Singh *et al.*, 2002; Bhushan *et al.*, 2013; Bhushan *et al.*,2013).

The interzonal differences in localization of hepatic total lipids may probably be due to more concentration of the same in cellular organelles which in turn are more susceptible to hypoxic conditions, and pyrethroids are capable of creating hypoxic conditions in mammalian liver (Bhushan *et al.*, 2010). Most of the lipid synthesizing enzymes are concentrated in the centrilobular zone, which



Note: I, II, III depict forms of FFa and TGS (lipogenesis)

Figure 6: flow chart showing interrelated pathways of gluconeogenesis and lipogenesis under stressful condition of pyrethroid intoxication.

has been the zone of maximum increase of total lipids, could be a reason of defective functionality of these enzymes.

The DNA content increased qualitatively in the hepatocytes of albino rats after acute and sub-acute intoxication of pyrethoids. Normally DNA is present mainly in the chromosomes along with small quantities in the mitochondria of the eukaryotic organisms. In case of mammals DNA exists as double stranded molecule, where the two strands wind each other forming a double helix.

Pyrethroids are also sable to cause mutagenic damage in mammals, probably a consequence of their ability to cause degenerative and necrotic changes to mammalian tissues (Tos-Luty *et al.*, 2001, Doneriya and Saxena, 2004, Manna et al., 2004; Bhushan *et al.*, 2013). These changes may be responsible for lysosomal damage and release of lysosomal enzymes (DNA hydrolases) and hence result in variety of consequences including alterations in the biochemistry of cell and nuclear membrane and entry of various enzymes including nucleases inside the nucleus that ultimately results in chromosomal alterations (Singh and Saxena, 2002;). Chromosomal alterations may have a variety of fates including altered DNA synthesis. Possible explanation for the increased DNA synthesis may be the altered chromosomal functions, which might have resulted in excessive DNA synthesis through mitogenic mechanism (Singh and Saxena, 2002; Sharma, 2006; Bhushan *et al.*, 2010; Sharma *et al.*, 2010).

Proteins are the most abundant and functionally diverse molecules in the living systems. Virtually, every living process depends on this class of molecules. For example enzymes and polypeptide hormones direct and regulate metabolism in the body, whereas diverse proteins in the muscle permit movement. In short, proteins display an incredible diversity of functions, yet all share the common feature of being a linear polymer of amino acids(Watson *et al.*, 2004).

Hepatic protein has been found to decrease qualitatively after acute and sub-acute intoxication of pyrethroids. The possible explanation for the qualitative reduction in the hepatic protein is likely due to proteolysis of structural protein to amino acids in order to get rid of the stress and also to counter balance the quick need of proteins to build up new cells under the stress of pyrethroids. Centrilobular zone followed by midzonal region appears to be most affected areas after histochemical localistion studies. In general, these areas respond differently to hypoxia and toxin exposure. Oxygen content of the blood follows a decreasing trend while traveling down from portal triad towards the central vein. Centrilobular zone is nearest to the central vein and also contain most of the enzymes responsible for the detoxification of any xenobiotic,

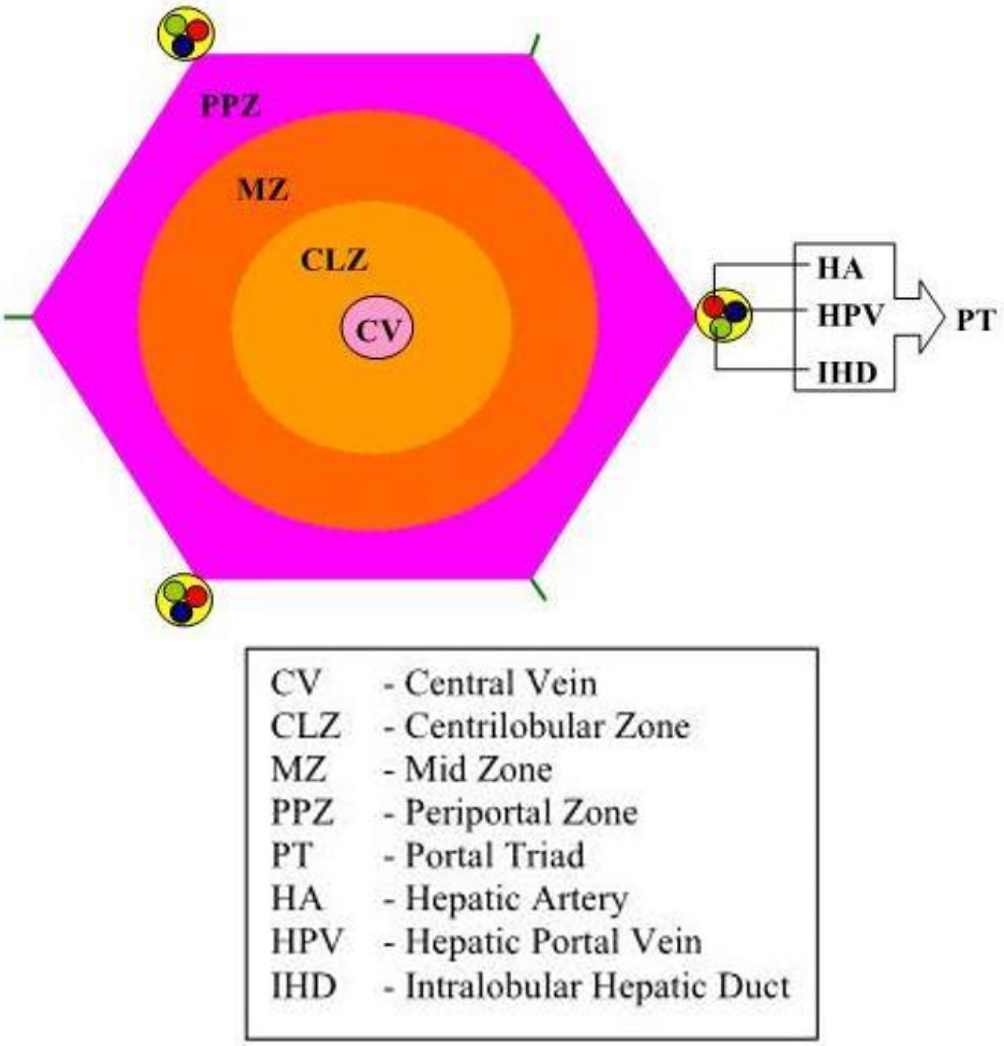


Figure 7: Diagrammatic representation of hepatic lobule of *Rattus norvegicus.*

therefore is the most affected region of the hepatic lobule (Stolz, 2002).

Structure activity relation ship

Present study also revealed the role of structure towards the toxicity among these type II pyrethroids. These chemicals differ from each other mainly on the basis of halogenated functional groups. These functional groups are responsible therefore for this difference in toxicity of respective pyrethroids, as these functional groups change the chemical properties to varying degrees. Moreover, the stabilities of carbon-halogen bonds are also different in case of different halogenated groups. This factor also have a say in further breakage of the carbon-halogen bonds during metabolism inside the host body as well as these bonds also have different fate during detoxification. In total we can conclude that attachment of different functional groups during development of these pyrethroids from the basic structures also leads to enhanced stability of these structures and there by increased life times and toxicity also to target as well as non-target organism(Key *et al.,* 1997; Bhushan *et al.*, 2013; Yadav *et al.,* 2014).

CONCLUSIONS

These facts (*vide supra*) strongly suggest that pyrethroid pesticides are having strong potential to disturb normal vital hepatic functions of mammalian body. In addition, they can also get deposited with in the body tissues by virtue of their lipophilic nature and their toxicity can also get enhanced further through biomagnifications and biotransformation. The use of such chemicals be thus done with great precautions, till much safer, efficient and eco friendly options are there with us.

The above facts suggest that the effect of experimental pyrethroid is restricted not only to the nervous system but it is having considerable potential to disrupt the normal functions of other body organs as liver in the present study. The aforesaid result points the necessity of undertaking some more studies to understand the working mechanism of the pesticide at ultrastructural and molecular level. Such studies will definitely be helpful for further understanding of the mode of action of the pyrethroid.

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