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Review (Derleme)

Some Effects of Toxins on Mammalia

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Abstract: Secretions and protein characterized toxins, which are produced by living things, may affect many organisms in different ways, and may alter the various structure of organisms with acute and chronic toxication. In this review, it was aimed to re-evaluate the studies on the possible negative effects of some toxins effective on mammals, and to create a resource for future studies by summarizing the obtained data. The available literature information were arranged as review by revising in the direction of the researches in Kafkas University, Faculty of Arts and Sciences, Laboratories of Biology Department. It has been noted that living beings were directly or indirectly exposed to diverse toxins. In this review, some effects of on mammals exposed to, have been tried to be determined by means of toxicological data. Although some of the toxins have no lethal in the reports, some others have destructive effects in the reports were revealed. Based on the examined data, it has been determined that different levels of toxicity are caused in the mammals, depending on the amount of exposure of the toxins. Also toxicity increases in parallel with the amount of toxin that is exposed and the exposure period. Additionally, it was reported that the effects may vary depending on the type of toxin. As a result, the research results evaluated are similar to each other.

Bazı Toksinlerin Memeliler Üzerindeki Etkileri

Anahtar Kelimeler:
Toksin,
Toksisite,
Toksikan,
Histolojik etkiler,
Memeliler

Özet: Canlılarca meydana getirilen salgı ve protein karakterdeki toksinler, çeşitli yollarla organizmaları etkileyebilir, akut ve kronik toksikasyonlarla organizmaların çeşitli yapılarını değiştirebilir. Bu derlemede, memeliler üzerinde etkili bazı toksinlerin muhtemel olumsuz etkileri üzerine yapılan çalışmaların yeniden gözden geçirilerek değerlendirilmesi ve elde edilen verilerin özetlenmesiyle gelecek çalışmalar için kaynak oluşturulması amaçlanmıştır. Elde edilebilen literatürel bilgiler, Kafkas Üniversitesi, Fen-Edebiyat Fakültesi, Biyoloji Bölümü Laboratuvarları'nda yapılan araştırmalar

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doğrultusunda gözden geçirilerek yeniden düzenlenmiştir. Canlıların doğrudan veya dolaylı olarak toksinlere maruz kaldığı bildirilmiş olup, bu derlemede toksinlerin maruz kalan memeliler üzerindeki etkileri, toksikolojik veriler vasıtasıyla belirlenmeye çalışılmıştır. Raporlarda bazı toksinlerin letal etkisi olmamasına karşın, diğer bazılarının yıkıcı etkileri olduğu belirtilmiştir. İncelenen verilere dayanarak, toksinlerin maruz kalınan miktarına bağlı olarak memelilerde farklı derecelerde toksisiteye neden olduğu tespit edilmiştir. Ayrıca maruz kalan toksin miktarı ve maruz kalma süresi ile paralel olarak toksisite artar. Ek olarak, etkilerin toksin türüne bağlı olarak değişiklik gösterebileceği bildirilmiştir. Sonuç olarak, değerlendirilen araştırma sonuçları birbiriyle benzerlik göstermektedir.

1. INTRODUCTION

Everywhere without exception, there are a lot of substances that affect living things in a way. The founder of modern toxicology, Paracelsus' famous phrase, "*Every substance is poison; there is no non-toxic substance, it's the dose that separates the poison from the drug.*", reveals this situation most clearly. The dose is perhaps the most important concept for toxicologists because the primary research topics are to determine the limits of harmlessness of substances. Unfortunately, while certain substances do not produce a toxic effect despite being taken in high amounts, some of them may threaten the life of the organism even at trace amounts. In this context, toxins have attracted attention over every period of time (Ayaz and Yurttagül, 2008; Sekkin and Kum, 2013; Uhlig et al., 2013; Baran Aksakal et al., 2014; Tok and Kayaalti, 2014).

In nature, some organisms have the potential to produce some biological products (such as toxins, enzymes …) capable of infecting other living organisms (Martins et al., 2005; Blunt et al., 2012-2013; Rangel et al., 2014, Hmani et al., 2017). Many biological originated metabolites have been identified from living things recently. Although some are useful for living things, many are poisonous towards a wide variety of organisms, including mammalia (Di Monte, 2003; Molina et al., 2005; Rangel et al., 2014). It is well known that toxins are responsible for disease and death not only in pet and wildlife animals but also in humans (Bennett and Klich, 2003; WHO, 2004; Ferreira et al., 2010; Gerssen et al., 2010; Cetinkaya and Elal Mus, 2012; Tumer, 2015). Toxins are natural poisons containing the most toxic elements known. Toxins produced by many living organism (Bacteria, fungi, dinoflagellates, algae, plants and animals such as corals, snails, frogs, arachnids, and snakes) are substances with harmful effects on other

living organisms (Hodgson, 2012; Rangel et al., 2014; Tok and Kayaalti, 2014; Doğan, 2016a,b; Doğan, 2017; Sant et al., 2017).

Toxins have also been associated with public health and agronomic problems, primarily food contamination (e.g. bacterial and fungal toxins) (Bhat, 2008; Milićević et al., 2010; Lizárraga-Paulín et al., 2011; Zain, 2011; Gallo et al., 2015).

Toxins in nature have two basic functions, predation and defense. Predation is killing a potential meal (e.g. spiders, jellyfish, wasps and sea anemones). Defence is deterrence the predator (e.g. honey bees, ants and monarch butterflies, and plants such as broccoli produce a toxin to dissuasion insects from eating them) (SLH, 2012).

1.1. The Main Types of Toxins

Toxins may be classified as exotoxins or endotoxins. Exotoxins excrete by an organism (e.g. bufotoxin). Endotoxins are morphologically part of bacteria (e.g. botulinum). It can cause degeneration to organisms, when the contents of toxins are contacted with or is absorbed by body tissues.

Toxins can be classified according to their body part. Hemotoxins (e.g. found in some snakes) harm erythrocytes and cause tissue degeneration in general. Phototoxins (e.g. alpha-terthienyl compound found in marigold plants) cause allergic reactions in sensitive individuals. Necrotoxins (e.g. necrotising fasciitis – flesh-eating bacteria) demolish cells they encounter and cause general tissue injury. And also neurotoxins [e.g., tetrodotoxin found in pufferfish and some grey side-gilled sea slugs (*Pleurobranchaea maculata*)] affect the nervous system of organisms.

Generally toxins, were classified in general based on origin as bacterial, fungal, plant and animal in this review.

One of the most important bacterial toxins in the world is botulinum toxin. Botulism arising from food is a critical, deathful affliction that is possible. Fortunately, it rarely occurs and does not spread between people. Intoxication predominantly results in the ingestion of probable neurotoxins that occur in contaminating foods. Spores are formed by *Clostridium botulinum* bacteria are resistant to heat and are widely found in the environment, and sprouts in the absence of oxygen, grows and then excretes the toxins. There are various types of botulinum toxin, and some types of them cause botulism in some animals [fishes, birds and mammals (types C, D and E)], especially in humans (types A, B, E and rare infrequently F). Botulinum toxins in inappropriately refined foods where the bacteria and spores survive, then grow and produce toxins, are taken into the body.

Although, it is primarily a foodborne toxicity, human botulism may also occur by intestinal infections in babies, injury infections and inhalation. On the other hand, Botox, is a pharmaceutical output preponderantly injected for clinical and cosmetic use, is produced by *C. botulinum* which is the same bacterium. The purified and highly diluted botulinum neurotoxin type A is employed in Botox treatments. The treatment is applied in the medical setting, adapted to the needs of the patient and rarely has side effects but is generally well tolerated (WHO, 2016a).

Another important bacterial toxin in the world is Shiga toxin. Shiga toxin, is produced by *Escherichia coli* bacterium, can cause heavy foodborne illness. *E. coli* is a bacterium commonly found in the large intestine of warm-blooded organisms. Some of *E.coli* strains can cause vital food poisonings, but most of *E.coli* strains are innocuous. The fundamental sources of Shiga toxin epidemics are raw or undercooked minced meat, raw milk, and contaminations of greenstuffs by feces. In most cases the disease is self-limited, but it can cause a serious malady including hemolytic uremic syndrome, especially in children and the elderly. Shiga toxin is heat-sensitive. When preparing food at home, make sure you do basic food hygiene administrations such as "cooking thoroughly". Following WHO's five key for safer food is an important precaution to prevent infections caused by foodborne pathogens such as Shiga toxin. (WHO, 2012, 2016b).

Cyanotoxins are a different group of biological originated toxins, when viewed from the perspective of chemical and biological. Despite water resources, most of the cyanotoxins detected so far seem to be more dangerous for terrestrial mammals than biota in the water. Cyanobacteria produce a variety of atypical metabolites. Despite the fact that some of metabolites, perhaps by chance, have other biotreatment effects, their natural function is uncertain. Research has focused primarily on humans and animals that act as toxins or as pharmaceutical beneficial compounds. Although there are also other non-toxic products in cyanobacteria, their biochemical and pharmacological properties are not completely known. Cyanotoxins fall into three large chemical groups: cyclic peptides, alkaloids and lipopolysaccharides. An overall assessment of the particular toxic substances in these large groups specified to date different genera Cyanobacteria, with primary target organs in humans is given in the Table (Creekmore, 1999; Sivonen and Jones, 1999; Park et al., 2001).

Table. General Characters of Cyanotoxins (Sivonen and Jones, 1999)

Toxin group[1]	**Primary target organ in mammals**	**Cyanobacterial genera**[2]
Cyclic peptides		
Microcystins	Liver	Microcystis, Anabaena, Planktothrix (Oscillatoria), Nostoc, Hapalosiphon, Anabaenopsis
Nodularin	Liver	Nodularia
Alkoloids		
Anatoxin-a	Nerve synaps	Anabaena, Planktothrix (Oscillatoria), Aphanizomenon
Anatoxin-a(S)	Nerve synaps	Anabaena
Aplysiatoxins	Skin	Lyngbya, Schizothrix, Planktothrix (Oscillatoria)
Cylindrospermopsins	Liver[3]	Cylindrospermopsis, Aphanizomenon, Umezakia
Lyngbyatoxin-a	Skin, gastrointestinal tract	Lyngbya
Saxitoxins	Nerve axons	Anabaena, Aphanizomenon, Lyngbya, Cylindrospermopsis
Lipopolisaccharides (LPS)	Potential irritant; affects any exposed tissue	All

[1] Many structural variants may be known for each toxin group

[2] Not produced by all species of the particular genus

[3] Whole cells of toxic species elicit widespread tissue damage, including damage to kidney and lymphoid tissue

Marine algae toxins, such as domoic acid, saxitoxin and brevetoxin, are bioaccumulated and grown in food chain by fish and shellfish, and anatoxins from freshwater cyanobacteria affect the nervous system; cyanobacteria containing microsystins or nodularin cause liver injure. Rather than the impacts of some of the detrimental algae are not about toxin production, are concerning low dissolved oxygen concentrations in water caused by algal proliferation, death, and decay, or night respiration. Occlusion of sunlight by increase of algae numbers and physical damage to the gills of fish caused by the form of some algae are the other harmful impacts. All of these effects can cause to mortality of aquatic invertebrates, aquatic plants, or fish and may produce an environment contributing to botulism. Other marine algal toxins (okadaic acid, neosaxitoxin, ciguatoxin, and Pfiesteria

exotoxin) and cyanobacterial toxins (saxitoxin, neosaxitoxin, and cylindrospermopsin) have not yet been identified as causes of mortality happenings, but increased awareness and forward research may establish a correlation (Tencalla, 1994; Creekmore, 1999). On a side note, marine biotoxins (lipophilic and hydrophilic toxins), may vary structures, toxicology and modes of action (Turrell and Stobo, 2007; Parades et al., 2011; Cetinkaya and Elal Mus, 2012).

Various fungal species produce toxins that have significant agricultural epidemiological and economic impact. *Aspergillus, Fusarium, Penicillium* and *Alternaria* species are responsible for the majority of agrarian mycotoxin contaminations. These fungi are common elements of microbial flora associated with many agricultural products such as corn, peanuts, nuts, grapes, coffee, cotton, wheat, barley and other cereals (Palencia et al., 2010; Singh et al., 2014). Depending on the host product and fungus species, mycotoxicogenic fungi can cause fruit rot in grapes caused by *Aspergillus*, corn ear rots caused by *Aspergillus* and *Fusarium* species, and *Fusarium* head degeneration and seedling disorders in cereal crops (Palumbo ve ark. 2008). Mycotoxins, which are major fungal toxins, are aflatoxins, citrinins, fumonisins, fusaric acid, trichothecenes, deoxynivalenol, AAL-toxin, alternariol, ochratoxins etc., each of them is produced by various fungal species. *Aspergillus flavus* and *Aspergillus parasiticus* are the main producers of aflatoxins; *Fusarium verticillioides* and *Fusarium proliferatum* produce fumonisins. The effects of these classes of mycotoxins on human and animal health has been comprehensively studied. Therefore, these mycotoxins have noticeable food safety apprehension, which lead to regulatory action to limit transmission of agrarian trade goods used for food and provender. Despite the fact that many scientific reports have been published about the existence of mycotoxins in foods and provenders, their effects on human and animal health needs more reports concerning the levels and effects of mycotoxin contamination in the environment (Singh et al., 2014).

Plant toxins, also known as plant allelochemicals or secondary plant chemicals, are believed to have developed as defensive mechanisms against plant pests, especially insects and mammals. Plant toxins can be sometimes repellent, but are not peculiarly toxic or they can be acutely toxic to a wide variety of organisms. There are various types of chemical of plant toxins such as sulfur compounds, lipids, phenols, alkaloids and glycosides. Plant toxins include some of abuse drugs such as cocaine, caffeine, nicotine, morphine, and the cannabinoids. Toxic

components of plants may be part of the human nutriments. Safrole with the carcinogenic characteristic found in pepper, and solanine and chaconine that were cholinesterase inhibitors and potential teratogens found in potatoes can be given as examples of that. Quinones and phenols are toxins commonly found in food. Poisoning of pets due to plant toxins is still an important issue in veterinary toxicology. Alkaloids are mainly organic based materials produced by dicotyledonous plants. These substances, which commonly have strong pharmacological activity, form the basis of many medicines. Many have been reported to be toxic by both inhalation and oral ingestion. Lipids and phenols are also known as other important plant toxins (Norton, 2008; Gilbert, 2011; Hodgson, 2012).

Venomous animals are able to produce a poison in a well-developed exocrine gland or cell group and can transmit their toxin during bite or sting. It is defined as, "The venom is the sum of all natural poisonous substances produced in the animal" (Ménez et al., 2006). There is no mechanism or structure for the poisonous animals to transfer their own poisons, and poisoning usually occurs through intake. Venomous or poisonous animals are extensively spread out in the animal kingdom from the unicellular protistan Alexandrium (*Gonyaulax*) to some mammals, involved platypus and short-tailed crocidura. More than 400 snake species are thought to be dangerous to humans. There are countless venomous and poisonous arthropods and they are found in just about every sea and ocean (Russell and Nagabhushanam, 1996; Mebs, 2002). Animal venom may also employ in the attack as well as in the capture and digestion of food, in defense, in protection against predators. Venom supplies a food-obtaining mechanism in snake. Defense is its secondary function. The entity of venom in the snake provides an extra contribution to speed, size, concealment or power. Venoms are used to paralyze prey in some animals (spiders), some to immobilize their prey (scorpions), and others to defend (some fishes, elasmobranches). On the other side, poisonous animals generally derive their toxins by the food chain (SCIELO, 2003; Watkins, 2008; Zhang, 2015).

By this review, it was aimed to summarize the available data and to constitute a source for further studies to be done by evaluating studies on the histopathological effects of bacteria, algae, fungus, plant and animal originated toxins on mammals that are contaminants of many materials worldwide and can cause both economic losses and health effects.

In natural ecosystems, the various biological activities or the presence of various toxins in the nature of the living things are important in terms of influencing the quality of

life and health of the other organisms. In this context, the histopathological effects of the toxins on mammals as a strong indicator of the effects of toxins have been assessed and interpreted by reviewing recent studies.

2. MATERIAL AND METHODS

The available literatural information was arranged as review by revising in the direction of the researches in Kafkas University, Faculty of Arts and Sciences, Department of Biology Laboratories.

3. RESULTS

Histological changes can be used as sensitive tools to detect the direct toxic effects of various compounds and are considered good indicators of environmental stress (Schwaiger et al., 1997; Fontanetti et al., 2014). Histopathological studies play a supporting role by providing more information about possible mechanisms of action of pesticides on biomarkers at the cellular and molecular level and on non-target organisms (Miller-Morey and Dolah, 2004).

Clostridium perfringens epsilon toxin (ETX) was given intravenously (i.v.) to rats (*Rattus norvegicus*) and mice (*Mus musculus*) at different sub-lethal doses to determine the histological and ultrastructural effects of ETX on mammals from highly preferred bacterial toxins. There were degenerative changes in neurons from the cortex, hippocampus, striatum and hypothalamus in histological analysis. Ultrastructurally, it was noted that necrotic neurons and apoptotic cells were observed in these same areas, among axons with accumulation of neurofilaments and demyelination as well as synaptic stripping. Lesions observed in the brain after sub-lethal exposure to ETX, result in permanent behavioral changes in animals surviving ETX exposure. It was reported that ETX can affect the brain of animals independently of death, producing changes on neurons or glia as the result of complex interactions, independently of ETX-Blood Brain Barrier's interactions (Morris et al., 2017).

The extracts of *Pseudanabaena galeata* and *Geitlerinema splendidum* (Cyanobacteria) were administered orally to mice at different doses (0.5, 1.0 and 2.0 g/kg body weight (b.w.). for one week to determine the toxic effects of cyanotoxins on mammals in another research. The acetic acid extracts of *P. galeata* didn't bring about death but did lead temporary indications, including eyebrow ptosis, straub tail, and pain. It was reported that there are disorganization of the hepatocellular chains, hyperemia, contraction of the centrilobular vein, and necrosis in the liver. Additionally, it was observed that differentiations in the folded

tubules of the kidneys and also unaffected lungs. The acetic acid extracts of *G. splendidum* induced transient symptoms, such as dyspnea, paralysis, and pain. And also these extracts leaded only one death. It was reported that there were hemorrhagic focuses, alveolar collapse, and granulomatous foci in lungs. The liver exhibited hemorrhagie, sinusoidal dilatation, hyperemia, contraction of the centrilobular vein, and disorganization of parenchymal structure in the liver. And also an inflammation and calcification in vessels somewhere. It was observed that necrosis and rupture of the contracted tubule cells in the kidneys. Advanced of investigation of the both extracts pointed out the deficiency of hemolytic activity, and the existence of two unknown anti-AChE materials in the acetic acid extracts of *G. splendidum*. In conclusion, new toxins are produced by *P. galeata* and *G. splendidum* that affect mammals when applied orally (Rangel et al., 2014).

In another investigation, mice were exposed to abrin, a potent plant toxin analogous to ricin that is derived from the seeds of *Abrus precatorius* plant, to determine the effects of plant toxins on mammals. In that study the researchers examined the in vivo nephrotoxicity potential of abrin toxin in terms of oxidative stress, inflammation, histopathological changes and biomarkers of kidney injury. Animals were exposed to 0.5 and 1.0 LD_{50} dose of abrin by intraperitoneal route and observed for 1, 3, and 7 days post-toxin exposure. Depletion of reduced glutathione and increased lipid peroxidation levels were observed in abrin treated mice. In addition, abrin also induced inflammation in the kidneys as observed through expression of MMP-9 and MMP-9/NGAL complex in abrin treated groups by using zymography method. Nephrotoxicity was also evaluated by western blot analysis of kidney injury biomarkers including Clusterin, Cystatin C and NGAL, and their results indicate severity of kidney injury in abrin treated groups. Kidney histology confirmed inflammatory changes due to abrin. The data generated in the present study clearly prove the nephrotoxicity potential of abrin (Sant et al., 2017).

4. DISCUSSION AND CONCLUSION

Generally, living things produce secondary metabolites to protect themselves, but they can cause the above-mentioned adverse effects on mammals. On the other hand, by examining the cellular and other mechanisms of toxins on living organisms and conducting other studies on those that have not yet been put into effect, new products can be introduced for use in a variety of areas, with improved knowledge about toxins. Based on examined information, it has been determined

that toxins can cause toxicity at different degrees depending on the amount of toxicity of the toxin the mammals are exposed to.

And also toxicity increases in parallel with the amount of toxin that is exposed and the exposure period. Additionally, it was reported that the effects may vary depending on the type of toxin.

As a result, the research results about negative effects on histological structure in mammals evaluated are similar to each other.

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