Phytochemicals as Immunomodulators for Environmental Pollutant-Induced Toxicities in Animals

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SUMMARY

The residual effects of environmental pollutants have been more profound in this era due to the irrational uses of the chemicals and have serious effects on the health of humans and animals. Phytochemicals have the potential to be the cheapest source of immunomodulators to mitigate the toxic effects of these pollutants, so their potential need to be explored more precisely through scientific trials. These are the natural resources which can be utilized due to their extensive biological functions being anti-inflammatory and immunomodulatory properties. Exposure to these pollutants can lead to a range of toxicities, including immune dysfunctions. Certain phytochemicals, such as carotenoids, flavonoids, terpenoids, and phenolic acids, can help modulate the immune response and decrease the harmful effects of environmental pollutants. Polyphenols are the largest group of antioxidants that are primarily found in plants and can interact with reactive oxygen species, reducing their concentrations and lowering the incidence of lipid peroxidation in animals. The protective effects of phytochemicals may relate to the type of pollutant, the duration, and dose of exposure. In addition to their immunomodulatory effects, phytochemicals have also been shown to have other health benefits, such as anti-cancer properties, neuroprotection, and cardiovascular protection. This makes them an attractive option for protecting against a range of environmental pollutants, which can have systemic effects on health.

INTRODUCTION

Over the past few decades, due to rapid industrial and human development, the ecosystem has been affected drastically and environmental pollution has emerged as a serious threat globally. Many factors have a potential role in this scenario including irrational use of chemicals and agrochemical products to improve crop yield through pest/insect control, household and sewage waste mining operations, and open-air dissolution have all contributed significantly to environmental pollution. Animals and humans both are exposed to these hazards in the form of residues of these numerous dangerous substances including heavy metals mainly through the industrial waste by-products being released in enjoinment without any prior treatment and this threat is increasing with every passing day (Xiao et al., 2019). When animals are exposed to toxic substances such as pesticides, chemical contaminants, heavy metals, fungal and microbial toxins, or even some pharmaceuticals, fatal accidental toxicity is common. Exposure to chemicals, whether natural or manmade, has emerged as a global public health issue. Toxic compounds can be ingested, inhaled, or directly contacted by humans or animals and can also be found in the soil, air, foods, and vegetables, as well as in pharmaceutical items (Xiao et al., 2019).

These harmful substances can cause noxious effects on the liver, kidney, heart, brain, and reproductive system as well as non-organ-directed noxiousness (carcinogenesis, teratogenicity, and hormonal disruption). Oxidative stress may play a role in adverse environmental consequences, which are the catastrophic sources of animal and human toxicity. Free radicals and oxidative signaling pathways that cause early aging and neurological illness might originate from exposure to

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environmental pollution (Junqueira et al., 2004). Many clinical abnormalities, including aging, neurological illnesses, malignancy, cardiovascular disorders, xenobiotic-induced toxicities, and diabetes have an association with oxidative stress (Valko et al., 2007). These circumstances have been shown to affect apoptosis, inflammatory processes, and redox status in a number of signaling pathways.

Oxidative stress is a term that refers to imbalanced conditions between the oxidants' production and the capability of cellular defense mechanisms to eliminate them. Normal metabolism of oxygen in aerobic organisms constantly produces reactive oxygen species (ROS) as a by-product. For example, mitochondrial respiration and rapid development associated with the production of significant amounts of reactive oxygen metabolites and other free radicals may produce oxidative stress in developing embryos and hatchlings (Sahin et al., 2011). Along with these another important source of exogenous stressors is the heat in the current livestock sector which is one of the critical issues affecting production and performance and leads to physical defects (Ajakaiye et al., 2011).

Natural or artificial compounds that regulate and maintain the immune system are known as immunomodulators. Immunomodulators control immune responses to aid in regaining immunity for the purpose of treating disorders. The incorporation of phytochemicals in diets stabilizes and changes the intestinal microbiota and reduces microbial toxic metabolites present in the gut, due to their antibacterial actions on numerous disease-causing bacteria, relieving gastrointestinal challenges and immunological stress and thus enhancing performance both in animals and humans (Settle et al., 2014). Reduction in oxidative stress and increase in antioxidant activity in many tissues, together with a consequent improvement in health, are two additional significant positive effects of including phytochemicals in the diet. Moreover, phytochemicals have immunomodulatory effects that include increased proliferation of immune cells, altered cytokines, and elevated antibody titers (Lee et al., 2017).

Synthetic antioxidants have received substantial consideration to enhance the health status, performance, and quality of animal products. However, possible side effects of synthetic antioxidants have been questioned by their innocence (Lin et al., 2016). Research on natural antioxidants in the field of animal nutrition is gaining much attention nowadays. Animal studies have shown that phytochemicals have favorable antioxidant effects, improving performance, product quality, and cellular antioxidant status either directly by changing specific molecular targets or indirectly by affecting the metabolic process through stable conjugates (Aggarwal et al., 2006). Therefore, it is essential to investigate the antioxidant capabilities and processes involved in dietary phytochemicals.

In this context, the use of natural dietary ingredients as remedies has drawn significant interest. Because of their anti-apoptotic, antioxidant, and anti-inflammatory qualities, phytochemicals are utilized to combat toxicities caused by radiation, toxins, and other environmental factors. They are employed to combat the chemical toxicity brought on by ingested medications or industrial contaminants. Against toxic substances, herbs or herbal mixtures have been shown to have both preventative and therapeutic effects. So in this chapter thorough information has been provided regarding the environmental pollutants-induced toxicities and the role of phytochemicals available as protective agents.

ENVIRONMENTAL POLLUTANT-INDUCED TOXICITIES AND THEIR SOURCES

Toxins are either biological or formed by living organisms such as fungi, bacteria, snake venom, or industrial chemicals. Several of these hazardous substances have been created by synthetic means and are now utilized as pesticides, herbicides, fungicides, or even medications. They are also produced during industrial processes and act as environmental contaminants like heavy metals.

NATURALLY INDUCED TOXICITIES

It has been reported that many preclinical models of naturally occurring toxins such as bacterial and fungal toxins can cause toxicities of multiple organs. A few of them have been discussed in detail. A variety of filamentous fungi, including Aspergillus, Fusarium, and Penicillium, produce mycotoxins, which are harmful secondary metabolites. It has been documented for its nephrotoxic, hepatotoxic, carcinogenic, and teratogenic deleterious effects, as well as for the economic losses when it contaminates the food chain and feed products (Luo et al., 2018). The common mycotoxins found in foods include aflatoxins, ochratoxins, fumonisins, patulins, and zearalenone. During liver injury caused by AFB1, serum enzymes including, aspartate transaminase, alkaline phosphatase (ALP), alanine aminotransferase (ALT), and LDH are secreted into the plasma. By neutralizing ROS and activating the Nrf2/HO-1 pathway, antioxidant defense mechanisms can be used to detoxify AFB1 and protect the liver from damage (Vipin et al., 2017). Other toxins include such as Gram-negative bacteria that have lipopolysaccharide (LPS) in their outer membrane. Upon infection, it causes sepsis, a generalized inflammatory response, and numerous organ dysfunctions.

CHEMICAL-INDUCED TOXICITIES

Organs like the liver, kidneys, heart, brain, gastrointestinal tract, and reproductive system are severely harmed by chemical toxicants such as heavy metals, pollution, pharmaceuticals, pesticides, and recreational drugs. Environmental disturbances have the potential to disrupt cellular redox processes and induce oxidative stress. The primary source of intracellular ROS generation is mitochondria (Ahmadian et al., 2017; Fard et al., 2016). The electron transport chain's proximity to mitochondrial DNA and the absence of protective histone proteins causes mitochondrial DNA damage induced by oxidative stress, which is accompanied by instability of the mitochondrial genome, disruption of the electron transport chain, collapse of the mitochondrial membrane, insufficient production of energy and eventually cell death (Ahmadian et al., 2017).

HEAVY METALS-TOXICITIES

Hepatotoxicity, nephrotoxicity, genotoxicity, and neurotoxicity are all outcomes of heavy metal toxicity, which includes mercury, lead, cadmium, iron, arsenic, and aluminum (Valko et al., 2005). Oxidative stress has generally been associated with metal-induced cytotoxicity. Several metal-induced toxicities have been studied in relation to DNA oxidative damage, lipid peroxidation, and changes in the balance of calcium and sulfhydryl (Pulido & Parrish 2003). In the context of a collapsed mitochondrial membrane potential, antimony (Sb) causes the formation of ROS and mitochondrial malfunction. Moreover, it activates the c-jun kinase (JKN) pathway, which in turn accelerates the oxidative stress cascade (Mann et al., 2006).

INSECTICIDE, PESTICIDE, HERBICIDE, AND FUNGICIDE TOXICITIES

Insecticides containing organophosphates (OP) are widely utilized in domestic and agricultural settings worldwide. Another pro-oxidant chemical that is frequently employed in agriculture and other settings exposes pesticides. One of the main mechanisms of pesticide toxicity has been identified as the induction of redox signaling (Eftekhari et al., 2018). After exposure to pesticides, accumulation of radical intermediates, DNA oxidative damage, and lipid peroxidation have been identified (Bagchi et al., 1995). Pesticides that are frequently used include carbendazim, malathion, phosphoramidite, dichlorvos, lindane, and lambda-cyhalothrin.

Organophosphorous pesticides (OPs) cause the death of brain and immunological cells by interacting with mitochondrial pathways (Carlson et al., 2000). According to studies, chlorpyrifos and dichlorvos can induce oxidative stress, depletion of glutathione, mitochondrial depolarization, and caspase-dependent apoptosis (Li et al., 2007). Another herbicide that causes oxidative stress is the organophosphorus chemical malathion, which alters antioxidant networks and produces reactive species in a variety of rat organs (Abdollahi et al., 2004). The Schematic diagram shows the mechanism of action of pesticide toxicity in cells through ROS production (Fig 1.).

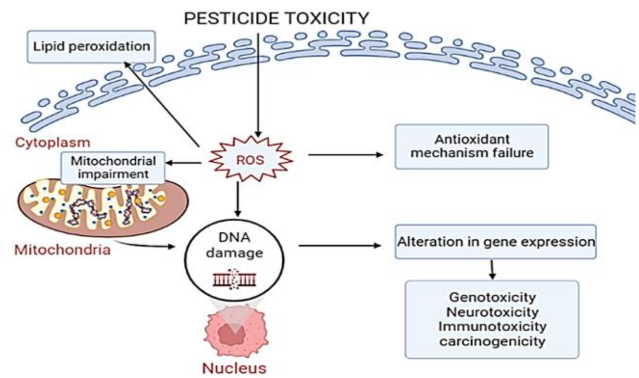

Fig 1. Mechanism of oxidative stress caused by pesticides

DRUG-INDUCED TOXICITIES

After administering the medication, one could encounter harmful and unanticipated adverse effects. This could be a result of off-target binding, its hazardous metabolites, inadequate kinetics, improper concentrations of on-target binding, or possibly both. Common medications that seriously harm the liver and kidneys include aspirin, acetaminophen, non-steroidal anti-inflammatories, diclofenac, and indomethacin (Alsherbiny et al., 2019). Due to their strong resistance to biological and environmental degradation, persistent organic pollutants linger in the environment and build up in the food chain.

HALOGENATED AND POLYCYCLIC AROMATIC HYDROCARBON (PAH)-INDUCED TOXICITIES

One of the most prevalent environmental contaminants, halogenated aromatic hydrocarbons (PAHs) produce a variety of toxicities, including genotoxicity, immunotoxicity, carcinogenicity, and teratogenicity (Kasai et al., 2008). The key starting point for the intracellular signaling of these substances is through the aryl hydrocarbon receptors (AhR), which are involved in the detoxification processes of several xenobiotics that cause oxidative stress, breaks in DNA strand, and mutagenic metabolites (Nebert et al., 2000). Benzo[a]pyrene (BAP) and Tetrachlorodibenzo-p-dioxin (TCDD), two of the most pervasive halogenated aromatic hydrocarbons that have been related to oxidative stress and a high risk of cancer in many organs (Kim and Lee, 1997; Emre et al., 2007).

IMMUNE SYSTEM AND ROLE OF IMMUNOMODULATORS AGAINST ENVIRONMENTAL POLLUTANTS

Non-specific immunity is also called innate immunity, comprised of activation and carrying innate leukocytes like macrophages, whereby increasing phagocytosis. Innate leukocytes recognize pathogens as they are captured. By engulfing them and releasing cytokines, these leukocytes initiate the immunological response and regulate the inflammatory response (Akira et al. 2006). Specific immunity known as adaptive immunity in the immune system commenced by the emergence of antigens. B and T cells are capable of identifying and excluding foreign stimuli or infections. Effector cytokines cause the helper T-cells to differentiate into Th1 or Th2 cell types. These cells, correspondingly, transmit signals to macrophages and B cells (Akira et al., 2006).

Toll-like receptors (TLRs) from the innate immune system are frequently studied pattern-identification receptors in animals. Through adapter proteins like MyD88 (myeloid differentiation primary response 88) and toll-IL-1-resistance domain-including adaptor, numerous signaling pathways are simultaneously activated as TLRs are activated, generating interferon. (Zhu et al., 2010). Nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPKs) are the two principal pathways that elicit immunological responses, and both of them are activated by the Src kinase (Yu et al., 2012).

MAPKs are a class of protein kinases, that regulate cellular processes. Extracellular signal-modulated protein kinase (ERK1/2), p38 protein kinase, and the modulation of inflammation and immunity in response to environmental stress are all members of the MAPK family c-Jun N-terminal kinase (Luo et al., 2018). The unrestricted form of NF-κB can enter the nucleus, bind to a specific region of DNA, and influence the expression of the genes it stimulates. In order to control inflammatory reactions and the immune system, the translated proteins are released into intercellular space (Yu et al., 2012).

The three frequently evaluated pro-inflammatory cytokines i.e. IL-1, IL-6, and tumor necrosis factor-alpha (TNF-α) that can be shown by macrophages and monocytes after entering pathogens are recognized. The cytokines affect metabolic processes, enhancing immune response and disease encounters for outstanding growth performance (Johnson, 1997; Shini et al., 2010).

PHYTOCHEMICALS AS IMMUNOSTIMULANTS

Plants and plant-based products are very effective as immunostimulants. From different studies, it has been revealed that herbal plants influence their beneficial effects on animals' immune systems mainly by producing secondary metabolites (Hashemi et al., 2010). Immune modulation and immunostimulants influence herbal plants and their derivatives including herbal plant polysaccharides, saponins, Isatis root, Astragalus root, Achyranthes root, and phytosterol has been widely considered. Even though there are few studies that have shown the mechanism of action of the immune-modulatory compounds of herbal plants, but accurate molecular mechanisms of many herbs are not well known, yet. Many polysaccharides from medicinal plants can activate the impression of many toll-like receptors (TLR). Furthermore, Th1/Th2 balance plays an essential role in immune modulation. Many nutrients and hormones quantifiable impact Th1/Th2 balance, containing plant sterols/sterolines, melatonin, and many other long-chain fatty acids like eicosatetraenoic acid (EPA) and docosahexaenoic acid (DHA) (Takeda et al., 2004).

FREE RADICALS' PRODUCTION MECHANISM

Free radicals are high-energy-containing atoms, ions, molecules, or compounds that have one or more unpaired electrons in their outer shell (Papadopoulou et al., 2017) and this causes them to be unstable and tend to become stable by gaining an electron from nearby particles (Halliwell & Gutteridge 2015). Free radicals are formed when ATP is produced in the mitochondria by oxygen present in the body cells that possess the oxidizing ability (Pham-Huy et al., 2008). The body rapidly produces free radicals in response to different cellular activities, as waste products of cellular chemical processes, or when exposed to chemicals, radiations, or environmental contaminants (Papadopoulou et al., 2017). High activity of free radicals accelerates intracellular damage, the breakdown of cell membranes and organelles, and changes the functional efficiency of cells caused by oxidative processes, and ultimately cell degradation and death occur (Phaniendra et al., 2015). This results from lipid peroxidation, an increase in malondialdehyde (MDA) levels, and the oxidation of "unsaturated fatty acids" occurring in cells and their components (Halliwell & Gutteridge 2015).

ROLE OF ANTIOXIDANTS AGAINST FREE RADICALS

Antioxidants can be defined as chemical compounds that serve as the body's first line of defense against the damaging effects of free radicals by reducing or suppressing biomolecule oxidation by scavenging ROS or donating an electron or and transforming them into stable species that are unable to react with the body molecules (Nimse & Pal 2015). Thus, antioxidants lower the intensity of oxidative stress, which affects the cellular structure and its function (Estévez, 2015), reduce diseases caused by it, and increase the body's immunity (Surai et al., 2019). The establishment of antioxidant systems in poultry production has been proven to be beneficial for surviving in an oxidative environment. It includes exogenous antioxidants (carotenoids, vitamin E) and endogenous antioxidants (GSH, glutathione, and the enzyme Co-Q) and they sufficiently fulfill the physiological needs of the body (Surai, 2019).

Antioxidants work by reducing or delaying the oxidation of biomolecules and making them less reactive toward body cells. Some antioxidants scavenge free radicals, neutralize them, and convert them into vitamins E or C which are less harmful. The antioxidant defense system of cells comprises three protection levels. 1st level is activated by the direct action of antioxidant enzymes (CAT, SOD, and GSH-Px) that cause the removal of free radicals (Ighodaro & Akinloye 2018). 2nd level is achieved by free radical scavengers (vitamins A, C, E, and glutathione) (Irshad & Chaudhuri 2002). 3rd level is attained by the removal or repairment of damaged biomolecules (methionine sulfoxide reductase, phospholipases, and proteosomes) (Ighodaro & Akinloye 2018).

PHYTOCHEMICALS AS ANTIOXIDANTS

Phytochemicals are non-nutritive substances, originating from plants and fungi, having dietary factors which play important functions in the body of animals (Abbas et al., 2015). These dietary components have many advantages such as they are highly available, cheaper, and relatively less toxic, and their nutritional therapy is used in the treatment and prevention of numerous diseases (Cardozo et al., 2013). Research on nutraceuticals, food ingredients, and natural health supplements has gained a lot of attention in recent years due to the defensive properties of these phytochemicals has been discovered in humans and animals (Barnes, 2001; Bergman et al., 2001). Based on their chemical structures which are involved in various bioactive actions, they are divided into four classes such as polyphenols, alkaloids, terpenoids, and sulfur compounds (Barbieri et al., 2017).

Many natural substances found in dietary sources have been identified to have antioxidant properties. Thymol, carvacrol, and 6-gingerol were found to have beneficial antioxidant effects (Aeschbach et al., 1994). These compounds are crucial in the search for natural antioxidants that can replace synthetic ones. Despite the widespread presence of antioxidants such as vitamins C and E, phenolic acids and flavonoids are thought to have antioxidant activity that is significantly higher than that of the key vitamins in fruits, vegetables, spices, and herbs (Wang et al., 1996). Polyphenols are chemical compounds found within plants that have over 8,000 structural variations and are distinguished by having aromatic rings with one or more than one hydroxyl group. They are further divided into different classes which include phenolic acids, flavonoids, stilbenes, and lignans (Rahman et al., 2006). When one of the above compounds interacts with ROS, scavenging causes an acquired electron to delocalize over the phenolic antioxidant and stabilize due to the aromatic resonance of the nucleus, which stops the continuity of the chain reaction of free radicals (Tsao & Deng 2004). This is just one of the many antioxidant qualities of phenolic compounds, in contrast to synthetic antioxidants, which have a single mode of action, polyphenolic substances block oxidation through a variety of ways (Kahkonen et al., 1999). They are also responsible for important biological actions like controlling oxidative stress, preventing debilitating disease, and lowering the chances of cardiovascular disease (Han et al., 2007).

Some examples of phenolic compounds (Fig 2) like flavonoids are polyphenolic substances that are present in many different types of plants and give seeds, grains, flowers, vegetables, leaves, fruits, and bark their color (Iskender et al., 2016). The beneficial antioxidant properties of flavonoids are largely responsible for their favorable impact on animal health (Panche et al., 2016). Carotenoids are pigments that give color to fruits and vegetables. They are soluble in body fat and can be converted into vitamin A. They function as an antioxidant and deal with free radicals that harm tissue all over the body (Engwa, 2018).

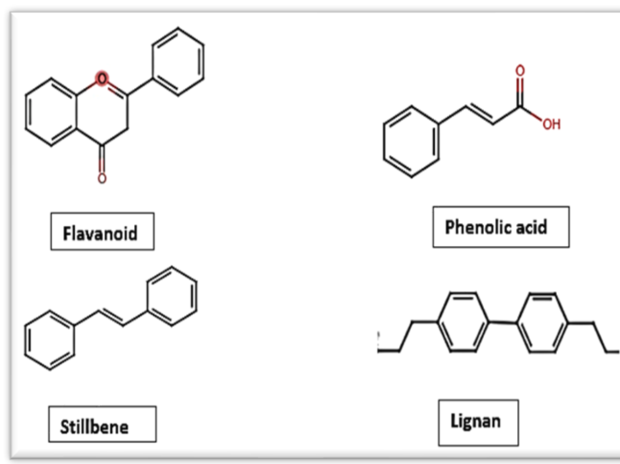

Fig 2. Chemical composition of different polyphenols (Lee et al., 2017).

INTERACTION OF PHYTOCHEMICALS WITH ROS (RELATED TO MOLECULAR TARGETS)

Cells contain various complex mechanisms for sustaining redox equilibrium, which can be categorized into two kinds of antioxidants, in order to counteract and eliminate the harmful effects caused by ROS. First are called direct antioxidants that have redox activity, administered in high doses and they can be regenerated or supplemented due to shorter half-life. While indirect antioxidants have a longer half-life and they augment the antioxidant capacity of cells through Nrf2 (master regulator of the antioxidant response) by increasing specific proteins which encode antioxidant proteins (Engwa, 2018). Key transcription factor, Nrf2 activates genes through antioxidant response element (ARE) located on promotor regions of different antioxidant enzymes (CAT, NAD(P), and SOD) which are involved in protection against oxidative stress. Under normal circumstances, Nrf2 is bound to cytoskeleton binding protein (Keap 1), however, when oxidative stress occurs, this binding is disrupted which leads to translocation and heterodimerization of Nrf2 in the nucleus and transcribes cytoprotective genes (Tapia et al., 2013).

Curcumin is an element found in turmeric, a polyphenolic phytochemical, that reduces oxidative stress and maintains various antioxidant enzymes' actions by controlling Nrf2 (Tapia et al., 2013). Chickens offered feed with turmeric has higher gene expression of SOD, which allows curcumin to enhance its antioxidant status. Sahin et al. (2012) indicated that the expression level of HO-1 and Nrf2 raised linearly by supplementing curcumin in heat-stressed quail. According to Garg and Maru (2009), curcumin boosted Nrf2's ARE binding and stimulated the activity, expression, and mRNA transcripts for GST and NQO1; the lung and liver of mice given dietary curcumin showed decreased oxidative stress. Increasing the basic feed for broilers by 0.3 and 0.6 g/kg of turmeric powder increased the activity of SOD and CAT.

Catechin majorly found in green tea; is a monomer of flavonols that includes a number of related chemicals like epicatechin, EGCG, and epigallocatechin (Sahin et al., 2010). Sahin et al. (2010) investigated the mode of action of EGCG in heat stress by supplementing EGCG in quail's diet. MDA levels in the liver decreased while Nrf2 expression increased. Katiyar et al. (2001) and Meng et al. (2008) found that human fibroblasts exposed to hydrogen peroxide and skin subjected to oxidative stress from UV radiation both benefit from the antioxidant properties of EGCG.

Resveratrol is a polyphenol present in peanuts, cranberries, and grapes that can stop the formation of free radicals and harmful effects of ROS preventing cytotoxic effects (Sahin et al., 2012). The resveratrol increased the activities of the antioxidant enzyme by enhancing the expression and accumulation of Nrf2 in the nucleus, which protected keratinocytes of humans from oxidative stress induced by ultraviolet-A radiations. Palsamy & Subramanian (2011) found that resveratrol therapy can stabilize and enhance the genetic expression of Nrf2/Keap1 and genes regulated by Nrf2, including CAT, SOD, NQO1, HO-1, and γ-GCS. This was discovered both in vivo and in vitro research in mice. According to Sahin et al. (2012) resveratrol administration elevated the activity of antioxidant enzymes of liver (CAT and SOD) in quail that received resveratrol supplementation. Resveratrol's cytoprotective properties have recently been used in the field of animal nutrition to combat the harmful effects of oxidative stress.

Traditional medicine uses the leaves of the mulberry plant, which are inexpensive and have medicinal applications. The leaves' high phenolic content, which has strong antioxidant properties, is primarily responsible for these benefits (Chan et al., 2009). Andallu et al. (2014) found that the extract of mulberry leaves has not only high reducing power but also able to scavenge free radicals effectively including NO, superoxide, and DPPH radicals. In-vivo study provides additional evidence for the antioxidant properties of mulberry leaves by demonstrating that lipid peroxidation was reduced in erythrocytic membranes that were given a treatment of mulberry leaves extract. Lin et al. (2016) identified that better oxidative status of serum indicators was merely one way that the antioxidant qualities exhibited in vitro may function and be reflected in vivo such as decreased MDA level and increased activity of SOD, but also changes in the fundamental gene expression, such as the increase in Nrf2 and antioxidant molecules (GST and HO-1), as well as decrease the formation of factors producing ROS.

Lycopene, a carotenoid found in large quantities in tomatoes, and its derivatives are very effective antioxidants that provide defense against cellular damage caused by free radicals (Ali et al., 2014). Lee et al. (2017) reported that lycopene can control molecular targets of a redox reaction, including activation of Nrf2 and protein kinases which also affect enzymatic activity. In quail raised under heat stress, Sahin et al. (2011) studied the potential health benefits of lycopene found in tomato powder. They discovered that adding tomato powder to the diet decreased the MDA levels in the blood, muscles, and liver of all the birds in both the heat stress and thermoneutral groups. Linnewiel et al. (2009) reported that rats receiving lycopene supplements showed enhanced gene expressions of glutathione, Nrf2, HO-1, and antioxidant enzymes (SOD, GSH-Px and CAT). They also stated that lycopene might neutralize ROS and stimulate the antioxidant machinery by activating Nrf2. The buildup of natural lycopene in tissue may be the cause of the positive benefits.

Turmeric belongs to the genus Curcuma, the main phytochemicals found in the rhizome of turmeric vary greatly depending on the environment and region. The turmeric rhizome powder is used in the majority of investigations to evaluate this photogenic (TRP). 42-day-old broilers were challenged with Sheep RBCs, and TRP introduction in the meal dramatically boosted blood IgG, IgA, and IgM levels and lowered the monocytic ratio (Emadi & Kermanshahi 2007). According to Nouzarian et al. (2011) 0.33%, 0.66%, and 1.0%

inclusions of TRP considerably decreased the content of abdominal fat and concentration of serum triglyceride. Consequently, dietary curcumin may control animal immunological responses and potentially improve growth performance.

There is a significant proportion of trans-cinnamaldehyde in several Cinnamomum species' essential oils. It has been shown that adding leaves of cinnamon or its oil extract to the diet enhances broiler growth and reduces the level of coliform bacteria in the small and large intestine (Emadi & Kermanshahi 2007). The main bioactive substance of cinnamon, cinnamaldehyde, has been observed in in-vitro experiments to decrease the expression of mRNA for pro-inflammatory cytokines like TNF, IL-1, and IL-6, while increasing the production of cytokines that have anti-inflammatory activity like IL-10 in LPS-activated J774A.1 cells. After that, NO generation, expression of both iNOS and COX-2 were downregulated (Pannee et al., 2014). According to Linnewiel et al. (2009), cinnamaldehyde could prevent LPS from activating NF-B and IRF-3, which would lower the production of the target genes of TLR4 (IFN-β and COX-2).

Carvacrol is a phenolic monoterpene, the primary active ingredient in the essential oils of oregano and thyme. Lu et al. (2014) reported that carvacrol decreased COX2 and IL1 mRNA levels as well as local levels of IL1 and PGE2 in mice. Carvacrol's anti-inflammatory actions were demonstrated by Zou et al. (2016) who found that it reduced the protein levels of MAPKs and NF-B, and also the production of the pro-inflammatory cytokines IL-1, IL-6, TNFα, INF and monocytic chemotactic protein-1 in the pigs' jejuna. Lu et al. (2014) identified when broilers were supplied essential oils that contained 81.89% carvacrol after being exposed to Eimeria oocysts, there was a decreased expression of LPS-induced TNF-factor and IL-6.

CONCLUSION

The effects of environmental pollutants on animals has been tremendously increased and becoming an emerging public health issue in most of the developing nations around the globe due to the potential health risks associated with exposure. Phytochemicals has the potential to be cheapest source of immunomodulators to mitigate the toxic effects of these pollutants, so their potentials need to be explored more precisely through scientific trials. They are naturally occurring substances found in plants that have been shown to have an extensive range of biological functions, including anti-inflammatory and antioxidant properties. Environmental pollutants are a major concern worldwide due to their adverse effects on the health of humans and animals. Exposure to these pollutants can lead to a range of toxicities, including immune dysfunctions. Research have shown that certain phytochemicals, such as carotenoids, flavonoids, terpenoids, and phenolic acids, can help modulate the immune response and decrease the harmful effects of environmental pollutants. NF-κB and Nrf2 both are the transcription factors that dominate in inflammatory and oxidative stress pathways and they are ideal targets for studying their correlation. Polyphenols are the largest group of antioxidants that are primarily found in plants and can interact with reactive oxygen species, reducing their concentrations and lowering the incidence of lipid peroxidation in animals. The protective effects of phytochemicals may relate to the type of pollutant and the duration and dose of exposure. In addition to their immunomodulatory effects, phytochemicals have also been shown to have other health benefits, such as anti-cancer properties, neuroprotection, and cardiovascular protection. This makes them an attractive option for protecting against a range of environmental pollutants, which can have systemic effects on health. Overall, the use of phytochemicals as immunomodulators for environmental pollutant-induced toxicities in animals is a promising area of research that has the potential to result in the growth of novel therapeutic interventions for the prevention and treatment of environmental pollutant-related diseases.

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