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The Effects of Pesticides on Liver Injury: Current Status on Pathophysiology

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Abstract

Increasing use of pesticide may be associated with severe hepatotoxicity. The underlying mechanism of pesticide - induced liver damage is poorly understood. Studies are selected by searching keyword pesticide, food and agriculture, pesticide and liver injury, herbicide, insecticide, fungicide. PubMed, Web of Science, Google Scholar, Embase, Scopus are used to obtain research articles, case studies, reviews in English language up to June 2025. It reveals that three main types of pesticides are commonly used: herbicides, insecticides, and fungicides. The toxicological effects of pesticides are linked to the development of non-alcoholic fatty liver disease (NAFLD), metabolic-associated fatty liver disease (MAFLD), non-alcoholic steatohepatitis (NASH), hepatitis, and hepatocellular carcinoma. Both *in vivo* and *in vitro* exposure to pesticides shows changes in hepatocyte morphology and cellular functions. Furthermore, pesticide exposure results in elevated liver enzyme activities, tissue inflammation, oxidative stress, leukocyte infiltration, and lipid accumulation. Pesticides can disrupt the gut-liver axis by diminishing beneficial gut microorganisms. These physiological alterations may be associated with significant liver injury. It can be inferred that improved safety protocols are crucial when applying hazardous pesticide agents. However, it would be wise to restrict the use of hazardous pesticides. Furthermore, the encouragement of organic farming should be promoted to mitigate pesticide-

related liver damage. It is essential to prohibit the use of pesticides that demonstrate the greatest toxicity to humans, along with those that persist in the environment for extended durations. Additionally, it is vital to protect public health by setting maximum permissible limits for pesticide residues in food and water.

Keywords: Pesticide; Liver injury; Non-alcoholic fatty liver disease, Oxidative stress; Liver inflammation

Introduction

In the modern era, the demand for pesticides is increasing gradually. As the population grows, efforts are underway around the world to produce a good quality and quantity of agricultural products at low cost using different pesticides. As per the data of 2019, around 2 million tons of pesticides are consumed worldwide for farming.[1] However, the global consumption of pesticide is increased to 3.39 million tons by 2024.[2] China stands for the leading position in pesticide use, followed by the USA and Argentina. It causes a lot of harm to the health and society through bioaccumulation and biomagnification. Bioaccumulation and biomagnification are two different processes that often occur in tandem with each other.[3] Bioaccumulation is the process by which toxic substances accumulate within individual organisms and enter a food web, while biomagnification is the process by which toxic substances are transferred from one trophic level to another (and thereby increase in concentration) within a food web. Through a multifaceted approach, it can be said that pesticides cause a lot of damage to the environment, including air, water, and soil. However, pesticides are directly or indirectly harmful to the human body through targeting different organs. A study of 137 countries around the world using the Global Pesticide Use and Trade (GloPUT) database has revealed that pesticide use is increased by about 20 % worldwide. On the other hand, using same data it is analyzed that the pesticide use is increased in low-income countries by 153%.[4] According to the article of Pathak et al., pesticide can be diversified into herbicide, insecticide, nematicide, fungicide, miticide, algicide, and rodenticide.[5] Two major classes of pesticides include natural and synthetic. Natural pesticides are further classified into plant and mineral oil-based. Whereas, synthetic pesticides are classified into inorganic and organic. Moreover, organic pesticides include pyrethroids, carbamates, organochlorines, and organophosphates.

Residual pesticide toxicity is a major risk factor for health hazards. As per the World Health Organisation (WHO), old and low-cost pesticides remain in the soil and water for many years, gradually becoming harmful to the health.[6] Many of these chemical pesticides have been completely phased out in developed countries but are still being used in developing countries. The global consumption of different pesticide includes herbicide (50%), fungicides and bactericides (22.5%), and insecticides (20.4%).[2] However, chemical formulation of pesticide may result in a series of health complications such as abnormal endocrine function, neurotoxicity, carcinogenicity, teratogenicity, and mutagenicity.[5]

Moreover, chemical toxicity of pesticide shows adverse effects on different human organs and body parts such as brain, heart, kidney, eye, skin, lung and many more.[7-11] Apart from this, the adverse effects of pesticides can lead to the severe liver diseases such as non-alcoholic fatty liver disease (NAFLD), hepatocellular carcinoma, hepatitis, etc.[12-14] There is evidence that high ZIP code-level organochlorine such as dichlorodiphenyltrichloroethane (DTT) significantly contributes to the liver injury and hepatocellular carcinoma (HCC).[13] Besides, in vivo sturdy shows that organophosphorus pesticide such as dichlorvos can cause a serious liver injury through reactive oxygen species (ROS) and autophagy-dependent mechanism.[15] Moreover, several other organophosphate pesticides have potential roles in in liver injury through abnormal alterations in liver function parameters and aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ratio.[16]

Recently, the research works on the chemical toxicity of pesticides on the liver is increasing. In this situation, there is an urgent need for in-depth analysis and evaluation of data obtained from various research studies from where the harmful effects of pesticides on the liver, is currently necessary to explain and understand. The present study attempts to analyse various existing research data to show how pesticides have a detrimental effect on the liver and damage it. Here are all the possible pesticides shown, their particular mechanism of action, and the various liver functions they target, which in turn causes the liver damage.

Pesticide Use in the Agriculture

Pesticides are categorized into herbicides, insecticides, and fungicides. Insecticides can be further divided into organochlorines, organophosphates, carbamates, and pyrethroids (Figure 1).[5] As per the Ministry of Agriculture and Farmers Welfare, Government of India, the use of pesticides during Kharif & Rabi Seasons has been described in detail.[17]

It has been noticed that the agricultural sector uses the most chemical pesticides (52%). Moreover, 8% of all agricultural activities use biopesticides. Whereas, 30% under total crop area does not come under any pesticide use. Depending on the nature of cultivation, the process of pesticide use also changes. It has been found that pesticides are used more when cultivating large areas. In this case, cotton, chillies and green vegetables are cultivated. It has also been found that less pesticide use is applicable in cultivation that takes up less space. In this case different crops such as oilseed, cereals, and pulses are harvested. As per the report as mentioned above, the highest percentage of area treated with pesticide is noticed in case of apple farming (100%) followed by jute (67%) and cotton (57%). Whereas, bajra (22%) and ragi (9%) show lowest use of pesticides.[2] According to the report of Government of India has issues a total of 2820 pesticides out of chemical pesticides (2182) and biopesticides.[77]

Pesticide Residues in Food and Environment

The vital use of pesticides boost agricultural production has become inevitable. Unfortunately, the uncontrolled and non-selective use of chemical pesticides often exceed the targeted areas. Moreover, pesticides as residues last for months or even years. This imprecision and lack of proper information cause significant health hazards to humans and other organisms. The detection of even minimal concentration of pesticide residues creates a significant barrier to international food trade. Hence, organic and safe farming and bioremediation are warranted in order to reduce pesticide residues as micropollutants in the surroundings. Sinha et al. have tested vegetables using total ion chromatography and demonstrated pesticide distribution (mean, μg/kg) based on food diversity.[18] According to the report chlorpyrifos (CPF), triazophos, phosalone, fenitrothion, acephate are majorly found in tomato (178.87 μg/kg), tomato (3.014 μg/kg), egg plants (50.85 μg/kg), egg plants (53.90 μg/kg), and tomato (59.64 μg/kg) respectively. Maximum residue level (MRL) is pivotal for maintaining agriculture trade policies. It is reported that MRL of glyphosate in wheat reaches to 0.5 ppm in 2020, which may result in the liver damage and carcinogenesis.[19] Pesticide causes environmental toxicity as it travels a long distance from 10 km to 500 km depending on the influencing conditions and factors such as wind speed, soil properties (texture, pH, and temperature), rainfall, etc.[5]

Major Entry Routes of Pesticides in Human Body

Three most important entry routes of pesticides in human are
1. absorption via dermal contact,
2. Ingestion through mouth, and
3. inhalation through nose and mouth (Figure 2).[20]

1. Absorption of pesticides through dermal contact

Those who use pesticides professionally, such as farmers, are affected by chemical toxicity due to the direct use of pesticides. However, like farmers, municipal workers, gardeners, foresters, and pest controllers are also equally affected by these harmful effects of pesticides. The use of pesticides can cause harmful effects of pesticide chemicals on the user's body. Various types of pesticides such as herbicides, fungicides, and insecticides contain harmful chemical compounds such as phenoxy acid herbicides, organophosphorus, organochlorine, urea, etc., which have harmful effects on the body. Pesticides have a direct effect on the human skin. The absorption of pesticides through the skin is directly dependent on several regulatory factors such as temperature, humidity, and concentration of the pesticide. The rate of percutaneous pesticide absorption is already examined in hand (0.23 ± 0.1 μg/cm ^{2}), leg (0.29 ± 0.2 μg/cm ^{2}), and forearm (0.29 ± 0.1 μg/cm ^{2}) using *in vivo* experiments.[21]

2. Ingestion of Pesticide Through Mouth

Mouth or oral cavity is considered as the first-line contact of pesticides. Based on the chemical structures of pesticides such as organophosphates, organochlorine, etc. bind to the epithelial tissue and result in the inflammatory response.[22, 23] The effect of different pesticides on oral cavity is well described by Salazar-Flores et al. in their article. Briefly, pesticides target tongue, gingival sulcus, buccal mucosa, soft palate, tooth surface, dental plaque, oral and salivary flora. The interaction of pesticide with oral cavity leads to the development of serious complications such as caries, periodontitis, and oral cancer.[24]

3. Inhalation Through Nose and Mouth

Inhalation of pesticide, especially the toxic volatile components effect respiratory system including nose, throat, and lung tissue.[25] The direct users of pesticide often encounter respiratory illness such as asthma and poor lung function. Long-term exposure of pesticide inhalation may result chronic diseases such as bronchitis, chronic obstructive pulmonary disorder (COPD), lung cancer, etc.[26, 27]

Effects of Pesticides on Liver

The toxic effects of various pesticides on liver are extensively studies and documented (Figure 3). There is a high risk of liver carcinogenesis due to pesticide exposure.[13] However, the underline mechanism of liver damage because of pesticide exposure is poorly understood. In here, an attempt has been made to unfurl the possible reasons of hepatotoxicity due to the harmful effects of different class of pesticides. Furthermore, various therapeutic agents are discussed here, which have been demonstrated to be advantageous in safeguarding the liver against pesticide-induced toxicity (Table 1).

1. Herbicides

Glyphosate is the most commonly used herbicide. An *in vivo*

mouse experiment shows hepatocyte morphological changes, inflammation, increased oxidative stress, respiratory chain blockage, increased gluconeogenesis and fatty acid synthesis, activation of the coagulation cascades system, and activated complement in the liver after 30 days of exposure to glyphosate-based herbicides (GBH).[28] According to a recent study, GBH may be connected to the etiology of steatotic liver disease linked to metabolic dysfunction.[29] Another study that used metabolomic analysis demonstrates that exposure to GBH causes an increase in the expression of hepatotoxic markers like proline, acylcarnitines, and derivatives of γ-glutamyl dipeptides, which promotes the development of NAFLD to NASH.[30] Furthermore, hepatic failure is also associated with GBH.[31] The herbicide 2,4-dichlorophenoxyacetic acid (2,4-D) is one of the most widely used. It has been shown that giving mice 2,4-D for six months causes an increase in oxidative stress, liver inflammation, and macrophage infiltration, all of which contribute to the development of nonalcoholic fatty liver disease (NAFLD).[32] Another study has shown that administration of 2,4-D in mice for 4 weeks elevates malondialdehyde level with reduced level of antioxidants such as glutathione reductase (GR), superoxide dismutase (SOD), and catalase.[33] In addition, studies employing a rat model reveal that the inhalation and oral administration of 2,4-D are correlated with an increased risk of steatosis.[34] However, the hepatotoxicity associated with 2,4-D is well established in the work of Martins et al.[35] The substance 2-bromo-4,6-dinitroaniline (BDNA) is widely applied in agriculture. Research indicates that BDNA contributes to a decline in gut microbial populations, such as Ruminococcaceae and *Akkermansia muciniphila*, which intensifies liver injury by promoting inflammation, lipid accumulation, and bile acid synthesis.[36] The herbicide metribuzin has been found to exhibit hepatotoxic effects in rabbits, as evidenced by increased liver MDA and GST levels, along with a reduction in GSH.[37] A case report indicates that the herbicide paraquat leads to liver injury in a patient.[38] Paraquat exposure results in significant hepatitis and hepatocyte damage in a patient, which is alleviated by cholestasis treatment.[39] Atrazine has been documented to cause hepatotoxicity through the elevation of liver enzymes and oxidative stress in a rat model.[40] Furthermore, exposure to the herbicide oxyfluorfen results in acute liver injury by modulating liver enzymes and related parameters.[41] Another investigation indicates that oxyfluorfen reduces sugar and lipid metabolism while elevating inflammatory markers (TNF-α, IL-6, and IL-8), which subsequently contributes to liver damage in zebrafish.[42] Diquat, a commonly utilized herbicide, is implicated in causing liver toxicity in ducks through mechanisms of mitochondrial apoptosis and autophagy.[43] Additionally, diquat leads to heightened lipid peroxidation and necrosis in rats, a condition that can be mitigated by selenium administration.[44] The herbicide bromoxynil impacts the liver by downregulating the NF-κB, JAK1/STAT3, and TLR4/MyD88 signalling pathways.[45] The toxicological effects of dicamba are linked to liver cancer and intrahepatic bile duct cancer.[46] The hepatotoxicity associated with pendimethalin results in increased inflammation, oxidative stress, hepatic necrosis, and leukocyte infiltration in rats.[47]

2. Insecticides

(a) Organochlorine (OC):

OC represents a significant category of insecticides utilized in agriculture, which can be further divided into dichlorodiphenylethanes, chlorinated cyclodienes, chlorinated benzenes, and cyclohexanes. Exposure to OCs has been linked to non-alcoholic fatty liver disease (NAFLD) and metabolic-associated fatty liver disease (MAFLD).[48-50] Research conducted on fish liver tissue indicates that organochlorines, including dichlorodiphenyltrichloroethane (DDT) and dieldrin residues, are associated with changes in lysosomes and nuclei, characterized by dilated and disorganized endoplasmic reticulum (ER) and swollen mitochondria in hepatocytes.[51] Furthermore, various animal studies have reported that OC pesticides lead to increased microsomal enzyme activity.[52] DDT has been associated with a heightened risk of HCC. Nonetheless, several factors, including smoking, alcohol intake, age, gender, occupation, and living environment, are also implicated.[53] Studies on rats exposed to organochlorines confirm the presence of 1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (DDE) as a metabolite of 1,1-Dichloro-2,2-bis(p-chlorophenyl)ethane (DDD) in the liver.[54] Additionally, the presence of OCs such as benzene hexachloride (BHC) and DDE has been confirmed in the blood of agricultural workers and public health professionals.[55] Hexachlorobenzene (HCB) and heptachlor (HEP) are reported to facilitate hepatocarcinogenesis in rats.[56] Moreover, a case study indicates that exposure to γ-benzene hexachloride (γ-BHC) results in oxidative stress-induced liver failure in a 30-year-old male farmer.[57] Toxaphene has been shown to enhance hepatic DNA synthesis and promote liver tumor progression in mice.[58] However, toxaphene is also associated with increased liver microsomal enzymes in rats.[59] Similarly, dicofol has been linked to elevated levels of microsomal proteins, including ethoxycoumarin O-deethylase, glutathione S-transferase (GST), cytochrome P-450, cytochrome c reductase, microsomal epoxide hydrolase, and aminopyrine N-demethylase.[60] The experimental mouse model indicates that exposure to dicofol leads to liver lipogenesis, inflammation, and dysfunction.[61] A study on freshwater catfish has demonstrated that aldrin exposure results in the transfer of cholesterol from the liver to the bloodstream, causing liver damage.[62] Exposure to OC chlordane is associated with increased lipid peroxidation and fatty infiltration in the liver.[63] Furthermore, chlordane affects hepatic energy metabolism by

decreasing the expression of Pklr and Gck genes, which are involved in glycogen/glucose metabolism, as well as the transcription factor HNF4A (hepatocyte nuclear factor 4-alpha), which is crucial for liver function and development.[64] OC chlorobenzilate has been identified as a liver carcinogen, leading to the formation of liver tumors in an experimental rat model.[65] Lindane is known to induce oxidative stress-related liver damage by decreasing the activity of SOD and catalase, as well as the GSH/GSSG ratio.[66] Exposure to lindane may be linked to degenerative changes in hepatocytes, characterized by glycogenic depletion, degradation of the rough endoplasmic reticulum, alterations in the dictyosome, and accumulation of secondary lysosomes.[67] Heptachlor is another organochlorine compound that causes liver injury in a mouse model due to lipid peroxidation and disruption of muscle membranes.[68] Additionally, dieldrin has been reported to induce liver tumors in mice through the activation of the constitutive androstane receptor.[69] Dose-dependent exposure to dieldrin in an experimental rat model reveals an increase in the concentrations of AST, ALT, and LDH-5, alongside a reduction in LDH-1, with notable histological changes such as focal necrosis, cytoplasmic vacuolation, and nuclear enlargement of hepatocytes.[70] Dieldrin exposure in rats has been shown to elevate hepatic MDA levels and DNA synthesis, indicating oxidative stress-related liver injury.[71] However, the increased DNA synthesis resulting from dieldrin exposure may lead to the development of hepatic cancer.[72] Another study indicates that dieldrin causes sodium accumulation and a reduction in calcium ions (Ca^{2+}) within liver cells.[73] Nevertheless, the accumulation of sodium ions (Na^{+}) may be associated with hepatocyte necrosis.[74] Exposure to endosulfan may be associated with heightened oxidative stress and changes in liver morphology, as evidenced in fruit bats.[75]

(b) Organophosphate (OP)

The relationship between OP pesticides and liver toxicity is succinctly outlined by Karami-Mohajeri.[76] Chlorpyrifos (CPF) stands out as one of the primary organophosphorus pesticides utilized in agricultural practices. An *in vivo* investigation employing a mouse model indicates that administering CPF orally for a duration of 12 weeks leads to liver inflammation, accompanied by a decrease in beneficial gut commensals such as Prevotella, Butyricimonas, and Akkermansia, while pathogenic bacteria like Desulfovibrio and Helicobacter increase.[77] Another research study reveals that CPF is a contributing factor to liver injury in mice, attributed to alterations in gut microbiota and heightened intestinal permeability.[78] Research conducted on eukaryotic liver cells (AML 12) and a mouse model demonstrates that CPF induces liver injury by promoting autophagy and apoptosis.[79] A study involving carp (a fish model) indicates that CPF exacerbates hepatotoxic injury by impairing the AMPK/SIRT1/pGC-1α pathway, which is crucial for energy metabolism and mitochondrial dynamics.[80] Nevertheless, the hepatotoxic effects of CPF may be mitigated by hydrogen-rich water, as evidenced in a rat model.[81] Engaging in aerobic exercise and supplementing with eugenol may offer protective benefits against CPF-induced liver tissue damage by enhancing acetylcholinesterase (AChE) activity and bolstering antioxidant defences in hepatocytes.[82] Additionally, red beetroot may provide protective effects against CPF-induced liver damage.[83] Moreover, essential oil from *Artemisia campestris* and fennel seeds also demonstrate protective properties against CPF-induced hepatotoxicity by reducing oxidative damage.[84,85] Furthermore, zinc supplementation has been shown to have a protective effect against CPF-induced hepatotoxicity by safeguarding membranous organelles and preventing the obstruction and constriction of biliary channels in hepatocytes.[86] Similar to CPF, triazophos is also implicated in hepatic injury, which may be counteracted by the aqueous extract of broccoli sprouts.[87] Additionally, methidathion is known to induce liver damage by promoting lipid peroxidation, as demonstrated by both *in vitro* and *in vivo* studies.[88] Nonetheless, supplementation with vitamin E and vitamin C may assist in mitigating liver toxicity induced by methidathion.[89] OP diazinon has been demonstrated to cause liver toxicity through the induction of oxidative stress and apoptosis.[90] An *in vitro* study utilizing HepG2 cells indicates that diazinon triggers oxidative stress and apoptosis, which could potentially be alleviated by tetrahydrocurcumin.[91] Furthermore, liver injury mediated by caspase-3 has been reported following combined exposure to diazinon and aspirin, which may be counteracted by selenium (Se).[92] In addition to resveratrol, crocin, silibinin, flaxseed oil, and thymoquinone have also been noted for their effectiveness against oxidative stress and liver injury induced by diazinon.[93-97] Research conducted on zebrafish reveals that diazinon significantly reduces DNA, RNA, and protein concentrations, which may be associated with altered nucleic acid and protein metabolism in the liver.[98] In this context, the root of the *Salvia miltiorrhiza* plant and reduced glutathione may provide protective benefits against diazinon poisoning in the liver.[99, 100] Similarly, malathion induces hepatic injury by promoting oxidative stress, inflammation, lipid peroxidation, and decreasing levels of antioxidants such as SOD, catalase, and glutathione peroxidase (GPx).[101,102] In this regard, studies suggest that resveratrol and wheat germ oil may effectively reduce oxidative damage to the liver, as demonstrated in rat models.[103,104] Parathion, another OP, has also been shown to be hepatotoxic due to the reduction of liver enzymes such as alkaline phosphatase.[105,106] Parathion-methyl exhibits potential mutagenic and carcinogenic effects on rat liver.[107] In this context, liver injury induced by methyl parathion may be prevented by sodium aescinate through the reduction of oxidative stress.[108] Additionally, ginger and vitamin C may prove effective against liver injury induced by methyl parathion.[109,110] Dimethoate, a potential OP, is

associated with increased oxidative stress, lipid peroxidation, elevated cytochrome P450 levels, and inhibition of AChE in the liver.[111] Rat studies indicate that dimethoate leads to changes in liver histopathology, including enlarged veins and sinusoids, necrotic changes in hepatocytes, an increase in Kupffer cells, leukocyte infiltration, and nuclear degradation.[112,113] The administration of dimethoate results in elevated levels of alkaline phosphatase (ALP), AST, ALT, and bilirubin.[114-116] Furthermore, dimethoate heightens oxidative stress, lipid peroxidation, and DNA damage within the liver.[117] Conversely, ferulic acid, alpha-lipoic acid, and a combination of vitamin E and N-acetylcysteine may offer protection to the liver against elevated liver enzymes (AST, ALT, and ALP), oxidative stress, lipid peroxidation, and DNA damage[118,119] Omethoate, another organophosphate (OP), has been demonstrated to cause oxidative damage to frog liver.[120] OP trichlorfon is shown to induce endoplasmic reticulum dilatation, mitochondrial vacuolization, lipid accumulation, a decrease in ALP levels and anti-inflammatory cytokines (IL-10), along with an increase in inflammatory cytokines (TNF-α, IL-1β, IL-6, IL-12, and TNF-β) in the hepatocytes of carp liver.[121,122] Additionally, exposure to trichlorfon leads to the inhibition of catalase, superoxide dismutase (SOD), acetylcholinesterase (AChE), and glutathione S-transferase (GST) activity in plasma, accompanied by central vein congestion, vacuolar degeneration, and necrosis.[123] Moreover, monocrotophos has also been identified as hepatotoxic due to increased lipid peroxidation and oxidative stress-induced DNA damage in rat liver.[124] Another investigation reveals that monocrotophos causes an increase in liver enzymes such as AST, ALT, and ALP in an albino rat model.[125] However, N-acetylcysteine may effectively counteract the toxic effects of monocrotophos in rat hepatic tissue by diminishing oxidative stress and apoptosis.[126] The impact of dichlorvos includes the initiation of autophagy through the suppression of immunity-related GTPase M and reactive oxygen species (ROS), which is subsequently followed by liver injury in a rat model.[15] It has been noted that dichlorvos is linked to autoimmune hepatitis.[127] In this context, L-arginine has been demonstrated to effectively mitigate dichlorvos-induced liver toxicity by decreasing inflammatory markers (IL-6, TNF-α, C-reactive protein, and Caspase 3) as well as liver function indicators (ALT, AST, ALP, total protein, gamma glutamyl or γ−GT, and albumin).[128] Furthermore, it has been reported that the antioxidant royal jelly, derived from honey bees, is effective in safeguarding the liver from dichlorvos toxicity by alleviating oxidative stress.[129] Additionally, vitamins C, E, and lycopene have been shown to provide protective effects against dichlorvos-induced hepatotoxicity.[130] On the other hand, fenitrothion is known to cause considerable liver damage by diminishing AChE activity.[131] Fenitrothion may also play a role in enhancing glucose metabolism in the liver through the inhibition of the AMPKα and IRS1/PI3K/AKT pathways.[132] Research indicates that saponarin, a natural flavonoid, has been shown to protect against fenitrothion-induced liver damage by modulating the JAK1/STAT3, TLR4/MYD88, and NF-κB pathways.[133] In this regard, gallic acid has been reported to be effective against fenitrothion-induced liver toxicity by reducing oxidative stress and liver function markers.[134] OP RPR-II has been shown to lower glycogen levels, LDH, GSH, while increasing GST activity and lipid peroxidation in the liver.[135] Mthamidophos, another OP, has been noted to induce liver damage by diminishing butyrylcholinesterase and paraoxonase 1 activity.[136] An experiment conducted on rabbits indicates that mthamidophos leads to an increase in liver enzymes (AST, ALT, ALP, and GST).[137] Phorate inflicts liver damage by elevating cytochrome P450 levels, liver enzymes (AST, ALT, ALP, γ−GT, acid phosphatase), and reducing catalase, SOD, and GSH activity.[138] Moreover, elevated serum protein levels in individuals have been linked to phorate exposure.[139] Fenthion significantly decreases butyrylcholinesterase levels in rat models, which may indicate potential liver toxicity.[140] Conversely, *Artemisia campestris* leaf powder may prove beneficial in mitigating oxidative liver damage.[141] Research on broiler chickens reveals that exposure to acephate can lead to degenerative changes in the endoplasmic reticulum, mitochondria, nucleus, and other cell organelles, ultimately resulting in liver injury.[142] An experiment on a mouse model shows that acephate inhibits carboxyamidase, leading to liver injury.[143] 1,2,3-trichloropropane (TCE), another OP, is known to cause severe jaundice, characterized by increased total bilirubin, necrosis of hepatocytes, and immune cell infiltration in the liver.[144] Additionally, TCE exposure may be associated with occupational liver disease.[145] Quinalphos (QP), a synthetic OP, is responsible for heightened oxidative stress and lipid peroxidation, which subsequently leads to liver injury.[146-149] Exposure to QP has been reported to cause changes in liver histopathology, including hepatocyte hypertrophy, necrosis, central vein rupture, and vacuolation.[148] However, vitamins E and C may offer protective effects against QP-induced liver damage by reducing oxidative stress.[149] A study on pregnant rats indicates increased activity of AST, ALT, ALP, and LDH following QP exposure.[150]

(c) Carbamates (CB)

A study on the human hepatic cell line L02 indicates that exposure to ethyl carbamate leads to heightened oxidative stress and a decrease in the activation of Nrf2 (nuclear factor erythroid 2-related factor 2), ultimately triggering ferroptosis in liver cells.[151] Vernolate, a significant thiocarbamate, is linked to the depletion of ALDH2 (mitochondrial aldehyde dehydrogenase) in rat liver, which may correlate with impaired liver function, inflammation, and damage to hepatocytes, potentially resulting in fatty liver disease.[152,153] Research indicates that thiourea induces liver injury in rats through a reactive oxygen-mediated increase in epoxide hydrolase and rGSTA2 (regulator of G protein signaling 2).[154] Additionally, another study reveals that thiourea exposure leads to proliferative lesions and liver carcinogenesis.[155] It has been

shown that malotilate contributes to increased lipid and collagen accumulation in the liver, which may be associated with hepatic fibrosis.[156] Zineb, a dithio carbamate, has been demonstrated to inhibit RNA and protein synthesis in the livers of rats and mice.[157] Furthermore, thiram is known to elevate AST and ALT levels while reducing serum cholinesterase and hepatic microsomal benzphetamine N-demethylase activity, which can lead to liver toxicity.[158] Exposure to maneb has been found to decrease the expression of SOD and GPx, further inducing ROS-mediated liver injury in mice.[159] Another study indicates that mancozeb exposure results in decreased levels of SOD, GPx, catalase, glutathione, and vitamin C, accompanied by histopathological changes.[160,161] However, the hepatotoxic effects of mancozeb may be mitigated by co-treatment with curcumin, as shown in a rat model. Dithane M-45 has been found to increase liver triglyceride levels and liver weight.[162] Nevertheless, the accumulation of liver triglycerides may be linked to hepatic steatosis.[163] Propoxur, a prominent pesticide within the methylcarbamate group, has been reported to cause increased lipid peroxidation and decreased SOD activity, which may be related to oxidative damage in rat liver.[164] Propoxur has been demonstrated to induce focal inflammation, oxidative DNA damage, and fibrosis in the liver of rabbits.[165] Lycopene, a potent antioxidant, is capable of safeguarding the liver against propoxur-induced toxicity.[166] Carbofuran is a significant insecticide that leads to increased levels of AT, ALT, glutamate dehydrogenase, and glycogen phosphorylase a in the liver tissue of fish models.[167] The effects of carbofuran include alterations in liver histopathology, such as nuclear pyknosis, cytoplasmolysis, and hepatocyte necrosis.[168] Furthermore, carbofuran-treated Wistar rats exhibit a higher number of hepatic cells per mm2, elevated serum γ−GT activity, and histopathological changes in the liver indicating mild periportal cellular infiltration and necrosis.[169] In carbofuran-treated rats, there is an observed increase in serum levels of AST, ALT, and LDH, alongside a decrease in SOD, GST, and catalase levels. Nevertheless, Citrus limon fruit extract may prove beneficial in managing carbofuran-induced liver damage by alleviating oxidative stress.[170] The exposure to carbaryl results in liver damage characterized by vacuolization and necrosis of hepatocytes, accompanied by infiltration of mononuclear cells, hemorrhage, congestion, and enlargement of sinusoids in toads (*Bufotes variabilis*).[171] The toxic effects of carbaryl are evident through the presence of enlarged, swollen, and empty hepatocytes with indistinct cell membranes, as well as enlarged nuclei devoid of membranes, indicating hepatocyte degeneration during carbaryl metabolism in mice.[172] However, similar findings have been reported in another study involving a mouse model.[173] Additionally, carbaryl exposure in catfish (*Clarias batrachus*) results in elevated serum levels of AST, ALT, acid and alkaline phosphatase, and LDH activity, along with increased glycolysis and protein catabolism, suggesting potential hepatocyte damage.[174] In fish models (*Lates calcarifer*), carbaryl exposure leads to oxidative stress induction and necrosis in the liver, as well as immune modulation through the elevation of interleukin-8 and complement component C3.[175] Another CB aminocarb induces liver toxicity as a result of reduced AChE levels and elevated ALP in the liver of rats.[176] The exposure of rats to aldicarb results in a decrease in AChE concentration, accompanied by necrosis and steatosis in the liver.[177]

(d) Pyrethroids (PYR)

PYR is a significant insecticide utilized worldwide. D-tetramethrin is a commonly employed PYR. Reports indicate that D-tetramethrin leads to inflammation, apoptosis, cell proliferation, vacuolation, nuclear distortion, lipid accumulation, and a decrease in glycogen levels in the liver of zebrafish.[178] Research demonstrates that another PYR, permethrin, causes liver damage in Wistar rats by inducing nuclear degeneration in hepatic parenchymal cells.[179] Furthermore, exposure to permethrin exacerbates hepatic and mitochondrial dysfunction, necrosis, and genotoxicity through DNA fragmentation.[180] Nevertheless, *Fumaria officinalis* extract may be beneficial in lowering liver enzymes and providing protection against permethrin-induced liver injury. Additionally, permethrin significantly inhibits the G2 phase of the cell cycle and M-phase (mitosis), resulting in the formation of binuclear hepatocytes, as evidenced in a rat model.[181] In a mouse model, the root extract of Taraxacum officinale has been shown to function as an antioxidant, safeguarding against permethrin-induced liver dysfunction.[182] The toxic effects of permethrin lead to nuclear enlargement, proliferation of Kupffer cells, hydropic degeneration, vacuolation in the cytoplasm, and capillary congestion in hepatocytes.[183] Moreover, the impact of permethrin results in the development of hepatocellular adenomas in the mouse liver.[184] Lambda-cyhalothrin (LCT), another PYR, induces lipid accumulation and activation of AMP-activated protein kinase, ultimately contributing to the progression of liver steatosis.[185] LCT causes liver intoxication in rats by elevating AST, ALT, AChE, and glucose levels.[186] Histopathological examinations of rabbit livers exposed to LCT reveal infiltration of inflammatory cells, necrotic changes, and fibrosis in the periportal regions.[187] A study conducted on a rat model indicates decreased glycogen and pyruvate levels alongside an increase in lactate.[188] LCT exposure leads to a significant increase in vascular endothelial growth factor 2 (VEGFR2) and nuclear factor-κB (NF-κB) in mice, as well as 3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethyl-cyclopropane carboxylic acid (CFMP) and 3-phenoxybenzoic acid (3-PBA) in rat liver.[189, 190] VEGFR2, NF-κB, CFMP, and 3-PBA could serve as potential biomarkers for liver damage induced by LCT. In this context, it has been shown that Panax ginseng effectively protects the liver from LCT toxicity by reducing hepatic oxidative stress and apoptosis.[191] Furthermore, curcumin may help prevent LCT-

induced liver injury by mitigating oxidative damage through the scavenging of free radicals and inhibiting DNA fragmentation.[192] Additionally, Rutin (quercetin-3-rutinoside and sophorin) and Vitamin E may provide protection to the liver against LCT poisoning by alleviating oxidative stress.[193] Flumethrin, another type of PYR, has been demonstrated to decrease UDP-glucuronosyltransferase, aniline hydroxylase, NADPH-cytochrome c reductase, and cytochrome P450 aminopyrine N-demethylase in rat liver microsomes.[194] However, Zinc oxide nanoparticles may offer protection against flumethrin-induced liver damage by reducing oxidative stress.[195] Moreover, the PYR fenvalerate elevates ALT levels, oxidative stress, intracellular calcium ions, and activates the ERK/IKK/NF-κB pathway in rat liver.[196] Nevertheless, the potential antioxidant quercetin may effectively reduce oxidative liver damage caused by fenvalerate.[197] Additionally, transcriptomic analysis indicates that exposure to fenvalerate in fish (*Odontobutis potamophila*) results in a significant upregulation of genes CYTB (cytochrome b) and ND1 (NADH dehydrogenase subunit 1), along with a downregulation of genes COX2 (cytochrome c oxidase subunit II) and COX3 (cytochrome c oxidase subunit III), highlighting the oxidative damage to the liver.[198] The exposure to fenvalerate leads to an increase in microsomal aniline hydroxylase activity and cytochrome P-450 levels, which subsequently affects the liver microsome and liver cell membranes.[199] Mice that are exposed to fenvalerate exhibit a decrease in kynurenine hydrolase and an increase in kynurenine aminotransferase, B-glucuronidase activity, and acid ribonuclease activity in the liver, impacting liver function and protein biosynthesis.[200] Deltamethrin is another PYR known to cause liver damage. A transcriptomic analysis of the liver in Paralichthys olivaceus indicates that deltamethrin induces differential expression of 697 genes related to metabolic disorders, inflammation, oxidative stress, and apoptosis.[201] Rat livers exposed to deltamethrin demonstrate increased lipid peroxidation alongside decreased levels of catalase, superoxide dismutase (SOD), glutathione S-transferase (GST), glutathione (GSH), glutathione reductase (GR), and glutathione peroxidase (GPx).[202] It has been reported that deltamethrin induces oxidative stress and liver steatosis, which may be mitigated by the potential phytochemical resveratrol through the activation of Nrf2 (nuclear factor erythroid 2-related factor 2).[203] Furthermore, N-acetylcysteine exhibits a hepatoprotective effect by lowering AST, ALT, and ALP levels while increasing GSH levels in mice exposed to deltamethrin.[204] Cypermethrin, another PYR, results in elevated levels of AST, ALT, and ALP, along with an increase in Kupffer cells and a decrease in hepatocytes due to necrosis, as well as methylation of the p53 promoter gene, leading to significant liver toxicity in mouse livers.[205] The hepatotoxic effects of cypermethrin in the liver of *Catla catla* are characterized by the induction of oxidative stress, DNA damage through Gadd45α and Bcl-2 gene expression, and histopathological alterations such as vacuolation, pycnosis, sinusoidal dilation, karyolysis, lymphocyte infiltration, and nuclear polymorphism.[206] Nevertheless, sesame oil may offer protective benefits against cypermethrin poisoning by reducing liver enzymes, oxidative stress, and DNA damage.[207] Additionally, quercetin-loaded chitosan nanoparticles have been shown to effectively protect the liver from cypermethrin poisoning.[208] Similar to cypermethrin, cyfluthrin is also implicated in hepatotoxicity as it decreases GPx and AChE levels while increasing MDA levels.[209] The impact of PYR bifenthrin on mouse liver indicates heightened oxidative stress and mitochondrial-dependent cell death.[210] Exposure to bifenthrin results in the induction of lipid peroxidation and oxidative stress in rats.[211] Sub-acute exposure to bifenthrin leads to an increase in interleukin 1ß, suggesting liver inflammation.[212] It has been shown that alphamethrin and chloropyrifos solutions affect the liver of *Clarias batrachus* by inducing histopathological changes, including hemorrhage, infiltration of inflammatory cells, steatosis, and the formation of thick fibrous connective tissue accompanied by necrosis of hepatocytes[213]

3. Fungicide

It has been reported that anti-fungal medications are significant risk factors for drug-induced liver injury.[214] In this context, we have examined the impact of fungicides on liver injury and the associated molecular mechanisms. The fungicides discussed in this section are based on the article published by Jampilek.[215] It has been noted that the combined effects of bupirimate, boscalid, dieldrin, bifenox, and propiconazole lead to increased cholesterol levels and the onset of steatosis and NAFLD.[216] Hepatorenal exposure in a rat model indicates an increase in MDA, upregulation of NF-κB, TNF-α, IL-1β genes, and a decrease in GSH and total antioxidant capacity, suggesting significant inflammation and oxidative stress-induced liver damage.[217] A study conducted on the HepG2 cell line exposed to zoxamide reveals heightened levels of oxidative stress and apoptosis/necrosis.[218] The exposure of HepG2 cells to tolfenpyrad results in disruptions of GSH and purine metabolism, alongside the induction of oxidative stress, mitochondrial damage, and cell death.[219] Tebuconazole, another fungicide, is associated with increased oxidative stress, abnormal metabolic activities, and the expression of liver X receptor α and peroxisome proliferator-activated receptor α, which contribute to liver injury in mice.[220] Exposure to dinocap leads to an increase in liver weight in rats.[221] The toxic effects of fluazinam have been shown to cause uncoupling of liver mitochondria, as demonstrated in rats.[222] Furthermore, it has been reported that exposure to fludioxonil inhibits catalase activity in bovine liver.[223] Additionally, propamocarb affects the synthesis and transport of hepatic bile acids in a mouse model.[224] Moreover, exposure to propamocarb results in dysbiosis of gut microbiota and reduced expression of genes related to glycolysis and lipid metabolism.[225] Exposure to the fungicide propamocarb in mice results in bile acid metabolic disease, attributed to heightened levels of ursodeoxycholic acid,

taurocholic acid, beta-muricholic acid, tauro-beta-muricholic acid, omega-muricholic acid, and tauro-omega-muricholic acid. These changes contribute to dysbiosis within the gut microbiota, an increase in flavin-containing monooxygenase 3 in the liver, and elevated NF-κB levels in the heart. This mechanism may suggest a potential dysfunction of the liver and heart induced by propamocarb.[224] Conversely, the accumulation of dimethomorph has been noted in the liver following exposure in rats.[226] Nevertheless, the toxicity of dimethomorph in the liver has not yet been established. Exposure to mandipropamid has been linked to an increase in liver weight in rat model.[227] The effects of benthiavalicarb reveal non-neoplastic changes, including increased liver weight, alterations in biochemical parameters, histopathological changes, and neoplastic developments such as hepatocellular adenoma and hepatoblastoma, among others.[228] Additionally, exposure to valifenalate results in elevated liver enzymes, increased uridine 5′-diphospho-glucuronosyltransferase levels, and liver injury.[229] The toxic effects of tricyclazole are characterized by increased reactive oxygen species (ROS), hepatocyte apoptosis, and abnormal carbohydrate and lipid metabolism, ultimately leading to liver damage in zebrafish.[230] The impact of metrafenone is associated with an increase in liver weight.[231]

Conclusion

The increasing application of pesticides poses a significant risk factor for serious health complications. The global utilization of pesticides is a major contributor to environmental pollution, which includes the contamination of soil, water, and air. Furthermore, exposure to pesticides is directly associated with occupational health risks. In this context, pesticide residues found in food and water can have detrimental effects, leading to considerable organ damage, such as liver dysfunction. A comprehensive review of literature encompassing various animal studies and cell culture analyses indicates that three primary categories of pesticides are frequently employed: herbicides, insecticides, and fungicides. The chemical toxicity and adverse effects of these pesticides are potentially linked to the risk of liver injury. The toxicological impact of pesticides is associated with the pathogenesis of non-alcoholic fatty liver disease (NAFLD), metabolic-associated fatty liver disease (MAFLD), non-alcoholic steatohepatitis (NASH), hepatitis, and hepatocellular carcinoma. Both in vivo and in vitro exposure to pesticides demonstrates alterations in hepatocyte morphology and cellular function. Additionally, pesticide exposure leads to increased liver enzyme activities, tissue inflammation, oxidative stress, leukocyte infiltration, and lipid accumulation. Pesticides have the potential to interfere with the gut-liver axis through reducing beneficial gut microbes. These physiological changes in the liver ultimately result in heightened liver fibrosis and altered liver function, which may correlate with severe liver damage or even hepatic failure. It has also been observed that the use of naturally derived antioxidants plays a beneficial role in preventing and controlling pesticide-induced liver damage. Following a thorough examination of various research articles, it can be concluded that enhanced safety measures are essential during the application of hazardous pesticide agents. Nevertheless, it would be prudent to limit the use of chemical pesticides. Moreover, the promotion of organic farming should be encouraged to reduce pesticide-induced liver injury and its clinical manifestations. It is imperative to ban the use of pesticides that exhibit the highest toxicity to humans, as well as those that remain in the environment for prolonged periods. It is also necessary to safeguard public health by establishing maximum allowable limits for pesticide residues in food and water.

Authorship Contribution Statement

SS was involved in study design, literature survey, data interpretation, writing, review, and editing of the article, AS, PM, NS, RPS, and GB were involved in review, and editing of the article.

Declaration

No potential conflict of interest was reported by the authors.

Ethical statements

There are no biological samples or subjects included in this study.

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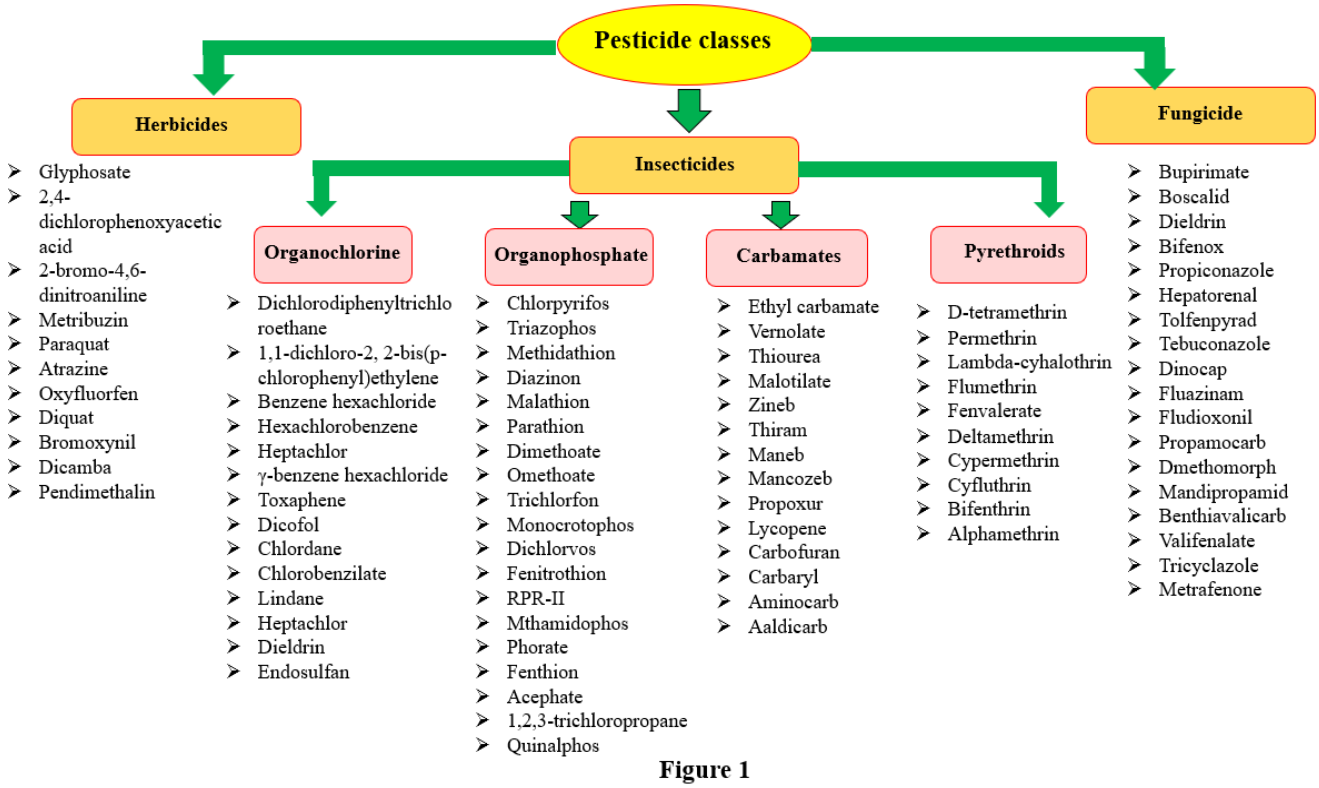

Figure 1

Figure1 Major classes of pesticides. Pesticides are diversified as herbicide, insecticide, and fungicide. Insecticides are further classified into organochlorines, organophosphates, carbamates, pyrethroids.

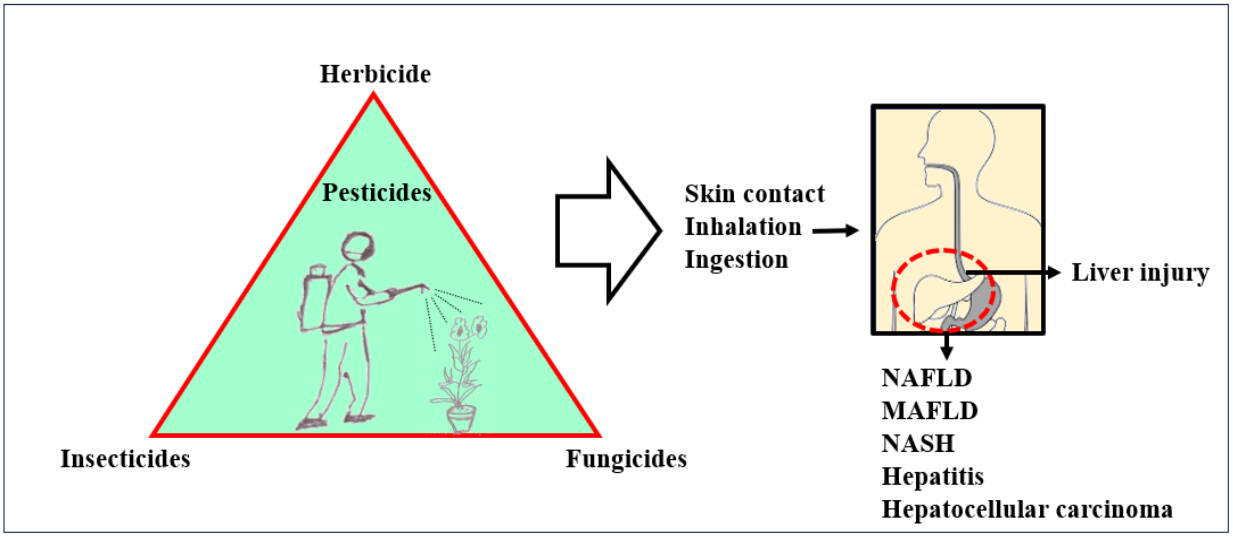

Figure 2

Figure 2. Role of pesticides in hepatotoxicity. Pesticides are mainly introduced into body through skin contact, inhalation through nose and mouth, and ingestion through mouth. Exposure of pesticides causes different liver diseases such as NAFLD, MAFLD, NASH, hepatitis, and hepatocellular carcinoma.

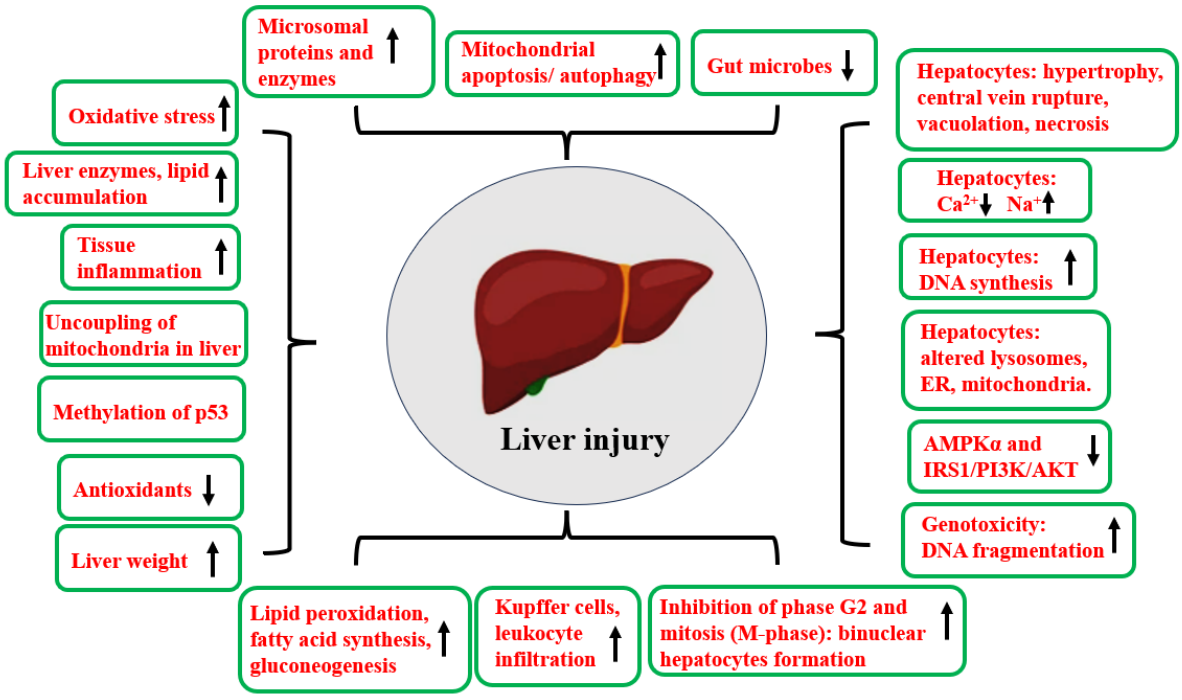

Figure 3

Figure 3. Pesticides significantly cause the changes of normal physiological processes in liver. The symbols "↑" and "↓" are respectively for the representation of "high" and "low".

Table 1. **Therapeutic agents for the prevention of pesticide-induced liver injury**

Sr. No.	Therapeutic agent	Pesticide	Therapeutic functions in liver	Reference
1	Eugenol	Chlorpyrifos	Increases AChE activity and reduces oxidative stress	Nikbin et al. 2020
2	Beet root	Chlorpyrifos	Increases Nrf2 expression and prevent liver histological changes, inflammation, oxidative stress.	Albasher et al. 2019
3	Essential oil from *Artemisia campestris* and fennel seeds	Chlorpyrifos	Reduction of oxidative stress	Saoudi et al. 2021; Samadi-Noshahr et al. 2020
4	Zinc supplementation	Chlorpyrifos	Safeguarding membranous organelles and preventing the obstruction and constriction of biliary channels in hepatocytes	Goel and Dhawan 2001
5	Root of the *Salvia miltiorrhiza*	Diazinon	Reduction of glutathione	Lu et al. 2010; Ren et al. 2010
6	Ferulic acid, alpha-lipoic acid	Dimethoate	Protection to the liver against elevated liver enzymes (AST, ALT, and ALP). Restoration of normal hepatic histomorphology.	Abdelsalam bioRxiv
7	Vitamin E and N-acetylcysteine	Dimethoate	Reduction of liver enzymes, oxidative stress, lipid peroxidation, and DNA damage	El-Saad and Elgerbed 2010
8	Vitamins C, E, and lycopene	dichlorvos	Reduces liver weight, serum total protein, albumin, triglyceride, low density lipoprotein-cholesterol VLDL.	Ogutcu et al. 2008
9	Saponarin	Fenitrothion	Targeting JAK1/STAT3, TLR4/MYD88, and NF-κB pathways	Hassan et al. 2025
10	*Artemisia campestris* leaf powder	Fenthion	Reduction of oxidative stress	Sefi et al. 2011
11	Vitamins E and C	Quinalphos	Reduction of reducing oxidative stress	Udayakumar et al. 2024
12	*Citrus limon* fruit extract	Carbofuran	Reduction of oxidative stress	Jaiswal et al. 2015
13	*Fumaria officinalis* extract	Permethrin	Lowering of liver enzymes	Kostka et al. 2000
14	*Panax ginseng*	Lambda-cyhalothrin	Reduction of hepatic oxidative stress and apoptosis	Abdul-Hamid et al. 2020
15	Rutin (quercetin-3-rutinoside and sophorin) and Vitamin E	Lambda-cyhalothrin	Reduction of oxidative stress	Abdellatif et al. 2020
16	Zinc oxide nanoparticles	Flumethrin	Reduction of oxidative stress	Fayeq et al. 2023
17	N-acetylcysteine	Deltamethrin	Lowering of liver enzymes (AST, ALT, and ALP) levels	Ameri et al. 2024
18	Sesame oil	Cypermethrin	Reduction of liver enzymes, oxidative stress, and DNA damage	Abdou et al. 2012
19	Quercetin-loaded chitosan nanoparticles	Cypermethrin	Hepatoprotective function	Ashraf et al. 2025