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Protective Potential of Vitamin C and E against Organophosphate Toxicity: Current Status and Perspective

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Abstract

Pesticides are an integral part of our daily life, used in agricultural fields, store rooms, residences and educational institutions to kill or repel pests. Several chemical subtypes of these compounds are available, of which organophosphate (OP) is major one. These are broad spectrum pesticides used to kill insect pests. OPs are useful but indeed they are most frequent reasons of pesticide poisoning across the globe. OP inhibits acetylcholinesterase activities that results in continuous hyper-excitable state of nicotinic and muscarinic receptors at neuromuscular junctions. Intentional or unintentional exposure to OPs causes abdominal pain, diarrhea, vomiting, muscular weakness, dementia, Central Nervous System (CNS) dysfunction and even death. Besides acetylcholinesterase inhibition, OPs are also known to trigger ROS generation within the cellular machinery which results in Oxidative Stress (OS). Free Radicals (FRs) are neutralized by antioxidant-defense system of the body. Vitamin C and vitamin E are the major exogenous antioxidants that scavenge a large amount of free radicals by donating their own electrons to FRs. This phenomenon reduces ROS and hence, OS is prevented. Therefore, vitamin C and E can be considered for daily dietary intake which might be providing prophylactic advantage against OP induced OS and pathophysiology in human beings.

Keywords: Ascorbic Acid, Organophosphates, Oxidative Stress, ROS, Tocopherol

1. Introduction

Our environment is full of various ubiquitous stressors such as UV radiation, pathogens, allergens, and different chemical pollutants. Pesticides are among the major chemical pollutants that have become an integral part of the ecosystem and affect mammals along with other non-target organisms. These are formulated to kill or repel pests to reduce economic loss[1,2]. These chemicals are in one way beneficial in increasing crop production through crop protection and reduction in need for man-power in farms and store houses. But, increasing rate of pesticide resistance due to frequent usage creates an open competition among the manufacturers to synthesize more effective and potent pesticides which might have greater side effects on human and other living creatures. Pesticide exposure has emerged as a global public health issue because of their wide-spread application, unintentional exposure, and release into environment[3,4]. Such chemicals are known to cause environmental pollution that exerts human health-issues resulting from acute and chronic exposure. Approximately among the 3 million cases of pesticide poisoning reported every year across the world, more than 250,000 deaths occur as per reports of World Health Organization[5]. The high rate of pesticide poisoning might be due to irrational use, little or

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no knowledge about the side effects and, most importantly lack of adequate safety information on the pesticide packages[6]. Despite of such a high number of death cases, there is still a huge demand of these chemicals around the world.

Majority of pesticides belongs to four categories such as organochlorine, Organophosphates (OPs), pyrethroids, and carbamates. Organochlorine pesticides (OCPs) are synthetic organic compounds widely used all over the world. These agents are categorized under Persistent Organic Pollutants (POPs) and composed of carbon, hydrogen, and chlorine atoms. OCPs bind to neuronal sodium channels to increase their permeability for sodium ions. This increased permeability facilitates uncoordinated discharge of neurons which harms central nervous system of target pests. Common OCPs used in India and other developing countries like China, Pakistan, Sri Lanka, and Bangladesh include Aldrin, Dieldrin, Chlordane, DDT, Diazion, Endosulfan, Lindane, and Methoxychlor. OCPs are used to control soil insects such as termites, rice water weevil, wireworms, corn rootworm, and grasshoppers. OP Pesticides are synthetic pesticides actively released into environment. These compounds are esters of phosphoric acid or thiophosphoric acid and works by inhibiting Acetylcholine Esterase (AChE) in synaptic sites of central and peripheral nervous system. This leads to accumulation of acetylcholine at synaptic junctions of neurons resulting in hyperexcitability of nerve fibers followed by paralysis and death of target pests. Acephate, Chlorpyrifos, Parathion, Malathion, Dichlorvos, Diazinon, and Tetrachlorvinphos are popular OP pesticides in developing countries of South Asia. OP pesticides are applied to control pests like fire ants, saw flies, caterpillars, termites, aphids, and leaf miners. Pyrethroids are organic compounds similar to the natural insecticide Pyrethrin produced from the flowers of pyrethrums (*Chrysanthemum cinerariaefolium* and *C. coccineum*). Pyrethroids prevent closure of the voltage gated sodium channels in the axonal membranes. This leads to permanent depolarization of axonal membrane and paralysis of the target animal. Common Pyrethroids include Cypermethrin, Permethrin, Deltamethrin, and Bifenthrin. These pesticides are used to control cockroaches, fleas, and termites in houses and other buildings. Carbamates are the N-methyl Carbamates derived from Carbamic acid (NH_2COOH). They cause carbamylation of AChE at neuronal synapses and neuromuscular junctions. Carbamates reversibly bind with AChE at synaptic region leading to paralysis and death of the target pests Aldicarb, Methomyl, Carbofuran, Trimethacarb, Carbaryl, Oxamyl, Ethienocarb, Propoxur, and Fenobucarb are common agents under this category. Carbamates are effective against aphids, thrips, lygus, mites, nematodes, fleahoppers, leafminers, and spiders.

OPs are commonly used pesticides as well as phosphoric acid derivatives of amides, esters, or thiol groups. These chemicals are extensively used in horticulture, agriculture, veterinary-medicine, forestry, and also for the control of some vector-borne diseases. OPs like malathion is frequently used to control ticks and mites[7]. In agricultural-sector, OPs are extensively implicated in eradication of pests including locusts, aphids, leaf-miners, fire-ants, thrips, and caterpillars. These pesticides augment both quantity and quality of agricultural-products[8]. OPs namely tris-(2-chloro,1-methyl-ethyl)-phosphate, tris-(2-chloroethyl)-phosphate, tri-n-butylphosphate, tri-iso-butylphosphate, triphenylphosphate and tris-(butoxyethyl)-phosphate are admired flame-retardants and plasticisers at public places[9]. Due to massive use of OP chemicals, their residues have been detected in drinking-water, grains, vegetables, fruits, soft-drinks, and other food items and hence, it provokes a global health concern[10]. OPs are cholinesterase inhibitors and known to amplify free radical generation and therefore sub-cellular Oxidative Stress (OS). OS is involved in onset of a number of diseases like atherosclerosis, inflammatory diseases, cardiovascular maladies, neurological disorders, and others. Therefore, the community should work to minimize the usage of harmful pesticides including OPs, at the same time their side effects to restrict adverse impacts on human health.

Vitamin C (ascorbic acid) and vitamin E (alpha-tocopherol) are the major exogenous antioxidants that scavenge a large amount of free radicals by donating their own electrons to FRs[11]. This phenomenon reduces Reactive Oxygen Species (ROS) and hence, OS is prevented. Therefore, vitamin C and E can be considered for daily dietary intake which might be providing prophylactic advantage against OP induced OS and pathophysiology in human beings.

The present literature aims to present the OP induced health hazards in human and other animals along with a discussion on protective potential of vitamin C and vitamin E in it.

2. OP Pesticides

OP pesticides were introduced by German scientists in 1938 and have been used as nerve poisons and chemical weapon during World War II[12]. At present, they are available commercially worldwide for domestic and industrial use[13,14]. Nearly half of all insecticides used in the world belong to OP category and hence they pose a greater risk of threat on health of humans[15]. Human may be exposed to OP pesticides through inhalation, ingestion or skin contact[16]. OP toxicity is a major cause of morbidity and mortality in most of developing

countries due to poor monitoring, lack of sufficient literacy, and unavailability of proper infrastructure and technology[17,18].

3. OP Poisoning and Clinical Impacts

3.1 Acute Effects of OP Poisoning

Clinical manifestations of OP poisoning are due to irreversible inhibition of acetyl cholinesterase activity resulting in accumulation of acetylcholine at the synaptic junction[19,20]. Excessive AChE causes disruption in nerve impulse flow in CNS, parasympathetic nerves, sympathetic nerves and neuromuscular junctions. OP poisoning has been demonstrated to exert acute cholinergic crisis[21,22]. Symptoms of acute toxicity occur within 1-12h following ingestion, inhalation or cutaneous absorption of OP. Gastrointestinal symptoms include abdominal pain, intestinal hypermotility, diarrhea, excessive salivation, and vomiting. Moreover, muscle tremors, drowsiness, headache, and confusion are also evident. Acute exposure to OP compounds over-stimulates sweat glands within the sympathetic nervous system to cause profound sweating. The muscarinic effects of excess acetylcholine include broncho-constriction which may lead to respiratory failure and even death. The nicotinic effects of acetylcholine are exerted through irregular and uncontrolled muscle contractions. Study of 71 elderly patients with OP poisoning were reported with acute cholinergic crisis with symptoms of respiratory failure (52.1%), aspiration pneumonia (50.7%), acute kidney injury (43.7%), severe consciousness disturbance (25.4%), shock (14.1%), and seizures (4.2%)[23].

3.2 Chronic Effects of OP Poisoning

Chronic exposure to OP causes a neurodegenerative disorder called OP-Induced Delayed Polyneuropathy (OPIDP), characterized by manifestation of symptoms of ataxia and upper motor neurone spasticity[23]. The cytoskeletal proteins comprising microtubules and neurofilaments are destabilized due to hyperphosphorylation which perhaps results in irregular aggregation of denatured proteins in axons that might contribute to neuronal degeneration[24]. Symptoms include weakness, numbness, cramping, and tingling sensation in lower limbs and may progress to paralysis. Chronic exposure to a large number of OP compounds causes OP-Induced Chronic Neurotoxicity (OPICN). Irregularities in neurological and neurobehavioural patterns are considered as other clinical signs. Parallel damages in peripheral and central nervous systems take place. Various parts of brain such as hippocampus, cortex, and cerebellum show neuropathological lesions due to increased neuronal death[24]. Neurological and neurobehavioural irregularities are intensified by simultaneous exposure to chemicals/agents that cause OS or neuronal cell death. In a cross-sectional study involving fifty-five agricultural workers exposed to OP, it was revealed that, onset of peripheral polyneuropathy is 3.6 times higher in workers intoxicated with OP other than non-exposed workers[25]. Moreover, lung dysfunction characterized by low Forced vital capacity in farmers is another outcome of low-level exposure to OP[26]. Midtling *et al.,*[27] studied cauliflower workers exposed to residues of OP insecticides like mevinphos and phosphamidon. They detected blurred vision, headache, weakness or anorexia in exposed individuals. In addition erythrocyte activity was significantly low in these workers.

4. ROS and OS

ROS are the intermediate oxygen carrying metabolites having unpaired electron which make them highly reactive to biological macromolecules such as lipids, proteins, and nucleic acids. They readily oxidize vital biomolecules that result in altered biochemical and physiological status of organisms. Major forms of ROS include superoxide anions ($O^{\cdot -}$), hydroxyl radicals ($OH^{\cdot}$), peroxyradicals ($ROO^{\cdot}$), alkoxy radicals ($RO^{\cdot}$), and singlet oxygen ($^1O_2$). ROS are spontaneously generated within the body through mitochondrial-electron transport system and peroxisomal β-oxidation of fatty acids[28–30]. Mitochondria-based metabolism of xenobiotics like certain drugs, pesticides etc. also produce free radicals within the cells. OPs are known to amplify generation of ROS within the exposed organisms and as a consequence OS occurs[31]. OS is the disruption of pro-oxidant and antioxidant balance within the body leading to potential health hazards[32]. OS has been considered as a leading cause of neurodegenerative diseases and cancer[33,34].

5. OP-Induced OS and Health Hazards on Human and Animal Models

5.1 Effects of OPs on Human Health

Exposure to OP activates cytochrome p450-based detoxification system of the body. The reaction mechanism of cytochrome p450 proceeds through the reduction of cytochrome-bound oxygen and generation of highly reactive species[35]. Several studies have confirmed that, OP pesticides generate ROS and triggers OS production in exposed

organism. Ogut *et al.*[36] conducted experiments to explore the effect of acute OP toxicity on certain biomarkers of OS in OP exposed patients. They found increased level of MDA (end product of OS-induced lipid peroxidation) and reduced levels of catalase and glutathione in patients suggesting towards OP induced OS. Another evident on OP induced OS in human was provided in a study where agricultural workers exposed to OP manifested significantly higher level of MDA and reduced level of glutathione in their blood plasma[37]. A study was conducted by Vidyasagar *et al.*[38] in eighty-four OP poisoned patients. They reported nearly doubled levels of MDA in OP poisoned patients. Lipid peroxidation has also been reported in human erythrocytes.

5.2 Effects of OPs on Animal Models

Exposure to subacute diazinon has been reported to increase serum levels of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, γ-glutamyl transferase, cholesterol, and triglycerides indicating towards improper functioning of liver in male Wistar albino rats[39]. In parallel, SOD levels were also much higher. Lipid peroxidation was also obvious in rat brain[40]. Exposure to chlorfenvinphos, another OP has also been linked to generation of ROS and lipid peroxides in rat liver[41]. Moreover, OP like Diazinon induces apoptosis of secondary and graffian follicles in rat ovary[42]. Sivaperumal and Sankar[43] documented that exposure to methyl parathion enhances activities of endogenous antioxidants (including Catalase, Glutathione-s-Transferase, SOD, and MDA) by several folds in fish model. Yu *et al.*[44] demonstrated OP induced increased apoptosis, enhanced lipid peroxidation, and DNA damage in retina of mice administered with chlorpyrifos. Singh and Drewes,[45] studied the effect of low-level (1.0 mg/kg.day) chronic acephate exposure in rats. They observed reduced GABA, dopamine, and tyrosine levels and glutamic acid decarboxylase activity in brains of treated rats. Moreover, plasma cholinesterase and RBC acetylcholinesterase activities were also inhibited. In another study, exposure to malathion induced histopathologic and ultrastructural changes in liver, kidneys, heart, and lungs[46]. Rats exposed to malathion at a dose of 100 mg/kg/day had elevated levels of MDA and 8-OHdG, whereas reduced levels of glutathione. In addition, superoxide dismutase, acetylcholinesterase, and catalase activities were low in blood, heart, liver, brain, and kidney tissues[47]. Selmi *et al.*[48] studied effect of malathion exposure in liver and kidney of prepubertal male mice. They observed histopathological lesions in the liver and kidney tissues along with depleted antioxidant enzyme activities. Parathion administered at doses of 20 mg/kg and 60 mg/kg of intravenous parathion revealed depression of acetylcholinesterase after 3 h of poisoning[49]. OP poisoning has potential to alter reproductive fitness in non-target organisms. For instance, exposure to dichlorvos reduces body and testis weights, FSH, LH, and testosterone levels as well as sperm morphology in treated male rats[50]. Monoamine oxidase, norepinephrine, and dopamine levels are targeted during co-exposure to dichlorvos and monocrotophos[51]. Ethion and Fenitrothion are pulmonotoxic in nature as they induce OS and histomorphological alterations in lung as evidenced by increased pulmonary inflammation and small as well as discrete foci in mouse and rat models[52,53]. Subacute diazinon exposure in aged male rats is associated with decreased RBC, Hb, and Htc levels[54].

6. Antioxidants

Organisms have a number of protective mechanisms to counteract deleterious consequences of excess free radicals within the body. Among them, antioxidants are the important ones that neutralize free radicals by donating or accepting electron(s) to eliminate unpaired state/configuration of radicals. They terminate redox chain reactions triggered by different chemical stressors such as OP based pesticides. Free radicals are maintained at low level by both non-enzymatic and enzymatic antioxidant defense machinery. Enzymatic antioxidants are usually endogenous and provide first line of defense against ROS. These include Catalase, Glutathione peroxidase, and Superoxide dismutase. Second line of defense against free radicals and OS is provided by non-enzymatic antioxidants from exogenous sources. Some vitamins and other substances like Flavonoids, Selenium, Zinc etc. belong to this category. Vitamins are inexpensive and readily available in market in both natural and synthetic forms. We need to fulfill the daily requirement of vitamins from fruits, vegetables or dietary supplements. Vitamins scavenge free radicals and in the process vitamins themself transform into less active free radicals that are less dangerous, with longer half-life in comparison to those radicals that have been neutralized. Interestingly vitamin C and vitamin E have been documented to scavenge free radicals during OP exposure.

6.1 Vitamin C (Ascorbic Acid)

Vitamin C or ascorbic acid is a natural water-soluble vitamin abundant in citrus fruit. In living organisms, it is required for a variety of metabolic processes such as anti-bacterial activities, detoxifying reactions and collagen formation in fibrous tissues, teeth, skin, and capillaries.

Additionally, vitamin C functions as a cofactor for enzymes relevant in several biosynthetic reactions that occur during synthesis of amino acid-derived macromolecules,

neurotransmitters, and neuropeptide hormones. It also acts as a cofactor for various hydroxylases that play integral part in regulation of gene transcription and epigenetic mechanisms[55]. Ascorbic acid from external sources is essential in trace amount for normal functioning of our body. Plants and most of the animals are able to synthesize vitamin C from glucose endogenously but primates have lost their ability to synthesize it, since, one of the enzymes (L-gulonolactone oxidase), important for synthesis of ascorbic acid was lost by mutation during primate evolution.

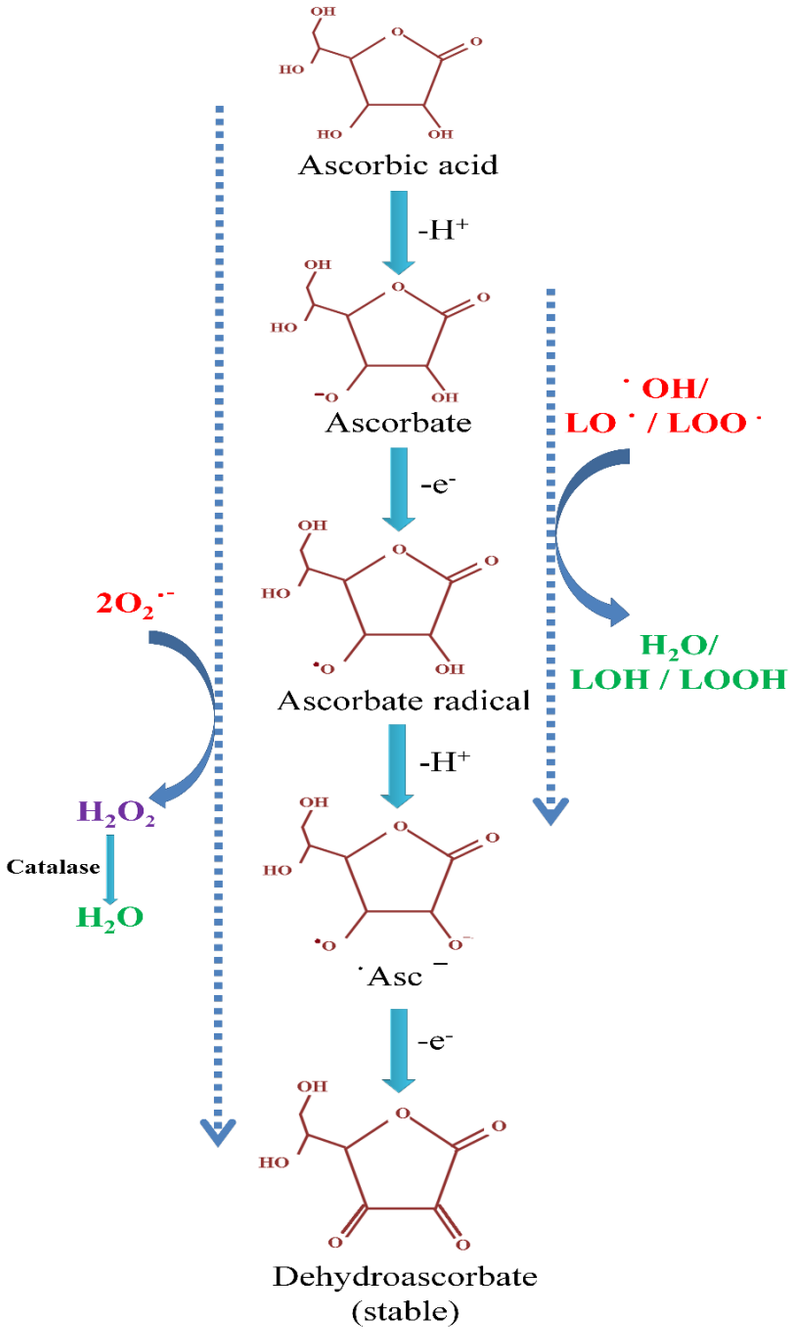

Figure 1. Antioxidant activity of vitamin C. Vitamin C undergoes de-protonation and release electrons to neutralize free radicals like $O_2^{\bullet-}$, $^{\bullet}OH$, $LO^{\bullet}$, $LOO^{\bullet}$ etc. Intermediate compounds like Ascorbate, Ascorbate radicals, $^{\bullet}Asc^{-}$ and dehydroascorbate are produced during the scavenging reactions.

6.1.1 Sources for Human

Fruits like guava, kiwi, green peppers, orange, strawberries, papaya, broccoli, grape fruits, and pineapple are rich sources of vitamin C. Low-priced synthetic forms are also available under different brand names.

6.1.2 Mechanism of Action as Antioxidant

Vitamin C is a mild reducing agent and an antioxidant that participate in neutralizing hydroxyl, alkoxyl, and lipid peroxyl (LOO·) radicals by converting them into stable products such as H_2O, alcohol, and lipid hydroperoxides respectively. Vitamin C typically neutralizes various ROS, most importantly ·OH by the transfer of single electron and in the process it alters itself into a resonance-stabilized radical, called semi-dehydroascorbate. Semi-dehydroascorbate with loss of another electron changes into more stable radical form, dehydroascorbate (Asc•) (Figure 1). With the help of NADH or NADPH dependent reductases, vitamin C itself is known to be readily regenerated from Asc•[56]. Vitamin C also neutralizes radical forms of other antioxidants like glutathione radical and vitamin E radical and regenerates these antioxidants.

6.1.3 Protective Potentials of Vitamin C against OP Induced OS and Injuries

Several studies around the globe have confirmed the protective potentials of ascorbic acid against OP induced OS and toxicity. Ambali and Ayo[57] demonstrated that vitamin C successfully ameliorates acute Chlopyrifos-induced sensory motor dysfunction and cognitive changes in Wistar rats. Vitamin C is beneficial against OP induced retinal damage in rats[58]. Moreover, vitamin C has been found to significantly reduce the symptoms of chlorpyrifos-induced OS in mice liver[32]. Diazinon induced renal injuries were significantly reduced following ascorbic acid co-administration[59]. Further, Ascorbic acid is beneficial in reducing acephate induced OS and subsequent injuries in *Drosophila melanogaster*[60,61]. In a study, erythrocytes treated with 1, 10, and 100 µM concentrations of diclorvos manifested increased lipid peroxidation and OS which were mitigated partially after treatment with vitamin C at 10 µM concentration[62]. Similar results were also noticed in rats orally exposed to methidathion at a dose of 8 mg/kg bw for 24 h. Elevated lipid peroxidation and OS markers were detected in treated individuals. Rats supplemented with vitamin C (200 mg/kg body weight, i.p.) showed reduced lipid peroxidation and OS[63]. Exposure to OPs such as chlorpyrifos, profenofos, diazinon, and malathion induces hepatic malfunction in rats which is characterized by altered levels of serum Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Alkaline Phosphatase (ALP), and Lactate Dehydrogenase (LDH). All these altered parameters become normal upon combinational therapy with vitamin C[64]. Milošević *et al.*[65] investigated the protective impacts of vitamin C on fenitrothion induced toxicity in rat liver. They found that, vitamin C has potentials to reduce oxidative stress and normalize ALT, ALP, LDH, and GGT levels. Moreover, treatment with vitamin C (ascorbic acid) at a dose of 200 mg kg^{-1} b.w. reduces MDA level and increases GSH level in malathion treated rats[66]. Rats treated with dichlorvos manifested endometrial damage and apoptosis which were ameliorated upon treatment with vitamin E[67].

6.2 Vitamin E (α-Tocopherol)

Vitamin E is a set of eight related isomers namely α-, β-, γ- and δ-tocopherols as well as tocotrienols (4 Tocopherols and 4 Tocotrienols). These isomers belong to fat soluble vitamins[68,69]. Among them, α-tocopherol has been studied extensively as it is abundant in nature. Cell utilizes it as a major membrane bound antioxidant. It protects the cytomembranes from lipid peroxidation. Vitamin E scavenges free radicals through a mechanism of electron transfer to yield a Vitamin E cation radical, which through fast de-protonation produces a less reactive and relatively stable vitamin E radical. Vitamin E radical can be transformed to its reduced form by other antioxidants such as ascorbate or retinol.

6.2.1 Sources for Human

Good sources of vitamin E include almonds, spinach, sweet potato, sunflower seeds, palm oil, and butternut squash. Similar to vitamin C, synthetic forms are also available under different brand names.

6.2.2 Mechanism of Action as Antioxidant

Vitamin E acts as a 'chain breaker' during lipid peroxidation in cell membranes. It terminates lipid peroxidation chain reactions by neutralizing lipid alkoxy radical ($LO^{\bullet}$) or lipid peroxyl radicals ($LOO^{\bullet}$) (Figure 2). The resultant tocopheroxyl radical is relatively stable and lack sufficient potency to initiate lipid peroxidation by itself, which is important for a good antioxidant[70,71]. Tocopheroxyl radical can be converted back to its reduced form by some antioxidants like ascorbate or retinol (Figure 3). Vitamin E alone is not so efficient in scavenging $^{\bullet}OH$ and alkoxyl radicals ($^{\bullet}OR$) in vivo[72].

6.2.3 Protective Potential of Vitamin E against OP Induced Toxicity and OS

Ambali and Aliyu[73] showed that vitamin E could mitigate the changes in sensory motor functioning and cognitive responses

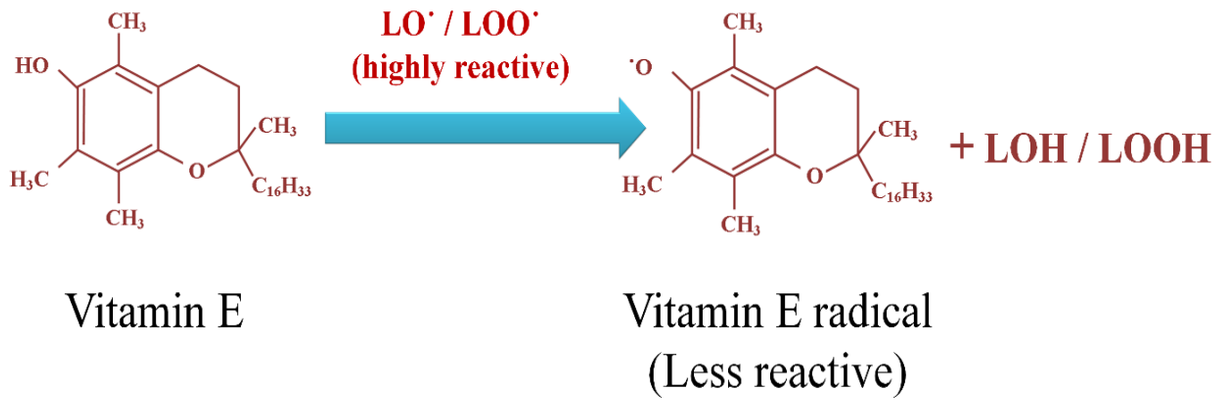

Figure 2. Vitamin E as a chain breaker during lipid peroxidation. Free radical like ˙OH attacks polyunsaturated fatty acids (PUFA) of biological membranes and generates lipid alkoxy radical (LO˙) or lipid peroxyl radicals (LOO˙) which initiate a chain reaction that damages adjacent membrane-bound PUFA. Vitamin E neutralizes LO˙ and LOO˙ thereby terminating the chain reaction.

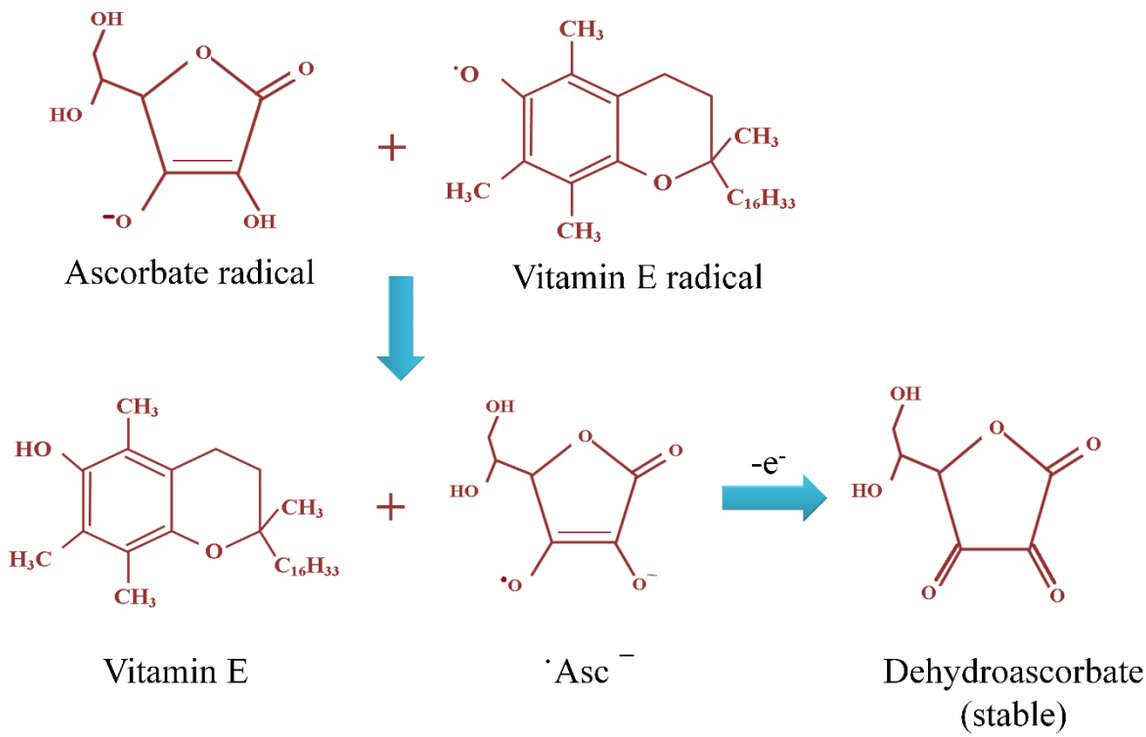

Figure 3. Regeneration of vitamin E (α-Tocopherol). Ascorbate through de-protonation converts vitamin E radical into its more stable configuration i.e., α-tocopherol. Upon loss of one electron, ˙Asc⁻ changes into dehydroascorbate which is stable.

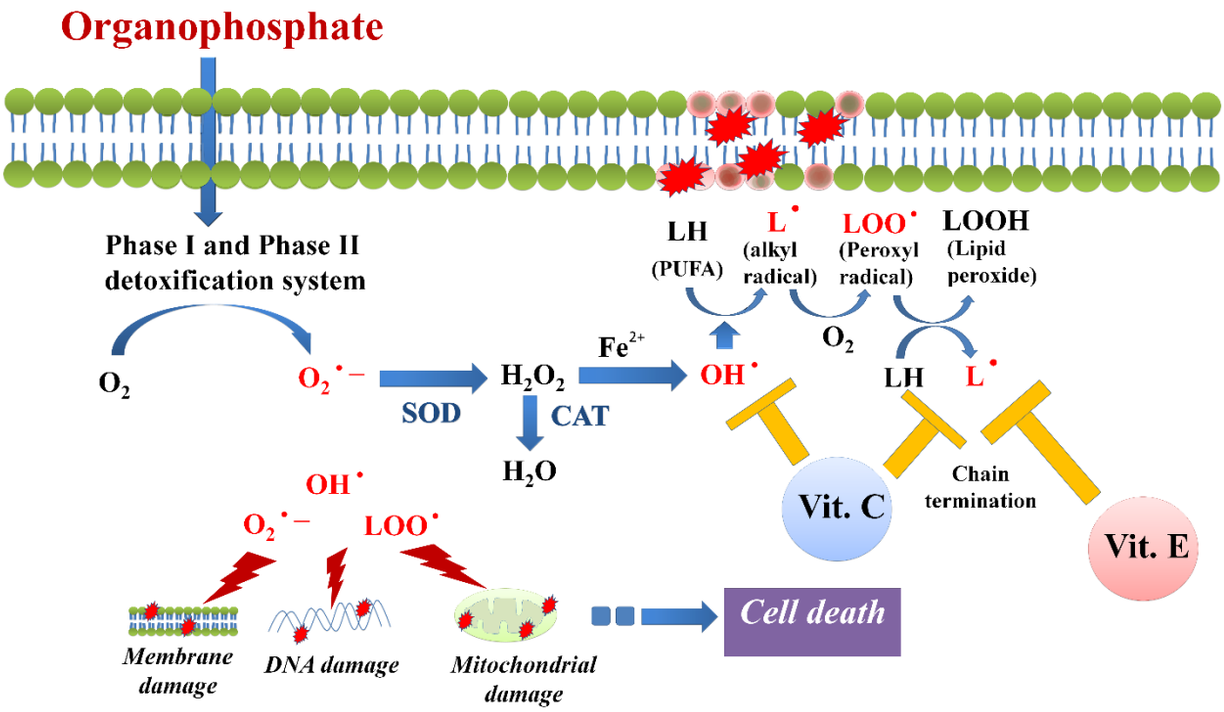

Figure 4. Vitamin C and vitamin E, as quenchers of OP-induced ROS within cellular environment. OP exposure activates Cytochrome p450 (CYP450) based detoxification system (Phase I) within the body. The reaction mechanism of CYP450 proceeds through the reduction of cytochrome-bound oxygen and generation of reactive superoxide anions ($O_2^{\bullet-}$). SOD catalyzes dismutation of superoxide anions to produce H_2O_2 which in turn decomposes to water and oxygen by catalase. In presence of Fe^{2+}, H_2O_2 can be converted into $^{\bullet}OH$ ion that oxidizes polyunsaturated fatty acids of biological membranes to generate lipid alkoxy radical ($LO^{\bullet}$) or lipid peroxyl radicals ($LOO^{\bullet}$). These reactive radical in turn can damage several cellular components such as plasma membrane, DNA and mitochondria leading to cell death.

induced by short-term acute exposure to Chlopyrifos (CPF) in Wistar rats. Probably the antioxidant property along with acetyl cholinesterase restoration ability plays significant role behind the protective/prophylactic/ameliorative potential of vitamin E. This can be further validated through the fact that supplementation with vitamin E successfully ameliorated CPF-induced haematological and biochemical alterations[74,75]. Vitamin E has been demonstrated to reduce Diazinon induced apoptosis in secondary and graafian follicles in rat ovary[42]. John *et al.*[76] demonstrated that vitamin E has the potential to ameliorate dimethoate and malathion-induced OS in rat erythrocytes. Therefore, like other chemicals, OPs contribute to OS and subsequent pathologies that can be ameliorated to some extent by vitamin E[77–87] (Table 1). Eroğlu *et al.*[62] human erythrocytes treated with 1, 10, and 100 µM concentrations of diclorvos. They observed increased lipid peroxidation and OS which were mitigated partially after treatment with vitamin E at 30 µM concentration. In another study, vitamin E ameliorated OS in rats treated with methidathion orally at a dose of 8 mg/kg bw for 24 h[63]. Vitamins E supplementation in rats has potential to lower lipid peroxidation and normalize endogenous antioxidant activities in rats orally treated with diazinon at a dose of 335 mg/kg b.w.[88] OP pesticides like ethion has tendency to disturb activity of membrane bound ATPases and Ca^{2+} homeostasis. Vitamin E (50 mg/kg b.w.) supplementation in rats orally exposed to ethion at a dose of 2.7 mg/kg b.wt. for 7-28 days partially restored activities of membrane bound ATPases and Ca^{2+} homeostasis[80]. Dichlorvos induced endometrial damage and apoptosis was reduced upon treatment with vitamin E in rats[67].

Table 1. OP toxicity and protective effects of Vitamin C and Vitamin E

Name of OP pesticide(s) and dose/concentration used	Name of Vitamin and the dose/ concentration used for the study	Exposure duration	Cell line / model organism	Observations	Reference
Diclorvos (1, 10, 100 µM)	Vitamin C (10 µM) and Vitamin E (30 µM)	Not mentioned	Human erythrocytes	Vitamin supplementation reduces Lipid peroxidation (LPO) and oxidative stress.	62
Methidathion (8 mg/ kg MD body; oral)	Vitamin C (200 mg/ kg body weight, i.p.) and Vitamin E (150 mg/kg body weight, i.m.)	24 h	Rat	Vitamin supplementation reduces Lipid peroxidation (LPO) and oxidative stress.	63
Chlorpyrifos (1mg kg^{-1} b.wt.); Profenofos (0.3mg kg^{-1} b.wt.); Diazinon (0.06mg kg^{-1} b.wt.); Malathion (29mg kg^{-1} b.wt.)	Vitamin C (200 mg kg^{-1} b.wt.)	24 days	Rat	Combination therapy with Vitamin C restored the normal range of serum Aspartate aminotransferase (AST), Alanine Transaminase (ALT), Alkaline phosphatase (ALP) and Lactate dehydrogenase (LDH); reduced liver damage.	64
Fenitrothion (20 mg kg-1 b.wt.)	Vitamin C (100 mg kg^{-1} b.wt.)	30 days	Rat	Vitamin C exhibited hepatoprotective role by reducing oxidative stress and normalizing AST, ALT, ALP, LDH and GGT levels.	65
Malathion (50 mg/ kg b.wt.)	Ascorbic acid (200 mg kg^{-1} b.wt.)	6 Weeks	Rat	Vitamin supplementation reduced MDA level and increased the GSH level.	66
Diazinon (335 mg/kg b.wt.; oral exposure)	Vitamin C (200 mg/ kg body weight, i.p.) and Vitamin E (150 mg/kg body weight, i.p.)	24 h	Rat	Vitamin supplementation reduced lipid peroxidation in rat myocardium	88
Methidathion (5 mg/kg b.wt.; oral exposure)	Vitamin C (20 mg/ kg body weight) and Vitamin E (50 mg/kg body weight)	4 weeks	Rat	Vitamin supplementation partially restored Cholinesterase acitivity and malondialdehyde levels in treated rats.	89

Chlorpyrifos (10.6 mg/kg b.wt.)	Vitamin C (100 mg/kg body weight)	17 weeks	Rat	Vitamin C alleviated chlorpyrifos induced deleterious alterations of lipid profiles (increased levels of TC, LDL-c and MDA)	90
Acephate (5 µg/mL)	L-ascorbic acid (25, 50, 100 µg/mL)	First to third instar larvae	*Drosophila melanogaster*	Co-administration with L-ascorbic acid reduced oxidative stress by normalizing oxidative stress markers such as Catalase, SOD, protein carbonyl contents and Lipid peroxidation.	31
Diazinon (335 mg/kg b.wt.; oral exposure)	Vitamin C (200 mg/kg body weight i.p.) and Vitamin E (150 mg/kg body weight i.p.)	24 h	Rat	Treatment with vitamins E and C together reduced LPO and the activities of GSH-Px and SOD compared with the diazinon group.	88
Dichlorvos (4 mg/kg b.wt.)	Vitamin C (20 mg/kg body weight i.p.) and Vitamin E (50 mg/kg body weight i.p.)	5 days a week for 4 weeks	Rat	Vitamin supplementation decreased MDA production; reduced the histopathological changes and the extent of apoptosis.	67
Ethion (2.7 mg/kg b.wt.; oral exposure)	Vitamin E (50 mg/kg body weight; oral exposure)	7, 14, 21, 28 days	Rat	Vitamin E supplimentation decreased lipid peroxidation; partially restored activities of membrane bound ATPases and Ca^{2+} homeostasis.	91,92

7. Conclusion

Non-targets organisms undergo unintentional continuous exposure to OP pesticides through consumption of OP-contaminated fruits and vegetable. OP exerts its toxic effects by AChE inhibition and triggers ROS generation inside the body. ROS in excess amount initiates a cascade of events that targets essential biomolecules such as lipids, proteins, and nucleic acids. Endogenous antioxidants through the process of deprotonation strive to stabilize free radicals. But under OP exposure, endogenous antioxidants cannot satisfactorily neutralize the reactive radicals. In these cases, exogenous antioxidants might be supportive to work synergistically with endogenous antioxidants and enhance the overall antioxidant capacity of the body. Several studies around the globe have suggested that, vitamin C and vitamin E having potentials to efficiently scavenge ROS can reduce OS in humans and other organisms (Figure 4). Hence, readily available and affordable vitamin C and vitamin E seems to have protective or prophylactic activities against health hazards originating from OP-induced OS. Therefore, these cost-effective vitamins might be considered in diet to ameliorate toxic effects exerted by OPs and other xenobiotics.

8. Conflict of Interest

Authors declare that, there is no conflict of interest.

9. References

1. Aktar MW, Sengupta D, Chowdhury A. Impact of pesticides use in agriculture: their benefits and hazards. Interdiscip Toxicol. 2009; 2(1):1-12. https://doi.org/10.2478/v10102-009-0001-7 PMid:21217838 PMCid:PMC2984095
2. Bjørling-Poulsen M, Andersen HR, Grandjean P. Potential developmental neurotoxicity of pesticides used in Europe. Environ Health. 2008; 7:50. https://doi.org/10.1186/1476-069X-7-50 PMid:18945337 PMCid:PMC2577708
3. Podder S, Akbari S, Roy S. Cryolite Induced Morphological Changes in The Compound Eye of Drosophila melanogaster. Fluoride. 2012; 45(1): 58-64.
4. Calvert GM, Karnik J, Mehler L, Beckman J, Morrissey B, Sievert J, Barrett R, Lackovic M, Mabee L, Schwartz A, Mitchell Y, Moraga-McHaley S. Acute pesticide poisoning among agricultural workers in the United States, 1998-2005. Am J Ind Med. 2008; 51(12):883-98. https://doi.org/10.1002/ajim.20623 PMid:18666136
5. Yang CC, Deng JF. Intermediate syndrome following organophosphate insecticide poisoning. J Chin Med Assoc. 2007; 70(11):467-72. https://doi.org/10.1016/S1726-4901(08)70043-1
6. Gbaruko BC, Ogwo EI, Igwe JC, Yu, H. Organophosphate induced chronic neurotoxicity: Health, environmental and risk exposure issues in developing nations of the world. Afr. J. Biotechnol. 2009; 8:5137-41.
7. Idriss S, Levitt J. Malathion for head lice and scabies: treatment and safety considerations. J Drugs Dermatol; 2009; 8: 715-20.
8. Chang MMF, Ginjom IR., Ng SM. Single-shot 'turn-off'optical probe for rapid detection of paraoxon-ethyl pesticide on vegetable utilising fluorescence carbon dots. Sens. Actuators B Chem. 2017; 242:1050-6. https://doi.org/10.1016/j.snb.2016.09.147
9. Andresen JA, Grundmann A. Bester K. Organophosphorus flame retardants and plasticisers in surface waters. Sci. Total Environ. 2004; 332:155-66. https://doi.org/10.1016/j.scitotenv.2004.04.021 PMid:15336899
10. Bala R, Dhingra S, Kumar M, Bansal K, Mittal S, Sharma RK, Wangoo N. Detection of organophosphorus pesticide-Malathion in environmental samples using peptide and aptamer based nanoprobes. Chem. Eng. J. 2017; 311:111-6. https://doi.org/10.1016/j.cej.2016.11.070
11. Shahidi F, Zhong Y. Novel antioxidants in food quality preservation and health promotion. Eur. J. Lipid Sci. Technol. 2010; 112: 930-40. https://doi.org/10.1002/ejlt.201000044
12. Costa LG. Toxic Effects of Pesticides. In: Klaassen CD. editors. Casarett and Doull's Toxicology: The Basic Science of Poisons, 8th ed. McGraw Hill; 2013. Available from: https://accesspharmacy.mhmedical.com/content.aspx?bookid=958&sectionid=53483747
13. Aardema H, Meertens JH, Ligtenberg JJ, Peters-Polman OM, Tulleken JE, Zijlstra JG. Organophosphorus pesticide poisoning: cases and developments. Neth J Med. 2008; 66(4):149-53.
14. Leibson T, Lifshitz M. Organophosphate and carbamate poisoning: review of the current literature and summary of clinical and laboratory experience in southern Israel. Isr Med Assoc J. 2008; 10(11):767-70.
15. Casida JE, Quistad GB. Organophosphate toxicity: Safety aspects of non-acetylcholinesterase secondary targets. Chem Res Toxicol. 2004; 17:983-98. https://doi.org/10.1021/tx0499259 PMid:15310231
16. Vale JA. Toxicokinetic and toxicodynamic aspects of organophosphorus (OP) insecticide poisoning. Toxicol Lett. 1998; 102-103:649-52. https://doi.org/10.1016/S0378-4274(98)00277-X
17. Peter JV, Cherian AM. Organic insecticides. Anaesth Intensive Care. 2000; 28(1):11-21. https://doi.org/10.1177/0310057X0002800102 PMid:10701030
18. Jaga K, Dharmani C. Sources of exposure to and public health implications of organophosphate pesticides. Rev Panam Salud Publica. 2003; 14(3):171-85. https://doi.org/10.1590/S1020-49892003000800004 PMid:14653904
19. Kishi M, Ladou J. International pesticide use. Introduction. Int J Occup Environ Health. 2001; 7(4):259-265. https://doi.org/10.1179/107735201800339254 PMid:11783855
20. Kwong TC. Organophosphate pesticides: biochemistry and clinical toxicology. Ther Drug Monit. 2002; 24(1):144-9. https://doi.org/10.1097/00007691-200202000-00022 PMid:11805735
21. Miranda J, McConnell R, Wesseling C, Cuadra R, Delgado E, Torres E, Keifer M, Lundberg I. Muscular strength and vibration thresholds during two years after acute poisoning with organophosphate insecticides. Occup Environ Med. 2004; 61(1):e4.
22. Yang CC, Deng JF. Intermediate syndrome following organophosphate insecticide poisoning. J Chin Med Assoc. 2007; 70(11):467-72. https://doi.org/10.1016/S1726-4901(08)70043-1
23. Yu JR, Hou YC, Fu JF, Wang IK, Chan MJ, Chen CY, Weng CH, Huang WH, Yang HY, Hsu CW, Yen TH. Outcomes of elderly patients with organophosphate intoxication. Sci Rep. 2021; 11(1):11615. https://doi.org/10.1038/s41598-021-91230-2 PMid:34079035 PMCid:PMC8172550
24. Abou-Donia MB. Organophosphorus ester-induced chronic neurotoxicity. Arch Environ Health. 2003; 58(8):484-97. https://doi.org/10.3200/AEOH.58.8.484-497 PMid:15259428
25. Grillo Pizarro Á, Achú Peralta E, Muñoz-Quezada MT, Lucero Mondaca B. Exposición a plaguicidas organofosforados y polineuropatía periférica en trabajadores de la región del Maule, Chile [Exposure to organophosphate pesticides and peripheral polyneuropathy in workers from Maule Region, Chile]. Rev Esp Salud Publica. 2018; 92:e201803006.
26. Peiris-John RJ, Ruberu DK, Wickremasinghe AR, van-der-Hoek W. Low-level exposure to organophosphate pesticides leads to restrictive lung dysfunction. Respir Med. 2005; 99(10):1319-24. https://doi.org/10.1016/j.rmed.2005.02.001 PMid:16102957
27. Midtling JE, Barnett PG, Coye MJ, Velasco AR, Romero P, Clements CL, O'Malley MA, Tobin MW, Rose TG, Monosson IH.

Clinical management of field worker organophosphate poisoning. West J Med. 1985; 142(4):514-8.
28. St-Pierre J, Buckingham JA, Roebuck SJ, Brand MD. Topology of superoxide production from different sites in the mitochondrial electron transport chain. J Biol Chem. 2002 22; 277(47):44784-90. https://doi.org/10.1074/jbc.M207217200 PMid:12237311
29. Liu Y, Fiskum G, Schubert D. Generation of reactive oxygen species by the mitochondrial electron transport chain. J Neurochem. 2002; 80(5):780-7. https://doi.org/10.1046/j.0022-3042.2002.00744.x PMid:11948241
30. Rosca MG, Vazquez EJ, Chen Q, Kerner J, Kern TS, Hoppel CL. Oxidation of fatty acids is the source of increased mitochondrial reactive oxygen species production in kidney cortical tubules in early diabetes. Diabetes. 2012; 61(8):2074-83. https://doi.org/10.2337/db11-1437 PMid:22586586 PMCid:PMC3402323
31. Rajak P, Dutta M, Khatun S, Mandi M, Roy S. Exploring hazards of acute exposure of Acephate in Drosophila melanogaster and search for l-ascorbic acid mediated defense in it. J Hazard Mater. 2017; 321:690-702. https://doi.org/10.1016/j.jhazmat.2016.09.067 PMid:27701059
32. Aly N, EL-Gendy K. Mahmoud F, El-Sebae, AK. Protective effect of vitamin C against chlorpyrifos oxidative stress in male mice. Pestic Biochem Phys, 2010; 97:7-12. https://doi.org/10.1016/j.pestbp.2009.11.007
33. Chen X, Guo C, Kong J. Oxidative stress in neurodegenerative diseases. Neural Regen Res. 2012; 7(5):376-85. https://doi.org/10.3969/j.issn.1673-5374.2012.05.009.
34. Reuter S, Gupta SC, Chaturvedi MM, Aggarwal BB. Oxidative stress, inflammation, and cancer: How are they linked? Free Radic Biol Med. 2010; 49(11):1603-16. https://doi.org/10.1016/j.freeradbiomed.2010.09.006 PMid:20840865 PMCid:PMC2990475
35. Schlichting I, Berendzen J, Chu K, Stock AM, Maves SA, Benson DE, Sweet RM, Ringe D, Petsko GA, Sligar SG. The catalytic pathway of cytochrome p450cam at atomic resolution. Science. 2000; 287(5458):1615-22. https://doi.org/10.1126/science.287.5458.1615 PMid:10698731
36. Ogut S, Gultekin F, Kisioglu AN, Kucukoner E. Oxidative stress in the blood of farm workers following intensive pesticide exposure. Toxicol Ind Health. 2011; 27(9):820-5. https://doi.org/10.1177/0748233711399311 PMid:21450927
37. Rastogi SK, Satyanarayan PV, Ravishankar D, Tripathi S. A study on oxidative stress and antioxidant status of agricultural workers exposed to organophosphorus insecticides during spraying. Indian J Occup Environ Med. 2009; 13(3):131-4. https://doi.org/10.4103/0019-5278.58916 PMid:20442831 PMCid:PMC2862445
38. Vidyasagar J, Karunakar N, Reddy MS, Rajnarayana K, Surender T, Krishna DR. Oxidative stress and antioxidant status in acute organophosphorous insecticide poisoning. Indian J Pharmacol. 2004; 36:76-79.
39. Abdel-Daim MM, Taha R, Ghazy EW, El-Sayed YS. Synergistic ameliorative effects of sesame oil and alpha-lipoic acid against subacute diazinon toxicity in rats: hematological, biochemical, and antioxidant studies. Can J Physiol Pharmacol. 2016; 94(1):81-8. https://doi.org/10.1139/cjpp-2015-0131 PMid:26550680
40. El-Demerdash FM. Lipid peroxidation, oxidative stress and acetylcholinesterase in rat brain exposed to organophosphate and pyrethroid insecticides. Food Chem Toxicol. 2011; 49(6):1346-52. https://doi.org/10.1016/j.fct.2011.03.018 PMid:21419823
41. Łukaszewicz-Hussain A. Organophosphate insecticide chlorfenvinphos affects superoxide dismutase, catalase and malondialdehyde in rat liver. Pol J Environ Stud. 2001; 10:279-82.
42. Sargazi Z, Nikravesh MR, Jalali M, Sadeghnia HR, Anbarkeh FR.Apoptotic Effect of Organophosphorus Insecticide Diazinon on Rat Ovary and Protective Effect of Vitamin E. IJT. 2016; 10:37-44. https://doi.org/10.32598/IJT.10.2.328.1
43. Sivaperumal P, Sankar TV. Toxic effects of methyl parathion on antioxidant enzymes and acetylcholinesterase activity in freshwater fish, Labeo rohita. Fish Tech. 2011; 48:59-66.
44. Yu F, Wang Z, Ju B, Wang Y, Wang J, Bai D. Apoptotic effect of organophosphorus insecticide chlorpyrifos on mouse retina in vivo via oxidative stress and protection of combination of vitamins C and E. Exp Toxicol Pathol. 2008; 59(6):415-23. https://doi.org/10.1016/j.etp.2007.11.007 PMid:18222074
45. Singh AK, Drewes LR. Neurotoxic effects of low-level chronic acephate exposure in rats. Environ Res. 1987; 43(2):342-9. https://doi.org/10.1016/S0013-9351(87)80034-8
46. Tós-Luty S, Obuchowska-Przebirowska D, Latuszyńska J, Tokarska-Rodak M, Haratym-Maj A. Dermal and oral toxicity of malathion in rats. Ann Agric Environ Med. 2003; 10(1):101-6.
47. Akbel E, Arslan-Acaroz D, Demirel HH, Kucukkurt I, Ince S. The subchronic exposure to malathion, an organophosphate pesticide, causes lipid peroxidation, oxidative stress, and tissue damage in rats: the protective role of resveratrol. Toxicol Res (Camb). 2018; 7(3):503-512. https://doi.org/10.1039/C8TX00030A PMid:30090600 PMCid:PMC6062150
48. Selmi S, Rtibi K, Grami D, Sebai H, Marzouki L. Malathion, an organophosphate insecticide, provokes metabolic, histopathologic and molecular disorders in liver and kidney in prepubertal male mice. Toxicol Rep. 2018; 5:189-95. https://doi.org/10.1016/j.toxrep.2017.12.021 PMid:29854588 PMCid:PMC5977160
49. Bunya N, Sawamoto K, Benoit H, Bird SB. The Effect of Parathion on Red Blood Cell Acetylcholinesterase in the Wistar Rat. J Toxicol. 2016; 2016:4576952. https://doi.org/10.1155/2016/4576952 PMid:27418928 PMCid:PMC4935959
50. Dirican EK, Kalender Y. Dichlorvos-induced testicular toxicity in male rats and the protective role of vitamins C and E. Exp Toxicol Pathol. 2012; 64(7-8):821-30. https://doi.org/10.1016/j.etp.2011.03.002 PMid:21458248
51. Dwivedi N, Bhutia YD, Kumar V, et al. Effects of combined exposure to dichlorvos and monocrotophos on blood and brain biochemical variables in rats. Human and Experimental Toxicology. 2010; 29(2):121-9. https://doi.org/10.1177/0960327109357212 PMid:20026515
52. Verma G, Sethi RS. Study of ethion and lipopolysaccharide interaction on lung in a mouse model. Lab Anim Res. 2020; 36:22. https://doi.org/10.1186/s42826-020-00055-z PMid:32742976 PMCid:PMC7390112
53. Coulombe PA, Lortie S, Côte MG, Chevalier G. Pulmonary toxicity of the insecticide fenitrothion in the rat following a single

field exposure. J Appl Toxicol. 1986; 6(5):317-23. https://doi.org/10.1002/jat.2550060504 PMid:3772007
54. Samarghandian S, Farkhondeh T, Yousefizadeh S. Toxicity Evaluation of the Subacute Diazinon in Aged Male Rats: Hematological Aspects. Cardiovasc Hematol Disord Drug Targets. 2020; 20(3):198-201. https://doi.org/10.2174/1871529X20666200305103007 PMid:32133967 PMCid:PMC8388065
55. Carr C, Vissers MCM. Synthetic or food-derived vitamin C- Are they equally bioavailable? Nutrients. 2013; 5:4284-304. https://doi.org/10.3390/nu5114284 PMid:24169506 PMCid:PMC3847730
56. Hossain MA, Asada K. Monodehydro- ascorbate reductase from cucumber is a flavin adenine dinucleotide enzyme. J Biol Chem. 1985; 260:12920-6. https://doi.org/10.1016/S0021-9258(17)38813-0
57. Ambali SF, Ayo JO. Sensorimotor performance deficits induced by chronic chlorpyrifos exposure in Wistar rats: mitigative effect of vitamin C. Toxicol Environ Chem. 2011; 93:1212-6. https://doi.org/10.1080/02772248.2011.585991
58. Mandi M, Khatun S, Rajak P, Mazumdar A, Roy S. Potential risk of organophosphate exposure in male reproductive system of a nnon-target insect model Drosophila melanogaster. Environ Toxicol Pharmacol. 2020; 74:103308. https://doi.org/10.1016/j.etap.2019.103308 PMid:31816565
59. Abdel-Daim M, Halawa S. Synergistic hepatocardioprotective and antioxidant effects of myrrh and ascorbic acid against diazinon-induced toxicity in rabbits. IJHEPS. 2014; 1:1-7.
60. Rajak P, Sahana S, Roy S. Acephate-induced shortening of developmental duration and early adult emergence in a nontarget insect Drosophila melanogaster. Toxicol Environ Chem. 2013; 95:1369-79. https://doi.org/10.1080/02772248.2014.880608
61. Rajak P, Dutta M, Roy S. Altered differential hemocyte count in 3rd instar larvae of Drosophila melanogaster as a response to chronic exposure of Acephate. Interdiscip Toxicol. 2015; 8:84-8. https://doi.org/10.1515/intox-2015-0013 PMid:27486365 PMCid:PMC4961902
62. Eroğlu S, Pandir D, Uzun FG, Bas H. Protective role of vitamins C and E in dichlorvos-induced oxidative stress in human erythrocytes in vitro. Biol Res. 2013; 46(1):33-8. https://doi.org/10.4067/S0716-97602013000100005 PMid:23760412
63. Altuntas I, Delibas N, Sutcu R. The effects of organophosphate insecticide methidathion on lipid peroxidation and anti-oxidant enzymes in rat erythrocytes: role of vitamins E and C. Hum Exp Toxicol. 2002; 21(12):681-5. https://doi.org/10.1191/0960327102ht304oa PMid:12540039
64. Mossa AH, Refaie AA, Ramadan A. Effect of exposure to mixture of four organophosphate insecticides at no observed adverse effect level dose on rat liver: The protective role of vitamin C. Res J Environ Toxicol. 2011; 5:323-35. https://doi.org/10.3923/rjet.2011.323.335
65. Milošević MD, Paunović MG, Matić MM, Ognjanović BI, Saičić ZS. Role of selenium and vitamin C in mitigating oxidative stress induced by fenitrothion in rat liver. Biomed Pharmacother. 2018; 106:232-8. https://doi.org/10.1016/j.biopha.2018.06.132 PMid:29966965
66. Taherdehi FG, Nikravesh MR, Jalali M, Fazel A, Valokola MG. Evaluating the protective role of ascorbic acid in malathion-induced testis tissue toxicity of male rats. Int J Prev Med 2019; 10:45. https://doi.org/10.4103/ijpvm.IJPVM_253_17 PMid:31143419 PMCid:PMC6528429
67. Oral B, Guney M, Demirin H, Ozguner M, Giray SG, Take G, Mungan T, Altuntas I. Endometrial damage and apoptosis in rats induced by dichlorvos and ameliorating effect of antioxidant vitamins E and C. Reprod Toxicol. 2006; 22(4):783-90. https://doi.org/10.1016/j.reprotox.2006.08.003 PMid:16973328
68. Herrera E, Barbas C. Vitamin E: action, metabolism and perspectives. J Phys Biochem. 2001; 57:43-56. https://doi.org/10.1007/BF03179812
69. Packer L, Weber SU, Rimbach G. Molecular aspects of alpha-tocotrienol antioxidant action and cell signaling. J Nutr. 2001; 131:369S-373S. https://doi.org/10.1093/jn/131.2.369S PMid:11160563
70. Witting PK, Upston JM, Stocker R. Role of alpha-tocopheroxyl radical in the initiation of lipid peroxidation in human low-density lipoprotein exposed to horse radish peroxidase. Biochemistry. 1997; 36(6):1251-8. https://doi.org/10.1021/bi962493j PMid:9063873
71. Stocker R, Bowry VW, Frei B. Ubiquinol-10 protects human low density lipoprotein more efficiently against lipid peroxidation than does alpha-tocopherol. Proc Natl Acad Sci U S A. 1991; 88(5):1646-50. https://doi.org/10.1073/pnas.88.5.1646 PMid:2000375 PMCid:PMC51081
72. Niki E. Role of vitamin E as a lipid-soluble peroxyl radical scavenger: in vitro and in vivo evidence. Free Radic Biol Med. 2014; 66:3-12. https://doi.org/10.1016/j.freeradbiomed.2013.03.022 PMid:23557727
73. Ambali SF, Aliyu MB. Short-term sensorimotor and cognitive changes induced by acute chlorpyrifos exposure in Wistar rats: ameliorative effect of vitamin E. Pharmacologia. 2012; 3:31-8. https://doi.org/10.5567/pharmacologia.2012.31.38
74. Ambali S, Akanbi D, Igbokwe N, Shittu M, Kawu M, Ayo J. Evaluation of subchronic chlorpyrifos poisoning on hematological and serum biochemical changes in mice and protective effect of vitamin C. J Toxicol Sci. 2007; 32(2):111-20. https://doi.org/10.2131/jts.32.111 PMid:17538235
75. Kammon AM, Brar RS, Sodhi S, Banga HS, Singh J, Nagra NS. Chlorpyrifos chronic toxicity in broilers and effect of vitamin C. Open Vet J. 2011; 1(1):21-7.
76. John S, Kale M, Rathore N, Bhatnagar D. Protective effect of vitamin E in dimethoate and malathion induced oxidative stress in rat erythrocytes. J Nutr Biochem. 2001 Sep; 12(9):500-4. https://doi.org/10.1016/S0955-2863(01)00160-7
77. Khatun S, Rajak P, Dutta M, Roy S. Sodium fluoride adversely affects ovarian development and reproduction in Drosophila melanogaster. Chemosphere. 2017; 186:51-61. https://doi.org/10.1016/j.chemosphere.2017.07.123 PMid:28763637
78. Khatun S, Mandi M, Rajak P, Roy S. Interplay of ROS and behavioral pattern in fluoride exposed Drosophila melanogaster. Chemosphere. 2018; 209:220-31. https://doi.org/10.1016/j.chemosphere.2018.06.074 PMid:29936113

79. Dutta M, Rajak P, Khatun S, Roy S. Toxicity assessment of sodium fluoride in Drosophila melanogaster after chronic sub-lethal exposure. Chemosphere. 2017; 166:255-66. https://doi.org/10.1016/j.chemosphere.2016.09.112 PMid:27700992
80. Rajak P, Ganguly A, Sarkar S, Mandi M, Dutta M, Podder S, Khatun S, Roy S. Immunotoxic role of organophosphates: An unseen risk escalating SARS-CoV-2 pathogenicity. Food Chem Toxicol. 2021; 149:112007. https://doi.org/10.1016/j.fct.2021.112007 PMid:33493637 PMCid:PMC7825955
81. Ghanty S, Mandi M, Ganguly A, Das K, Dutta A, Nanda S, Biswas G, Rajak P. Lung surfactant proteins as potential targets of prallethrin: An in silico approach. Toxicol. Environ Health Sci. 2022; 14(1):89-100. https://doi.org/10.1007/s13530-021-00119-0 PMCid:PMC8788395
82. Rajak P, Roy S, Pal AK, Paramanik M, Dutta M, Podder S, Sarkar S, Ganguly A, Mandi M, Dutta A, Das K, Ghanty S, Khatun S. In silico study reveals binding potential of rotenone at multiple sites of pulmonary surfactant proteins: A matter of concern. Curr Res Toxicol. 2021; 4:2:411-423. https://doi.org/10.1016/j.crtox.2021.11.003 PMid:34917955 PMCid:PMC8666459
83. Dutta M, Rajak P, Roy S. Determination of chronic median lethal concentration of sodium fluoride in Drosophila melanogaster and exploring effect of sub-lethal concentrations on differential hemocyte count. Proc. Zool Soc. 2019; 72:111-117. https://doi.org/10.1007/s12595-017-0235-x
84. Sarkar S, Rajak P, Roy S. Toxicological evaluation of a new lepidopteran insecticide, flubendiamide, in non-target Drosophila melanogaster Meigen (Diptera: Drosophilidae). IJT. 2018; 12(3): 45-50. https://doi.org/10.32598/IJT.12.3.477.1
85. Rajak P, Khatun S, Dutta M, Mandi M, Roy S. Chronic exposure to acephate triggers ROS-mediated injuries at organismal and sub-organismal levels of Drosophila melanogaster. Toxicol Res (Camb). 2018;7(5):874-887. https://doi.org/10.1039/C8TX00052B PMid:30310664 PMCid:PMC6116822
86. Rajak P, Dutta M, Roy S. Effect of acute exposure of acephate on hemocyte abundance in a non-target victim Drosophila melanogaster. Toxicol Environ Chem. 2014; 96:768-76. https://doi.org/10.1080/02772248.2014.980131
87. Rajak P, Roy S. Heat Shock Proteins and Pesticide Stress. In: Asea, A., Kaur, P. (eds) Regulation of Heat Shock Protein Responses. Heat Shock Proteins. Springer, Cham. 2018; 13. https://doi.org/10.1007/978-3-319-74715-6_2
88. Sutcu R, Altuntas I, Buyukvanli B, Akturka O, Ozturka O, Koylu H, Delibas N. The effects of diazinon on lipid peroxidation and antioxidant enzymes in rat erythrocytes: role of vitamins E and C. Toxicol Ind Health. 2007; 23(1):13-7. https://doi.org/10.1177/0748233707076758 PMid:17722735
89. Akturk O, Demirin H, Sutcu R, Yilmaz N, Koylu H, Altuntas I. The effects of diazinon on lipid peroxidation and antioxidant enzymes in rat heart and ameliorating role of vitamin E and vitamin C. Cell Biol Toxicol. 2006; 22(6):455-61. https://doi.org/10.1007/s10565-006-0138-5. https://doi.org/10.1007/s10565-006-0138-5 PMid:16964585
90. Sulak O, Altuntas I, Karahan N, Yildirim B, Akturk O, Yilmaz HR, Delibas N. Nephrotoxicity in rats induced by organophosphate insecticide methidathion and ameliorating effects of vitamins E and C. Pestic Biochem Phys. 2005; 83(1):21-8. https://doi.org/10.1016/j.pestbp.2005.03.008
91. Ambali SF. Shittu M, Ayo JO, Esievo KA, Ojo SA. Vitamin C Alleviates Chronic Chlorpyrifos Induced Alterations in Serum Lipids and Oxidative Parameters in Male Wistar Rats. Am J Pharmacol Toxicol. 2011; 6(4):109-118. https://doi.org/10.3844/ajptsp.2011.109.118
92. Bhatti GK, Bhatti JS, Kiran R, Sandhir R. Alterations in Ca^{2+} homeostasis and oxidative damage induced by ethion in erythrocytes of Wistar rats: ameliorative effect of vitamin E. Environ Toxicol Pharmacol. 2011; 31(3):378-86. https://doi.org/10.1016/j.etap.2011.01.004 PMid:21787708