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Review Article
A Brief Review on the Recent Advances in Phytotoxin Mediated Oxidative Stress

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Abstract

The phytotoxins are small molecules including peptides or proteins obtained from plant sources that are harmful to organisms in very low concentrations. Several phytotoxins have been shown to be involved in pathogenesis and generation of various diseases. Among the most potential effects of phytotoxins, the inhibition of many physiological and biochemical processes in plants as well as in animals is noteworthy. The phytotoxins have been shown to induce production of reactive oxygen species (ROS) by altering the balance between the oxidants/prooxidants and antioxidants through promoting lipid peroxidation (LPO) and depleting the antioxidative cellular reserves. The present review illustrates the recent advances made in research in the direction of understanding the chemical nature of phytotoxins, biochemical consequences due to onset of oxidative stress and alterations at the levels of mitochondrial functions, carbohydrates metabolism and T-cell responses in biological systems.

Key words: Phytotoxins, physiological, oxidative stress, biochemical

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INTRODUCTION

A toxin is a poisonous substance of natural origin involving microorganisms, plants and animal species. The term was first used by organic chemist Ludwig Brieger (1849-1919). Toxins can be small molecules, peptides or proteins that are capable of causing disease on contact with or absorption by the body tissues interacting with biological macromolecules such as enzymes or cellular receptors. Toxins vary greatly in their toxicity, ranging from usually minor (such as a bee sting) to almost immediately deadly (such as botulinum toxin)[1,2]. Many plants might appear innocent and harmless at first glance, but there are many which produce toxins dangerous to humans and other animals. Phytotoxins are the toxins of plant origin. The effects of phytotoxin have been mostly reported in terms of inhibition of the physiological and biochemical processes in plants as well as animals[3]. The production of phytotoxins (toxic plant secondary metabolites) for defense is a widely known phenomenon and is even present in agricultural crops[4].

These plants causing harm to the organisms through indirect and direct exposures of plant components. Indirectly, it releases chemicals into the environment through root exudation, leaching and volatilization and passively through decomposition of plant residues which may be taken up by organisms through inhalation, dermal contact, ingestion and accidental events[5]. The phytotoxins interrupt the growth of organisms by altering their physiological and biochemical processes[6,7]. However, the direct exposure may be caused when the plant components or plant parts are directly taken up through inhalation or contact or along with other foodstuffs[8,9]. Toxicity of berberine and sanguinarine in different living system. Both berberine and sanguinarine are isoquinoline derivatives and both have a positive moiety which interacts with a number of nucleophilic and anionic moieties of many biomolecules that distort their structure and responsible for the altered function of biomolecules[10,11].

An extensive survey of available literature indicates that phytotoxin induced oxidative stress (OS) has been considered as a possible mechanism of toxicity and hence it has been a focus of toxicological research these days. The phytotoxins have been shown to induce production of reactive oxygen species (ROS) by altering the balance between the oxidants/prooxidants and antioxidants through promoting lipid peroxidation (LPO) and depleting the antioxidative cellular reserves (both the enzymatic and non-enzymatic) leading to a condition of OS[12-14]. The range of its impact spans from tissue injury and aging through apoptosis to onset of various known/unknown diseases. However, the exact mechanism(s) of their actions in plant and animal systems has still not been completely known[15,16].

Though the existing reports reflected the occurrence of different phytotoxins produced by many plant species and consequences of their exposures in biological systems but still a systematic information on various other aspects such as their chemical nature, impact on metabolic and immune systems as well as perturbations in the redox status in the organisms exposed to such phytochemicals is missing. The present review article is an endeavour to summarise the recent advances made in the direction of understanding the multifaceted aspects of phytotoxins with special reference to their antioxidative potential and pathogenesis in mammalian systems.

PHYTOTOXINS INDUCED OXIDATIVE STRESS AND IMPACT ON IMMUNE SYSTEMS

Oxidative stress can repress the activity of T cells and thus alter the immune response. A decrease in the glutathione-s-transferase (GSH) pool, which elicits OS by raising the intracellular redox potential, causes a marked inhibition of the T cell proliferative response[17]. Several laboratories have reported that oxidative stress inhibits interleukin 2 (IL-2) transcription. This cytokine is produced primarily by helper T cells and regulates the growth and function of various cells involved in cellular and humoral immunity. Sublethal concentrations of H_2O_2 elicit a decrease in IL-2 mRNA levels. Moreover, they repress the transcription of a reporter gene driven by the IL-2 gene promoter, whereas, they activate the promoter of the c-*jun* gene[18].

PHYTOTOXINS MEDIATED OXIDATIVE STRESS AND IMPACT ON MITOCHONDRIAL FUNCTIONS

The mitochondrion is a one of the most powerful generators of ROS within the cell. In this organelle, the electron-deficient dioxygen molecule O_2 is brought close to electron suppliers. Indeed, the respiratory chain involves several successive complexes containing electron carriers (cytochrome c, ubiquinone, etc.) that allow the progressive and controlled reduction of O_2 into water. A dysfunction at one step of this chain may thus result in massive production of ROS. Typically, the inhibition of complex III leads to H_2O_2 release[19]. In addition, several stimuli, such as tumor necrosis factor (TNF) a or ceramide have been shown to induce mitochondrial H_2O_2 release. Crawford *et al.*[20] have shown that mitochondrial RNAs undergo specific degradation upon oxidative stress[20].

Phytotoxins induced oxidative stress and metabolic consequences: The production of ROS associated with the glycation process was reported to inhibit insulin mRNA production in pancreatic beta cells. The oxidative stress activates stress-induced pathways that damage the beta cells by inducing defective insulin biosynthesis and secretion and ultimately apoptosis. Finally, the oxidative stress might also be involved in the hyperglycaemia-induced insulin resistance, which impacts on beta cell function[21]. Assies *et al.*[22] has been reported that oxidative-stress-induced alterations in fatty acid synthesis and one carbon metabolism[22].

Phytotoxins induced oxidative stress and impact on endocrine system: Several studies have reported that oxidative stress can alter hormonal regulation. Oxidation by tetrathionate of the glucocorticoid receptor (GR) resulted in the formation of a disulphide bridge within the protein[23]. In addition, the generation of intracellular H_2O_2 caused hyperoxia and repressed the expression of the tyrosine hydroxylase gene in adrenal-gland-derived cell line[24]. Interestingly, several cytochrome P450 (CYP) isoforms have been shown to release ROS during their catalytic cycles, especially with uncoupled substrates. This ROS production could contribute to repress the expression of oxidative- stress-sensitive genes.

Phytotoxin induced oxidative stress and their responses: Recently, a large number of plants has been studied for their phytotoxic potential. Among them, foliar extracts of *Helianthus annuus* L. (sunflower) was found to contain chlorogenic and isochlorogenic acids, naphthol derivatives and scopolin[25]. It belongs to family Asteraceae and native to North America, the taxa occupy a variety of habitats ranging from open plains to salt marshes. It has various alkaloid, flavonoids, volatile oils and terpenoids[26,27]. The sunflower also actively influences the growth of surrounding plants[28-30]. Phytotoxicity of sunflower residues against *Sorghum vulgare*, *Zea mays*, *Pennisetum americanum* and *Cyamopsis tetragonoloba* has been reported by Batish *et al.*[31] (Table 1, Fig. 1)[31].

The autumn crocus (*Colchicum autumnale*) is a spring and winter flowering species of plant, belongs to the family Iridaceae and native to Great Britain and Ireland, when they bloom they have large flowers with no leaves, which explains their nickname naked ladies. It is a poisonous plant and all parts have been found to contain toxins, particularly the bulb which has the biggest concentration of toxin. Side effects of the exposure with its poison can cause anything from skin allergies to death. There are many documented cases of accidental death related to the autumn crocus (for example, some people have mistaken it for wild garlic and eaten it).

Fig. 1: *Helianthus annuus*

Table 1: Phytotoxicity of some plants

Plants	Families	Plant parts	Effects	References
Helianthus annuus (Sunflower)	Asteraceae	Foliar extracts	Influences the growth of surrounding plants	Azania *et al.*[30]
Colchicum autumnale (autumn crocus)	Iridaceae	Whole plant	Varies effects from skin allergies to death	Bajramovic-Omeragic *et al.*[32]
Ricinus communis (castor plant)	Euphorbiaceae	Oil	Lethal to humans and stops protein being made in the body	Kowser *et al.*[34]
Atropa belladonna (Deadly nightshade)	*Solanaceae*	Berries and leaves	Causes hallucinations	Berdai *et al.*[35]
Aconitum napellus (Monk's-hood)	Ranunculaceae	Root and whole plant	Nervous system and cardiovascular damage	Tuinema *et al.*[36]
Tageteserecta (Marigold)	Asteraceae	Whole plant	Causes damage to the nervous system as well as the digestive and respiratory systems	Santos *et al.*[38]
Eupatorium adenophorum (Crofton weed)	Asteraceae	Leaves	Causes congestion, degenerative to necrotic epithelium changes and gastric mucosa was congested and revealed desquamation of the superficial lining cells in some places etc.	Kaushal *et al.*[42]
Lepidium meyenii (Maca)	Brassicaceae	Root	Innocuous to mice	Valerio and Gonzales [39]
Uncaria tomentosa (cat's claw)	Rubiaceae	Whole plant	Acute oral toxicity in mice	Valerio and Gonzales[39]

Fig. 2: *Colchicum autumnale*

Fig. 3: *Ricinus communis*

Symptoms of poisoning by this plant may often look like those seen for arsenic poisoning and there is no antidote for it. However, in small amounts, it has been shown to be beneficial to treat gout and rheumatism, as well as leukaemia and is used in medicines for these conditions (Table 1, Fig. 2)[32].

The castor oil plant, *Ricinus communis*, also known as *Palma christi* or wonder tree, is a perennial scrub of the spurge family Euphorbiaceae and originated from Africa. *Ricinus communis*, produces seeds which contain the toxin known as ricin[33]. This toxin can be lethal to humans if ingested and the castor oil plant is known as the most lethal plant in the world (as little as four or five seeds can provide a lethal dose),

Fig. 4: *Atropa belladonna*

although cases involving fatalities are quite rare as the effects take a while to appear. It is known to interfere translation process in the exposed organisms. A full recovery, however, can often be made with the appropriate treatment. Due to its toxicity, the plant possesses a natural defense against the pests. The ricin is still under investigation to evaluates its potential to be used as an insecticide (Table 1, Fig. 3)[34].

Belladonna, or *Atropa belladonna*, is a member of the *Solanaceae* family of plants and one of the deadliest plants in the UK. Both, its berries and its leaves are highly toxic, as they contain alkaloids which have anticholinergic properties and they can cause side effects such as hallucinations (Fig. 4)[35]. It has been observed that consumption of 2-5 berries is enough to kill a child, while 10-20 can kill a fully-grown adult. As with *Aconitum napellus*, it has often been used to make poison-tipped arrows for assassination. *Aconitum napellus* is more commonly known as 'monkshood' or 'wolfsbane'. It is a perennial plant which grows with hairless stems and rounded, hairless leaves. It contains toxic alkaloid compounds, including a cardiac poison which has been used throughout history to tip weapons to eradicate enemies. It has an unpleasant taste that means it is rare to be poisoned by accident. Aconite, a chemical produced in the roots of the plant, is used in some Chinese medicines. However, overdose due to misuse of these medicines can lead to damage of nervous system and cardiovascular system and even death in some extreme cases (Table 1, Fig. 5)[36].

Tagetes erecta L. is a member of Asteraceae family having industrial and medicinal value. It contains phytochemicals including pyrethrins, thiophenes and lutein[37]. Often used as a nematicide and an insecticide, the toxin from the *Tagetes*

Fig. 5: *Aconitum napellus*

Fig. 7: *Lepidium meyenii*

Fig. 6: *Tagetes erecta*

Fig. 8: *Uncariato mentosa*

erecta (marigold) plant (more specifically the marsh marigold) causes damage to the nervous system as well as the digestive and respiratory systems in the larvae of many insects. This toxin is mainly found in the growing shoots of the plant and can cause irritation and blistering if it comes into contact with the skin. However, if the toxin is ingested, it can be very dangerous once digested. This plant has been reported to be used in herbal medicine (Table 1, Fig. 6)[38].

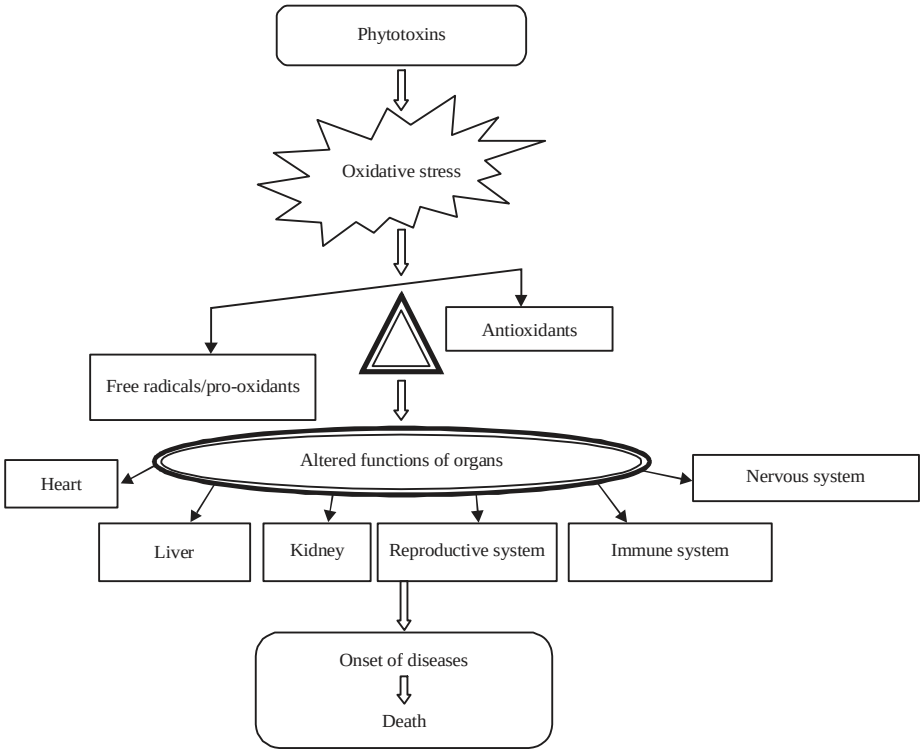
Lepidium meyenii or maca is an herbaceous biennial plant of the Brassicaceae family native to the high Andes of Peru. Maca, a root vegetable grown in the Peruvian Andes, has been used as a food and medicine in South America for several hundred years. It exhibits the potential to enhance strength and endurance. The, In can warriors were known to often consume maca before long journeys and battles. Studies were performed in 30 days old mice receiving acute doses of micro-pulverized maca ranging from 11-15 g kg^{-1} mice to evaluate its impact from 8 h after administration up to 7 days post-administration. It was observed that ingestion of doses <15 g kg^{-1} is innocuous to mice (Fig. 7). In another study with the animals consuming aqueous (polar) and hydroalcoholic (relatively non-polar) extract preparations of *Uncaria tomentosa* (cat's claw) indicated a low degree of acute oral toxicity[39]. *Uncaria tomentosa* belongs to family Rubiaceae, is a woody vine native to the Peruvian Amazon widely used in folk medicine for many purposes (Table 1, Fig. 8)[40].

Eupatorium adenophorum is a well-known noxious invasive weed belonging to genus and family Eupatorium and Asteraceae, respectively[41]. It has been reported that

administration of freeze dried *E. adenophorum* leaf powder to mice results into toxicity. All the animals that received *E. adenophorum* leaf powder became dull. The hair coat was found to be rough and the pinnae of the ears and the paws was found to be a yellowish tinge. The loss in body weight was also recorded (Fig. 9). The urine from the animals in the test group became positive for bilirubin at 24 h and the color reaction increased thereafter. There was a significant decrease in the feed intake of the animals in the test group. All the animals in the test group were moribund when euthanized 48 h after the start of feeding the *E. adenophorum*. Postmortem examination of the animals in the test group revealed that the subcutaneous tissue and musculature were yellowish. The gastric mucosa was severely congested, with haemorrhages in two animals. The intestine showed mild to moderate congestion. There was a significant increase in the total and conjugated bilirubin concentration in the plasma. The creatinine, urea and protein contents in the plasma were comparable in the test and control groups. There were significant increases in plasma alkaline phosphatase, 5'nucleotidase, aspartate and alanine aminotransferases and lactate dehydrogenase activities, but no significant change was observed in leucine aminopeptidase or acid phosphatase activity[42]. Focal areas of necrosis and biliary proliferation were observed throughout the liver parenchyma of the poisoned animals. Hepatocytes showed megalocytosis. The bile ducts were dilated and their epithelium showed degenerative to necrotic changes. The gastric mucosa was congested and revealed desquamation of the superficial lining cells in some places. The other organs examined did not reveal any detectable histological lesions (Table 1)[43].

Fig. 9: *Eupatorium adenophorum*

The cascade of oxidative stress mediated events taking place in a biological system exposed to the phytotoxins is summarized in Scheme 1.



Scheme 1: Multifacilated impacts of phytotoxins

CONCLUSION

The summary of the present review illustrates the current understanding of phytotoxins in the direction of its recent advances. The alterations in the biochemical consequences due to the onset of oxidative stress caused by phytotoxins generated free radicals. Oxidative stress also responsible for alterations at the levels of mitochondrial functions, carbohydrates metabolism and T-cell responses in biological systems. The phytochemical constituents of plants vary from one to another. The presence and the amount of particular compound responsible for the nature of plant. Sunflower actively influences the growth of surrounding plants. Side effects of the exposure with Autumn crocus poison can cause anything from skin allergies to death. Due to castor oil plant toxicity, the plant possesses a natural defense against the pests. Marigold plant causes damage to the nervous system as well as the digestive and respiratory systems in the larvae of many insects and also used as herbal medicine. Cat's claw indicated a low degree of acute oral toxicity. It is also used as folk medicine. *Eupatorium adenophorum* administration is responsible for several biochemical and physiological changes.

The phytochemicals having toxic effects on organisms by using very low concentrations are defined as phytotoxin. It is proteinaceous in nature. A number of phytotoxins have been reported to be involved in pathogenesis and responsible for the onset of various diseases. The phytotoxins alter biological responses by inhibiting several physiological and biochemical processes in plants as well as in animals. The mechanism involved in toxicity of phytotoxin is production of reactive oxygen species (ROS). Oxidative stress causes lipid peroxidation (LPO) and alterations of mitochondrial functions, carbohydrates metabolism and immune responses in biological systems. It also depleted the antioxidative cellular reserves and causes injury to liver, kidney and heart. The phytotoxins also affects the reproductive system, nervous system, immune system and cardiovascular system. The efforts are needed to conduct extensive research in the direction of mitigation of adverse impacts of phytotoxicants using antidotes of biological origins.

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