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Hesperidin, a flavone glycoside isolated from citrus fruits, can be used to facilitate Chlorpyrifos pollution side effect

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ABSTRACT

Chlorpyrifos (CPF) is an organophosphate pesticide widely used in agriculture. It poses significant health risks due to its neurotoxic, hepatotoxic, and reproductive effects. Given that current treatments for the health problems caused by hazardous toxins are inadequate and highlight the need for new treatments, this study investigated the effects of hesperidin, a flavonoid from citrus fruits, in reducing the harmful effects of CPF exposure. Based on the results, hesperidin treatment significantly improved cell viability and reduced oxidative damage markers such as malondialdehyde (MDA) and superoxide dismutase (SOD) levels, along with oxidative stress factors. It can augment the antioxidant cellular defenses via the ERK/Nrf2 signaling pathway, reduce inflammatory targets, and inhibit lipid peroxidation. Histopathological analysis of the organs showed that hesperidin reduced inflammation and collagen accumulation in liver tissue, suggesting its protective role in maintaining liver structure. Furthermore, hesperidin appears to counteract the pro-apoptotic effects of CPF, as evidenced by lower levels of cell death markers. These findings highlight the potential of hesperidin as a therapeutic agent against CPF-induced damage and emphasize its antioxidant and anti-inflammatory properties. This study supports further research into hesperidin and similar plant compounds as potential solutions to pesticide-related health issues. This research advances our understanding of how natural substances can mitigate the harmful effects of environmental pollutants and paves the way for future studies in this area.

Keywords: Chlorpyrifos, Side effects, Hesperidin, Organs.
Article type: Review Article.

INTRODUCTION

Pesticides are integral to agricultural practices and public health initiatives, as they effectively target agricultural pests, minimize food wastage, and regulate disease-carrying vectors that threaten humans and animals alike. By the continuous increase in the global population, the necessity for enhanced food production has resulted in a greater reliance on pesticides. Among the most prevalently utilized are organophosphate pesticides (OPs),

synthesized from phosphorus-containing compounds, including phosphoric and phosphorothioic acids (Sharma *et al.* 2019). Annually, around 2 million tons of pesticides are applied worldwide, with forecasts suggesting an escalation to 3.5 million tons by 2020, of which approximately 40% comprises OPs. Despite their more than fifty years of application for pest management, the utilization of OPs has markedly surged following the prohibition of organochlorine pesticides (Carvalho 2017; Tudi *et al.* 2021). This increase is primarily attributed to the relatively short environmental persistence of OPs and their comparatively diminished health hazards relative to organochlorine alternatives. Nevertheless, inappropriate methods concerning the use, storage, transportation, application, and disposal of pesticide residues pose threats to non-target organisms. OPs may infiltrate organisms via three principal exposure routes: oral, respiratory, and dermal (Kwong 2002; Sidhu *et al.* 2019). Chlorpyrifos, scientifically designated as O, O-diethyl O-3,5,6-trichloro-2-pyridyl phosphorothioate, manifests as white or colorless crystalline substances and is employed to manage a variety of pests, such as termites, mosquitoes, and nematodes. It has been approved for application in both agricultural and non-agricultural contexts since 1965 (Nandi *et al.* 2022). Human exposure to this pesticide can transpire through ingestion, inhalation, or dermal contact with mucous membranes. As a result, CPF is frequently identified in environmental samples, eliciting considerable public health apprehensions. Between the years 2000 and 2019, a plethora of studies examined the neurodevelopmental, hepatic, and gastrointestinal repercussions associated with CPF; however, numerous potential effects of this toxicant remain insufficiently investigated, suggesting that CPF formulations may not guarantee safety for consumers (Saunders *et al.* 2012). In Iran, CPF is widely utilized in agricultural practices, with its residues on crops presenting health risks to humans, as indicated by various scholarly investigations. CPF has been detected in diverse environmental matrices, including surface waters, seawater, and precipitation (Kermani *et al.* 2021). In research conducted by Zhong *et al.*, samples of arctic air and seawater were gathered during an oceanographic expedition from the North Pacific to the Arctic Ocean. Their results confirmed the occurrence of CPF in that region, with concentrations ranging from 0.08 to 0.85 pg L^{-1} in seawater and 0.5 to 2 pg m^{-3} in the atmosphere. Generally, marine waters exhibited lower CPF concentrations than surface waters. Remarkably, precipitation demonstrated relatively high CPF levels, with concentrations fluctuating between 30 to 200 ng L^{-1} (Zhong *et al.* 2012; Wołejko *et al.* 2022). Current therapeutic interventions exhibit constrained efficacy in halting and averting the symptomatic advancement of degeneration, primarily serving to mitigate symptoms instead of addressing fundamental pathologies. Consequently, there is an urgent need to innovate alternative pharmacological substances aimed at the prevention and safeguarding of these age-related disorders. Naturally occurring substances present viable options that may assist in the management of the progression of such conditions. Aromatic botanicals represent a significant class of herbal agents historically employed as protective substances. A plethora of natural polyphenols, including flavonoids, phenolic acids, and vitamins, have been shown to confer notable health benefits for humans. These phytochemicals' antioxidant and anti-inflammatory characteristics have been validated through comprehensive investigations (Zeng *et al.* 2021; Yönden *et al.* 2022; Pyrzynska 2022). Hesperidin belongs to the flavone group, a subclass of flavonoids, and is found in citrus fruits like oranges, grapefruits, tangerines, limes, and lemons. After oral consumption, hesperidin undergoes hydrolysis by intestinal microbiota, resulting in aglycone, which is then converted to glucuronide in the large intestine. These metabolites are further processed into phenolic acids. Research indicates that hesperidin may help alleviate neurodegenerative symptoms associated with conditions such as Alzheimer's, Parkinson's, Huntington's disease, depression, multiple sclerosis, brain ischemia-reperfusion injury, and traumatic central nervous system injuries while also mitigating CPF effects in various animal models (Al-Goblan *et al.* 2014; Crescenti *et al.* 2022). Although pesticide use has enhanced product quality, its potential impacts on vital organs remain uncertain, prompting further investigation by researchers.

Organophosphate pesticides and their effect on organs

Pesticides are widely employed in agricultural practices and public health initiatives to eliminate food-related pests, decrease food spoilage, and control vectors responsible for transmitting diseases to humans and animals. As the global population continues to expand, the demand for heightened food production has increased pesticide dependency. Notably, organophosphate pesticides rank among the most frequently utilized, deriving from phosphorus compounds such as phosphoric and phosphorothioic acids (Sharma *et al.* 2019). Each year, roughly 2 million tons of pesticides are utilized globally, with expectations of rising to 3.5 million tons by 2020, of which approximately 40% are OPs. In addition, it is estimated that more than 3 million people are subjected to OP

exposure annually, resulting in around 300,000 deaths worldwide (Bernal-González *et al.* 2023; Sharma *et al.* 2019). The dietary route predominates for absorption, while respiratory uptake is contingent upon the compounds' chemical characteristics and environmental stability. The polarity and solubility of the substances involved influence dermal absorption. Upon entry into the organism, OPs are distributed and metabolized into more water-soluble forms to facilitate excretion (EFSA *et al.* 2017; Carvalho 2017; Wołejko *et al.* 2022).

Annually, an estimated 2 million metric tonnes of pesticides are employed globally, with China identified as the predominant nation in this regard, followed by the United States and Argentina, where usage is escalating rapidly. Nonetheless, research in 2020 indicated that worldwide pesticide consumption was anticipated to rise to approximately 3.5 million metric tonnes (Sharma *et al.* 2019). The summary of the structure and kinds of pesticides is mentioned in Fig. 1.

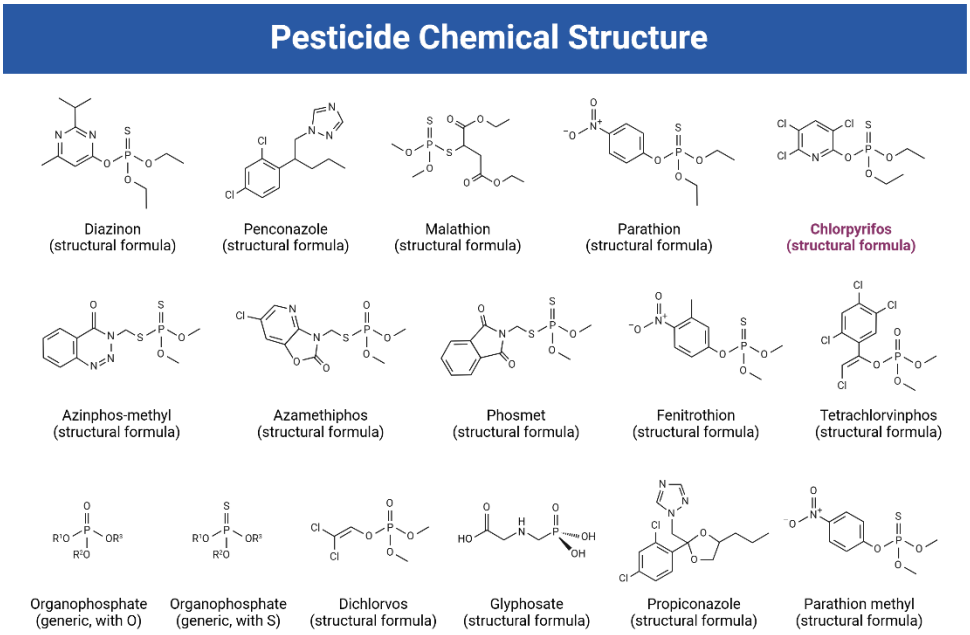

Fig. 1. Summary of different pesticides and structures.

Organophosphates possess multiple mechanisms of action, with the neurotoxic mechanism being the most thoroughly investigated. This mechanism entails the inhibition of the enzyme acetylcholinesterase (AChE) via the phosphorylation of the serine amino acid located at the carboxyl-terminal site within the enzyme's active site. Such inhibition obstructs the hydrolysis of the neurotransmitter acetylcholine, leading to increased concentrations of ACh at the synaptic cleft. This accumulation results in excessive activation of both muscarinic and nicotinic receptors, potentially inducing toxic effects in the impacted organisms' neuronal and non-neuronal tissues. As a result, the perturbation of the cholinergic system by OPs may correlate with a variety of sensory, motor, immunological, endocrine, and neurological disturbances, which could contribute to the development of several diseases, including cancer, hypersensitivity, neurodegenerative ailments, infections, and diabetes (Ahmad *et al.* 2024). In recent decades, agricultural practitioners have adeptly employed pesticides to alleviate the potential for considerable crop losses attributable to pests, weeds, and various diseases. However, the pervasive application of these agrochemicals has concurrently led to varying degrees of environmental contamination. Presently, pesticide residues are discernible across multiple environmental matrices, including air, water, soil, and sediments, resulting in human exposure to various pesticides from assorted origins (BRIEF 2022; Wisnujati 2023). Epidemiological investigations disclose that pesticide poisoning affects at least 3% of agricultural laborers in developing countries. Moreover, exposure to these chemicals is closely associated with the emergence of numerous health problems, including malignancies, congenital anomalies, immune system impairments, respiratory disorders, as well as neurobehavioral and reproductive complications. Prior studies have established that pesticides can adversely affect diverse tissues and organs by inducing genetic alterations, epigenetic modifications, endocrine disruption, mitochondrial dysfunction, oxidative stress, endoplasmic reticulum stress, a compromised unfolded protein response, defective autophagic processes, and disruption of the ubiquitin-proteasome pathway (Alavanja 2009).

The central and peripheral nervous systems are the primary targets for chlorpyrifos toxicity, primarily due to the chlorpyrifos-oxon metabolite's capacity to inhibit acetylcholinesterase activity, which is essential for terminating neurotransmission at cholinergic synapses. Evidence suggesting toxicological effects of chlorpyrifos in tissues outside the nervous system is minimal. Standard toxicological bioassays have not identified significant toxicity in organ systems other than the nervous system, particularly at doses below those that produce overt neurological effects. At doses that do not result in apparent maternal toxicity, chlorpyrifos is not regarded as teratogenic (Eaton *et al.* 2008). While studies on mutagenicity and chronic animal bioassays for carcinogenicity have yielded mainly negative results for chlorpyrifos, a recent epidemiological investigation involving pesticide applicators indicated a significant exposure-response trend linking chlorpyrifos use to lung and rectal cancer. However, this association was based on a limited number of cases, with fewer than 10 excess cases of rectal cancer observed in the two highest exposure groups. The small sample size and uncertainty regarding exposure levels necessitate caution in interpreting this statistical association as indicative of a causal relationship (Eaton et al. 2008). More than one study would be required to establish a consistent causal link between chlorpyrifos and the lung or rectal cancer. While these studies highlight potential issues, the simultaneous collection of exposure-related and outcome data hinders the establishment of a proper temporal sequence. Additionally, the "within-individual" variability and other errors associated with single test results for urinary and sperm measurements pose significant limitations to the research (Eaton *et al.* 2008). No evidence suggests that chlorpyrifos is hepatotoxic, nephrotoxic, or immunotoxic at doses lower than those that lead to significant cholinesterase poisoning. A series of clinical studies involving male patients at a fertility clinic revealed an inverse correlation between urinary 3,5,6-trichlorpyridinol(TCPy) levels and various indicators of male reproductive health. Therefore, it can only be concluded that this report identifies correlations between urinary TCPy levels and various male reproductive outcomes, which warrants further investigation in more robust studies (Eaton *et al.* 2008). For the last twenty years, the assessment of exposure to chlorpyrifos has predominantly utilized the urinary biomarker 3,5,6-trichloro-2-pyridinol (TCPy), which is a metabolic byproduct of chlorpyrifos. Until recently, most studies measuring TCPy in urine operated under the assumption that chlorpyrifos was the exclusive source of TCPy, thereby equating the molar equivalents of TCPy found in urine to daily chlorpyrifos exposure. This assumption suggested that exposure to chlorpyrifos was widespread, as most population-based studies with detection limits exceeding 1 $\mu g\ L^{-1}$ (ppb) reported TCPy in over 95% of urine samples (Farahat *et al.* 2011). On the other hand, the detrimental effects of OPs on the immune system have predominantly been investigated in mammalian species, utilizing models such as rats, mice, rabbits, and humans. The principal outcomes observed in these animal studies are summarized below (Díaz-Resendiz *et al.* 2015). In murine, rat, and rabbit models, exposure to malathion has resulted in modifications in macrophage cell migration, with analogous results documented in albino rats subjected to subchronic exposure to phosphamidon. Furthermore, in rat models, *in vitro* exposure to malathion has been shown to directly diminish nitrite production, while LPS-stimulated macrophages exhibited a reduction in TNF-α secretion. Similarly, chronic exposure to acephate in rats led to decreased levels of TNF-α and inducible nitric oxide synthase (iNOS) in LPS-activated macrophages. Organophosphates are also associated with the dysregulation of mast cells and basophils, potentially contributing to allergic responses. In this regard, malathion has been found to enhance mast cell degranulation and phagocytic activity in murine models (Banerjee *et al.* 1998; Massoud *et al.* 2022). In humans, repeated exposure to immunomodulatory contaminants complicates the evaluation of specific immunotoxic effects attributable to OPs. Nonetheless, scientific literature suggests that OPs manifest immunotoxic effects. In this regard, OPs have the potential to modulate neutrophil-mediated immunity, as evidenced in individuals with occupational exposure (Banerjee *et al.* 1998). Moreover, metabolites of the pesticide malathion have been demonstrated to trigger histamine release in human basophilic cells. The complement system, a crucial component of the immune defense against pathogens, may also be affected by OP exposure. Dimethoate and chlorpyrifos have been found to disrupt pro-inflammatory cytokines (IL-1β and IL-8), while downregulating the anti-inflammatory cytokine (IL-10), as well as the signaling pathways involving Akt and ERK in dendritic cells exposed to OPs. Exposure to malathion has been shown to inhibit the production of interferon-beta (IFN-β) by macrophages (Rajak *et al.* 2021; Camacho-Pérez *et al.* 2022).

Natural product components effects on OP side effects

Flavonoids and their respective subclasses exhibit multi-targeting capabilities at active cerebral sites. Several phytochemicals, such as quercetin, fisetin, and rutin, have been identified as neuroprotective agents against Aβ

accumulation. Moreover, epigallocatechin-3-gallate (EGCG, a green tea polyphenol) has exhibited inhibitory properties against neurotoxicity induced by Aβ. These compounds have significantly impacted various other neurodegenerative diseases (PD, HA, and ALS; Zeng *et al*. 2021). In light of the aforementioned considerations, medicinal plants and their associated phytochemicals are strongly advocated as alternative and adjunctive therapies for neurodegenerative diseases. Notably, flavonoids and their subclasses have been identified as particularly effective against age-related conditions. Thus, the current investigation explored the neuroprotective properties of hesperidin, recognized as one of the most potent isoflavones (Celik *et al.* 2016; Crescenti *et al.* 2022). Plants represent a preeminent source for the biosynthesis of bioactive natural compounds, offering considerable alternatives to the currently employed chemical or synthetic pest control substances. All natural compounds produced by plants are categorized into primary and secondary metabolites. Primary metabolites include fundamental building blocks of life, such as nucleic acids, proteins, lipids, and carbohydrates. Secondary metabolites are further classified into phenolics (which encompass phenolic acids, lignin, tannins, flavonoids, stilbenes, lignans, and coumarins), terpenes (including carotenoids, cardiac glycosides, plant volatiles, and sterols), and nitrogen-containing compounds (such as glucosinolates and alkaloids; Farahat *et al.* 2011). Secondary metabolites play a crucial role within plants, contributing to their defensive mechanisms against herbivorous organisms and insects. Essential oils fall within the category of bioactive agents derived from plants. These essential oils (also referred to as aromatic oils) consist of volatile natural products that plants produce as part of their self-defense strategy, distinct from nutritional functions such as attraction and protection. These oils are characterized by their distinctive odor and comprise natural antimicrobial and antioxidant substances. Essential oils are typically utilized in various applications, including incense, cosmetics, pharmaceuticals, perfumery, household cleaning agents, aromatherapy, and flavor enhancers in beverages and food (Yuan *et al.* 2016; Hattiwale *et al.* 2022; Mazinani *et al.* 2022; Silveira Martinez *et al.* 2022). Flavonoids are categorized as secondary metabolites derived from plants, recognized for their potent antioxidant capabilities. Based on variations in their chemical structures, flavonoids can be delineated into categories such as flavonols, flavanones, isoflavones, and anthocyanins. Prior research has demonstrated the utilization of various cellular and animal models to explore the *in vitro* and *in vivo* interactions between plant-derived flavonoids and pesticides. The findings substantiate the protective role of flavonoids in counteracting pesticide-induced toxicity, offering novel therapeutic strategies for injuries resulting from acute or chronic pesticide exposure (Farahat *et al.* 2011). Consequently, this manuscript provides a critical review of the dietary flavonoid hesperidin, which exhibits preventive properties against pesticide-induced toxicity and explores the potential mechanisms of action. Furthermore, we address the unresolved issues that warrant attention in future investigations and highlight the challenges associated with the advancement of flavonoids as therapeutic agents for pesticide poisoning. To our knowledge, this constitutes the inaugural systematic review that encapsulates specific flavonoids with ameliorative capabilities against pesticide-induced toxicity and elucidates the mechanisms underlying the interactions between dietary flavonoids and pesticides, which could inform the development of effective intervention strategies aimed at alleviating the toxic repercussions of pesticide exposure in affected individuals (Zeng *et al.* 2021).

Hesperidin

Hesperidin ($C_{28}H_{34}O_{15}$) is a flavanone glycoside, predominantly occurring in citrus fruits such as lemons, sweet oranges (*Citrus sinensis*), and grapefruits. The identification of this compound has also been confirmed in immature sour oranges, Ponderosa lemons, *Citrus unshiu*, and *C. mitis*. Beyond the *Citrus* genus, it can be extracted from various other plant families, including Fabaceae, Papilionaceae, Betulaceae, Lamiaceae, and *Zanthoxylum* species (*Z. avicennae* and *Z. cuspidatum*), along with *Acanthopanax setchuenensis*. Neohesperidin (an isomer of hesperidin) is a bitter compound located in bitter orange (*Citrus aurantium*; Pyrzynska 2022). Hesperidin possesses an aglycone (hesperitin or methyl eriodictyol) linked to rutinose and/or as a disaccharide within its molecular architecture. Consequently, hesperidin can be classified as a β-7-rutinoside of hesperetin. Notably, hesperidin and its derivatives are prevalent in citrus fruits (Rutaceae family), including orange (*C. sinensis*), grapefruit (*C. paradise*), tangerine (*C. reticulata*), lime (*C. aurantifolia*), and lemon (*C. limon*). The concentration of these compounds within citrus fruits is contingent upon the specific fruit variety, the part of the fruit analyzed, climatic conditions, and the degree of ripeness (Kim *et al.* 2019; Imperatrice *et al.* 2022; Wdowiak *et al.* 2022). As noted in the review by Gattuso *et al.*, 100 mL suitable juice contains 20–60 mg hesperidin for oranges, 8–46 mg for tangerines, 4–41 mg for lemons, and 2–17 mg for grapefruits. The citrus

flavedo (the pigmented outer layer of the peel) and albedo (the white spongy inner layer) exhibit higher concentrations of hesperidin than freshly squeezed juice. Commercial juices, particularly those extracted with peel components, are abundant in this flavanone. Beyond citrus fruits, hesperidin has also been identified in mint species (*Mentha*), honeybush (*Cyclopia maculata*), and flavored teas. Notably, hesperetin, the aglycone derivative of hesperidin, is less prevalent than its glycosidic forms (Gattuso *et al.* 2007). Hesperidin exerts antioxidant activities, such as radical scavenging activity, a high reducing power, iron chelating activity, anti-inflammatory and antimicrobial effects, and stimulation of endogenous antioxidant genes in most organisms (Fig. 2). Upon oral administration, hesperidin is hydrolyzed by rhamnosidases produced by gut microbiota in the small intestine and primarily in the colon, converting it into its aglycone form (hesperetin), which is subsequently transformed into glucuronides in the large intestine (Gattuso *et al.* 2007). Hesperetin is detectable in plasma approximately three hours post-ingestion, predominantly as glucuronides (87%) and sulfoglucuronides (13%), with peak concentrations occurring between five and seven hours. These compounds subsequently undergo ring fission and catabolism, yielding phenolic acids and their corresponding metabolites. Nonetheless, hesperidin is characterized by low solubility in water and limited bioavailability. Various strategies have been proposed to enhance its bioavailability, stability, and controlled release, including the micronization and encapsulation of hesperidin, particularly for pharmaceutical applications (Gattuso *et al.* 2007; Pyrzynska 2022).

Biological effects of hesperidin due to CPF toxicities

Numerous biological and pharmacological properties have been documented for hesperidin. It exhibits antioxidant, anti-inflammatory, and anti-carcinogenic effects. Hesperidin has demonstrated a notable mediatory role in both extrinsic and intrinsic apoptosis pathways across various cancer cell types. Both hesperidin and its aglycon, hesperetin, have shown efficacy against a range of malignancies, including gastric, colon, lung, liver, breast, and prostate cancers. In addition to the anti-cancer properties of hesperidin, the influence of isoflavones on cancer-related inflammation has also been established. It has been shown to inhibit inflammatory-mediated cancers by modulating levels of inflammatory mediators (Gattuso *et al.* 2007).

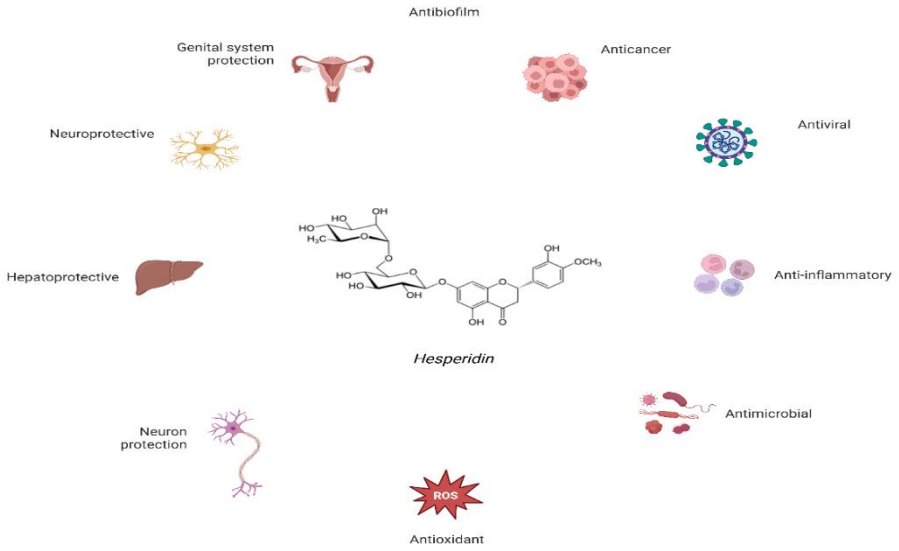

Fig. 2. The different effect of hesperidin on various organs.

There is significant interest in using plants as rich sources of natural antioxidants. Hesperidin, a notable component, is recognized for its antioxidant properties and medicinal benefits, including anti-diabetic, anti-inflammatory, wound-healing, and protective effects on the liver, heart, and nervous system. The compound vinyl phenol hesperidin combines vinyl phenol, a natural phenolic compound found in several plants, with hesperidin, a flavanone glycoside present in citrus fruits. This combination may offer potential health advantages, particularly regarding antioxidant and anti-inflammatory effects (Parhiz *et al.* 2015). The impact of hesperidin administration on vascular disorders, including edema, hemorrhaging, pleurisy, Henoch-Schonlein purpura (HSP), and tuberculosis, has been noted, primarily through the capillary permeability reduction and capillary resistance

enhancement. It also demonstrates antihypercholesterolemic, antihyperlipidemic, antihypertensive, and diuretic effects and functions as a calcium channel blocker (Yap *et al.* 2021). The *in vivo* application of phosphorylated hesperidin produced an anti-fertility effect. Biological actions attributed to hesperidin include immuno-modulatory activity, anti-depressant effects, anti-allergic properties, ultraviolet protection, platelet aggregation inhibition, and wound healing potential. Beyond the previously mentioned biological functions, hesperidin exhibits significant neuroprotective effects in various neurodegenerative conditions, including Alzheimer's, Parkinson's, stroke, and Huntington's disease (Yap *et al.* 2021; Ayomide *et al.* 2023). Additionally, Hesperidin (Hsd) and its aglycone, hesperetin (Hst), represent two flavonoids derived from citrus species that exhibit many biological activities, particularly in the realms of antioxidant and anti-inflammatory effects. Recent investigations have demonstrated that the antioxidant capacity of Hsd/Hst extends beyond mere radical scavenging, as it enhances cellular antioxidant defenses. A plenty of *in vitro* and *in vivo* experiments have been performed to assess the efficacy of Hsd, its metabolites, or its synthetic derivatives in attenuating inflammatory targets such as NF-κB, iNOS, and COX-2, in addition to various indicators of chronic inflammation (Parhiz *et al.* 2015). One of the merits of hesperidin therapy is its safety profile, non-accumulative characteristics, and minimal adverse effects, even during gestation. It has been safely administered at doses up to 5% without inducing mutagenic, toxic, or carcinogenic impacts in mice, even after 13 weeks (Y. Li *et al.* 2019; Wdowiak *et al.* 2022). The restricted bioavailability of hesperidin and hesperetin is another critical aspect that should be addressed. Various strategies have been proposed to mitigate this challenge. For instance, the micronization of hesperetin has significantly improved bioavailability and facilitated its absorption into the systemic circulation (Gattuso *et al.* 2007; Parhiz *et al.* 2015). Research has shown that free radicals produced by pesticides in animal models can be effectively neutralized by antioxidants such as vitamin C, vitamin E, taurine, α-lipoic acid, β-carotene, and glucosinolates. Flavonoids, secondary metabolites found in plants, are recognized for their potent antioxidant capabilities. Based on their distinct chemical structures, they can be categorized into various types, including flavonols, flavanones, isoflavones, and anthocyanins. Previous research has employed various cell and animal models to explore the interactions between plant flavonoids and pesticides, both *in vitro* and *in vivo*. The findings support the protective role of flavonoids against pesticide-induced toxicity and suggest new therapeutic approaches for addressing acute or chronic exposure injuries (Zeng *et al.* 2021). Numerous epidemiological and experimental studies have established a link between pesticide exposure and the development of various human diseases. Specifically, pesticide exposure has been correlated with several cardiovascular issues, including abnormalities in electrocardiograms, myocardial infarction, functional remodeling, and histopathological damage such as hemorrhage, vacuolization, and signs of apoptosis and degeneration. Furthermore, it has been associated with increased oxidative stress in both systemic and cardiac tissues and DNA damage in cardiac cells, which may result in functional impairments (Li *et al.* 2015). Initial research indicates that pesticide chemicals can trigger oxidative stress, generating free radicals and disrupting the antioxidant or free radical-scavenging enzyme systems. Increasing evidence suggests that oxidative stress is a primary factor in stimulating apoptosis across various diseases, including cardiovascular conditions, with reactive oxygen species (ROS) promoting this process. Consequently, this mechanism may be mitigated by abundant natural antioxidants (Li *et al.* 2015; Mitkovska & Chassovnikarova 2020). Demethylation has been documented in various species, including mice, rats, cattle, salmon, and humans, across multiple tissues such as the brain, liver, heart, and spleen. Internal factors contributing to changes in genomic methylation patterns are often linked to variations in gene expression and the activities of DNA methyltransferases, particularly DNA methyltransferase 1 (DNMT1), as well as demethylases. Alongside these internal influences, external factors such as pharmaceuticals, tobacco, environmental toxins, dietary habits, and ultraviolet radiation also play a significant role in this process. Several dietary components can influence DNA methylation through at least two distinct mechanisms. Firstly, nutrients can impact the availability of methyl groups, affecting the biochemical pathways involved in methylation. For instance, the consumption of folate may alter the DNA methylation pattern of the p53 gene, potentially leading to liver cancer. At the same time, arsenic present in the diet has been associated with DNA hypomethylation in the liver. Additionally, the intake of vitamin A and its derivatives can modulate DNA methylation by influencing the metabolism of methyl groups (Xing *et al.* 2015; Pallotta *et al*. 2019; Barzi *et al*. 2020). In mice exposed to CPF, liver enzyme and hormone levels were elevated relative to the other groups. Additionally, the mRNA expression of Bax in the embryos significantly increased in the CPF group compared to the sham and control groups. The expression of Caspase3 and Caspase9 proteins indicated a heightened apoptosis rate in the embryos of the CPF group (Vahabi Barzi *et al.*

2022). Prolonged exposure to Chlorpyrifos appears to adversely affect pregnancy and enhance the apoptotic mechanisms during embryonic development, potentially leading to abortion or the occurrence of teratogenic disorders in embryos. In the other experimental study, the CPF group of mice exhibited a significantly lower number of embryos and maternal weight than the other two groups. Additionally, the mRNA levels of Caspase3 and Caspase9 were markedly elevated in the CPF group. Protein expression analysis corroborated the findings observed at the mRNA level. Furthermore, the percentage of Caspase9 DNA methylation in embryos from the CPF group was higher than in the other groups. This suggests that exposure to chlorpyrifos may influence DNA methylation patterns and enhance the expression of apoptotic genes. Consequently, prolonged exposure to chlorpyrifos could potentially impact pregnancy by promoting apoptosis in developing embryos, which may result in abortion or teratogenic effects in newborns (Barzi *et al.* 2020; Vahabi Barzi *et al.* 2022). In an experimental study, forty adult female bulb/c mice were allocated into four distinct groups: hesperidin (20 mg kg^{-1}, i.p.), malathion (3 mg kg^{-1}, i.p.), malathion + hesperidin, and a control group. Following an uninterrupted treatment period of 35 days, findings indicated that exposure to MAL induced structural and architectural abnormalities within the ovaries. Furthermore, MAL treatment resulted in a reduction of follicular counts across all three developmental stages: primary, secondary, and tertiary, alongside diminished serum concentrations of sex hormones, lowered immunoreactivity of FSHR and PCNA, and decreased enzymatic activity of CAT and SOD (Talebi *et al.* 2024). Conversely, it led to an elevation in MDA, IL-1β, and TNF-α levels and an upraise in the number of atretic follicles. Nonetheless, it was noted that HES demonstrated efficacy in mitigating the harmful effects of malathion across all previously mentioned parameters. The administration of HES, through the upregulation of PCNA and FSHR protein expression and the activation of antioxidant defenses, successfully ameliorated the adverse effects of MAL on ovarian tissues (Talebi *et al.* 2024). Chlorpyrifos is an organophosphate insecticide with moderate toxicity previously prohibited for vegetable use due to high residue levels. Its acute toxicity primarily impacts the nervous and cardiovascular systems. Research indicates that chlorpyrifos poisoning prompts heart tissue to generate excessive free radicals, rendering it particularly susceptible to oxidative stress and peroxidative damage (Chu *et al.* 2024). Saffron (*Crocus sativus* L.), a traditional Chinese medicine, has been utilized globally for centuries and is recognized for its diverse pharmacological properties, including antioxidant effects. The therapeutic benefits of saffron are primarily attributed to crocin, which has been shown to effectively mitigate cardiotoxicity, hepatotoxicity, and DNA damage (Talebi *et al.* 2024). Research indicates that crocin can ameliorate histopathological alterations induced by doxorubicin and reduce the cardiotoxic effects of diazinon. Khalaf *et al.* demonstrated that the cardiotoxicity associated with chlorpyrifos is primarily linked to oxidative stress and that crocin can counteract this toxic effect through its antioxidant properties (Khalaf & El-Mansy 2019; Yang *et al.* 2021). Propolis, a natural colloidal substance with numerous pharmacological benefits, is extensively utilized in medicine, health foods, cosmetics, and other sectors. Rich in flavonoids and polyphenols, propolis is associated with various physiological activities, including anti-inflammatory, antioxidant, and immunomodulatory effects. A recent study has indicated that the consumption of propolis may lower the risk of cardiovascular diseases linked to chlorpyrifos exposure by enhancing the regulation of PON1 and XO mRNA genes, which leads to an increase in cellular enzymatic and/or non-enzymatic antioxidants (Ibrahim *et al.* 2019). Pomegranate (*Punica granatum* L.) is a widely recognized fruit abundant in polyphenols, including ellagic acid and ellagitannin. Research indicates that both its juice and methanol extract from the peel possess protective effects against cardiotoxicity induced by chlorpyrifos, likely due to their antioxidant, antiapoptotic, and membrane-stabilizing characteristics (El-Wakf *et al.* 2018; Omar *et al.* 2023). Chlorpyrifos (CPF) is recognized as a hepatotoxic compound that adversely affects multiple organs. In contrast, hepatic macrophages play a vital role in preserving the integrity of liver tissue. This study aimed to investigate the effects and potential mechanisms of niosomal hesperidin (Nio + Hesp), a flavanone glycoside derived from citrus fruits, on the polarization of M1-M2 liver macrophages and the inflammatory response in brain, liver, and ovarian tissues. Following CPF administration, hepatic lesions characterized by sporadic foci of coagulation necrosis, inflammatory cell infiltration, and regenerative fibrosis were observed, accompanied by a significant increase in CD163 and CD68 gene expression (Sharifnia *et al.* 2023). These results indicate that both M1 and M2 macrophages are involved in the development of CPF-induced hepatic lesions and highlight the significance of analyzing macrophage phenotypes concerning hepatotoxicity, particularly in the context of M1/M2 polarization, which can be downregulated by niosomal hesperidin (Rahman *et al.* 2018; Sharifnia *et al.* 2024). The CPF toxin induces histopathological damage to the liver by overproduction of reactive oxygen species (ROS). The liver

samples from the CPF control group exhibited notable vein congestion, localized necrosis of hepatocytes, disruption of hepatic cords, and infiltration of inflammatory cells. Hesperidin has been shown to have a hepatoprotective effect by decreasing oxidative stress and malondialdehyde levels, enhancing antioxidant capacity, and exhibiting anti-inflammatory properties (Aja *et al.* 2020). In addition, CPF exposure led to follicular accumulation, a decline in oocyte maturation rates, and an elevation in oocyte mortality. These findings suggest that CPF adversely affects oocyte nuclear maturation. In the ovaries of mice treated with CPF, inflammatory cells gathered in the ovarian center, resulting in follicular apoptosis due to inadequate blood supply. The level of inflammation was significantly diminished by the administration of hesperidin, with a more pronounced reduction observed in the hesperidin group. Both hesperidin and niosomal hesperidin treatments resulted in increased follicles at various developmental stages (Sharifnia *et al.* 2023). Cho, in 2006, assessed the antioxidant and neuroprotective properties of hesperidin utilizing a cell-free bioassay system and primary cultured rat cortical cells. Hesperidin is identified as a robust antioxidant, effectively inhibiting lipid peroxidation triggered in rat brain homogenates by Fe^{2+} and L-ascorbic acid. Consistent with these observations, hesperetin protected primary cultured cortical cells against oxidative neuronal injury induced by H_2O_2 or xanthine. Moreover, it was observed to mitigate excitotoxic neuronal damage from excessive glutamate in the cortical cultures (Aja *et al.* 2020). Collectively, these findings elucidate the pronounced antioxidant and neuroprotective effects of hesperetin, suggesting its potential utility in safeguarding neurons from various insults linked to numerous neurodegenerative disorders. Owing to its diverse pharmacological properties within the human organism, hesperidin stands out as one of the most intriguing and potentially beneficial bioflavonoids. Citrus fruits and their juices are extensively consumed globally, serving as readily accessible dietary sources for its acquisition. Commercially available supplements containing hesperidin, either in isolation or in conjunction with other citrus-derived bioflavonoids, are prevalent. Furthermore, the processing of citrus by-products offers a substantial reservoir of hesperidin, attributable to the significant volume of peel generated. Exploiting these by-products could facilitate the development of innovative nutraceuticals or enhance existing formulations.

CONCLUSION

The scholarly article concludes by asserting that the flavonoid hesperidin possesses the potential to offer a protective effect against the detrimental impacts associated with chlorpyrifos, thereby indicating the necessity for further comprehensive investigations and rigorous research endeavors to elucidate the underlying mechanisms by which hesperidin exerts its protective effects, as well as to thoroughly explore the range of its associated health benefits for individuals who may be exposed to such harmful substances. In addition, hesperidin and citrus fruit peel extract could possess antioxidant properties with a wide range of therapeutic applications. Further work is needed to produce novel drugs from this natural source.

Future directions

Gaining a deeper understanding of the implications of CPF exposure will aid in evaluating the overall health risks linked to its agricultural use. Future studies should clarify the specific mechanisms by which hesperidin protects against CPF-induced toxicity. This research should examine its effects on oxidative stress pathways, inflammatory responses, and cellular apoptosis. This research would contribute to understanding the durability of its benefits over time. The results imply that other natural polyphenols and flavonoids may also offer protective benefits against pesticide toxicity. Future investigations could examine a broader spectrum of these compounds, evaluating their efficacy and safety in alleviating the effects of organophosphate exposure. Given the extensive application of CPF in agriculture, research needs to examine the public health ramifications of hesperidin as both a dietary supplement and a therapeutic agent. This may include community-oriented studies to assess its effectiveness in practical, everyday scenarios. Additionally, the outcomes of such research could guide regulatory frameworks concerning the use of organophosphate pesticides and the integration of natural substances like hesperidin into agricultural methods, thereby promoting food safety and enhancing public health. These prospective avenues seek to enrich our comprehension of hesperidin's potential in mitigating pesticide toxicity and aim to advance the overall domain of environmental health and safety.

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