Geliş(Recevied) :27.07.2020
Kabul(Accepted) :13.11.2020

Review Article
Doi: 10.30708.mantar774315

Potential Cardiogenic Effects of Poisonous Mushrooms

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Abstract: Natural resources have been the savior of people at every stage of human history. Mushrooms are very valuable food sources, especially in the rainy seasons. They can be grouped as poisonous, edible or inedible, depending on their nutritional status. These groups have positive or negative effects. Some types of mushrooms have different medicinal properties thanks to their bioactive compounds. It is necessary to characterize their toxicological profiles, especially before using mushroom species for human consumption, as toxic substances are identified even in some edible species. Mycetism, known as mushroom poisoning, is an international health problem. There are those that cause deadly poisoning and limited symptoms of poisoning in mushrooms. Poisonous mushrooms are divided into many classes as cytotoxic, neurotoxic, myotoxic, gastroirritan mushrooms according to their types or symptoms they cause. It is known that mushroom poisoning can cause serious toxicity on the liver, kidneys and central nervous system. However, its effect on heart function has not been determined yet. This study focused on poisonous mushrooms and their cardiological effects.

Key words: Cardiogenic effects, poisonous mushrooms, syndromes, wild mushroom

Zehirli Mantarların Potansiyel Kardiyojenik Etkileri

Öz: İnsanlık tarihinin her aşamasında doğal kaynaklar insaların kurtarıcısı olmuştur. Mantarlar özellikle yagmur mevsimlerinde yoğun olarak bulunan oldukça değerli gıda kaynaklarıdır. Mantarlar beslenme durumlarına göre zehirli, yenir veya yenmez olarak gruplandırılabilir. Bu grupların olumlu veya olumsuz etkileri vardır. Bazı mantar türleri yapılarındaki biyoaktif bileşikler sayesinde farklı tıbbi özelliklere sahiptir. Özellikle insan tüketimi için mantar türlerini kullanmadan önce, bazı yenilebilir türlerde bile toksik maddeler tanımlandığı için toksikolojik profillerini karakterize etmek gerekir. Mantar zehirlenmesi (MP) olarak bilinen mycetism, uluslararası bir sağlık sorunudur. Mantarlar içerisnde ölümcül zehirlenmelere neden olanlar ve zehirlenme semptomları sınırlı olanlar vardır. Zehirli mantarlar türlerine veya neden oldukları semptomlara göre sitotoksik, nörotoksik, miyotoksik, gastroirritan mantarlar olarak birçok sınıfa ayrılır. Mantar zehirlenmesinin karaciğer, böbrekler ve merkezi sinir sistemi üzerinde ciddi toksisiteye neden olabileceği bilinmektedir. Ancak bunun kalp fonksiyonları üzerindeki etkisi henüz belirlenmemiştir. Yapılan bu araştırmada zehirli mantarlar ve görülen kardiyolojik etkileri üzerinde durulmuştur.

Anahtar kelimeler: Kardiyojenik etkiler, zehirli mantarlar, sendromlar, yabani mantar

Introduction

Mushrooms are living organisms that reproduce by spores and do not contain chlorophyll (Akgül et al., 2017). Spores in humid environments germinate and form fruiting bodies, especially after rains. Although there are 140.000 mushroom species identified from past to present, approximately 2.000 of these are safe for human health (Sevindik, 2018). Mushrooms were originally known as a source of food. Many studies in later processes have revealed that mushrooms have medicinal properties (Rathee et al., 2012; Sevindik et al., 2018; Gürgen et al., 2020; Selamoglu et al., 2020). Medicinal effects of some mushroom species such as antioxidant, antilipidemic, antimicrobial, anticancer, anti-inflammatory, anti-proliferative, DNA protective, hepatoprotective have been known (Lull et al., 2005; Canli et al., 2016; Liu et al., 2017; Sevindik et al., 2017; Wasser, 2017; Bozdogan et al., 2018; Muszyńska et al., 2018; Mushtaq et al., 2020; Sevindik and Akata, 2019; Sevindik, 2020). In addition, mushrooms rich in glucans can stimulate the immune system and provide people with health benefits. In addition, mushrooms contain high protein content, vitamins, fibers and minerals (Mhanda et al., 2015; Kim et al., 2016; Süfer et al., 2016; Sevindik et al., 2020). Since toxic compounds are identified even in some edible species, it is necessary to characterize their toxicological profiles before being consumed by humans.

Results

Mushroom Poisoning

Mushroom poisonings known as mycetism or mycetismus is an international health problem. Especially in the spring and autumn, high mortality is observed with the appearance of mushrooms after heavy rains (Tegzes et al., 2002; Eren et al., 2010). Some mushrooms are known to be poisonous in the mushroom kingdom, and cases of mycetism are reported annually in many countries around the world. Many of cases of these mycetism are due to the mixing of species from their empirical and traditional knowledge with their toxic counterparts (White et al., 2003; Flesch and Saviuc, 2004; Jo et al., 2014; Ozaltun and Sevindik, 2020). Among the known mushroom species today, about 100 species are poisonous to humans, but new toxic compounds are constantly identified within the fungi (Eren et al., 2010; Yardan et al., 2010). Toxicity differences can be observed even among the species of the same genus in the mushroom kingdom. Even one type of the same breed can be poisonous, while the other type can be eaten. Different toxins and different clinical symptoms are observed even among poisonous species (Kirchmair et al., 2012; Méndez-Navarro et al., 2016). Some of the poisonous mushroom species can be fatal, while some species have limited symptoms. People who consume poisonous mushroom species often have gastrointestinal symptoms like vomiting, nausea, diarrhea. But depending on the type of poisonous mushroom, signs of poisoning can reach serious levels. Although the duration of symptoms and symptoms varies depending on the amount of mushroom consumption and the type of toxic compound, it appears between 30 minutes and 2 hours on average. Mushroom poisonings are classified as early diagnosis and late diagnosis. Early diagnosis is made in the first 6 hours after consumption, and late detection is done after 6 hours (Nordt and Manoguerra, 2000; Eren et al., 2010). The onset of early or late symptoms is a marker for prognosis (Levine et al., 2011). Since the compound that provides toxicity in cases of mycetism is different, the symptoms change. Symptoms of cases of mycetism have a very wide range. Therefore, early diagnosis and interventions are very important for patients. Mycetism is usually diagnosed based on clinical findings and the presence of toxin in plasma, serum and urine (Durukan et al., 2007; De Oliveira, 2009). However, in most countries, toxin determination is not performed in daily practice. Generally, mushroom consumption history and clinical findings are very important for diagnosis. A detailed history should be obtained from patients in case of cases of mycetism. In addition to the importance of early diagnosis for effective treatment methods, it is the prevention of absorption of toxins by applying activated charcoal after gastric lavage. In addition to this treatment, treatment is supported with different drugs such as beta-lactam antibiotic, silymarin complex and antioxidant drugs (eg ascorbic acid, cimetidine and NAC). Hemodialysis is not recommended unless renal failure develops as a result of excessive thirst. Liver transplantation is considered a life-saving procedure in cases of acute massive hepatic necrosis (Barriot et al., 2000; Enjalbert et al., 2002).

Syndromes

Mycetism can generally be examined under two groups. Group 1 syndromes are poisonings that show symptoms between 30 minutes and 6 hours after consumption. Healing is seen in a short time with stomach wash or symptomatic treatments. Group 2 syndromes are poisonings that show symptoms between 6-24 hours.

These types of poisoning are serious poisonings because their symptoms are delayed and cause liver and kidney diseases. Poisoning treatments should be started in a hospital setting without wasting time (Diaz, 2005; Kaufmann, 2007; White et al., 2019).

Group 1 syndromes

Muscarinic Syndrome

The mushrooms that cause this syndrome are muscarine-containing species, such as *Clitocybe* (Fr.) Staude and *Inocybe* (Fr.) Fr. members. Clinical symptoms appear on average between 30 minutes and 2 hours following consumption (Beuhler and Graeme, 2005). Clinical symptoms seen include bradycardia, miosis, salivary secretion, lacrimation, diarrhea, nausea, vomiting and bronchospasm. Depending on the amount of consumption, symptoms manifest themselves on average for 6-24 hours. Symptoms are usually eliminated by applying activated charcoal and fluid therapy (Azzolina et al., 2011; Lima et al., 2012; Karimi and Razavi, 2014).

Gastrointestinal Syndrome

The mushroom species that cause this syndrome are Omphalotus olearius (DC.) Singer, *Chlorophyllum molybdites* (G. Mey.) Massee, *Entoloma lividum* Quél., *Hypholoma fasciculare* (Huds.) P. Kumm, *Boletus satanas* (Current name: *Rubroboletus satanas* (Lenz) Kuan Zhao & Zhu L. Yang), *Agaricus xanthodermus* Genev. and *Russula emetica* (Schaeff.) Pers. species (Azzolina et al., 2011; Karimi and Razavi, 2014). Symptoms usually appear between 1-6 hours. The symptoms seen are vomiting, nausea, diarrhea, abdominal pain, drowsiness and blurred vision, similar to muscarin syndrome. The treatment method applied in muscarinic syndrome is applied (Beuhler and Graeme, 2005; Karimi and Razavi, 2014).

Coprinus Syndrome

The mushroom species that causes this syndrome is *Coprinopsis atramentaria* (Bull.) Redhead, Vilgalys & Moncalvo. The syndrome gets its name from this species. Generally, symptoms appear within 30 minutes of consumption. Alcohol consumption with this fungus causes symptoms to be more severe (Azzolina et al., 2011; Karimi and Razavi, 2014). Symptoms include flushing, nausea, vomiting, weakness, agitation, palpitations, and tingling in the legs. Symptoms usually disappear spontaneously about 2 hours after stopping alcohol consumption. However, it can present serious problems in people with heart conditions (Danel et al., 2001; Karimi and Razavi, 2014).

Psilocybin Syndrome

The mushrooms that cause this syndrome are species belonging to the genus *Psilocybe* (Fr.) P. Kumm, *Stropharia* (Fr.) Quél., *Conocybe* Fayod and *Panaeolus* (Fr.) Quél. Generally, *Gymnopilus spectabilis* (Current name: *Phaeolepiota aurea* (Matt.) Maire), *Panaeolus foenisecii* (Current name: *Panaeolina foenisecii* (Pers.) Maire), *Conocybe cyanopus* (G.F. Atk.) Kühner, *Psilocybe caerulescens* Murrill, and *P. cubensis* (Earle) Singer are mushroom species that contain psilocybin. Symptoms usually manifest between 30 minutes and 2 hours. Visual hallucinations are common among symptoms (Peden et al., 1982; Passie et al., 2002; Karimi and Razavi, 2014). Other symptoms include increased heart rate, mydriasis, chills, and sweating. Effects can be seen for up to 8 hours. However, visual hallucinations usually lose their effect after 1 hour. In addition, there may be difficulties in visual and auditory senses due to continuous use. Healing usually happens without treatment. Symptoms disappear after an average of 8 hours (Hasler et al., 2002; Beuhler and Graeme, 2005; Karimi and Razavi, 2014).

Pantherina-Muscaria Syndrome

The mushrooms that cause this syndrome are *Amanita muscaria* (L.) Lam. and *A. pantherina* (DC.) Krombh species. The compound that causes poisoning is ibotenic acid. Symptoms appear between 30 minutes and 2 hours on average following consumption (Azzolina et al., 2011). Symptoms include visual impairment, difficulty speaking, visual hallucinations, delirium, salivation, dizziness, fatigue, vivid dreams and deep sleep. Symptoms usually disappear completely after 24 hours. Atropine can be used for long-term symptoms or clinical situations (Tsujikawa et al., 2006; Lima et al., 2012; Karimi and Razavi, 2014).

Group 2 syndromes

Orellanus syndrome

The mushrooms that cause this syndrome are *Cortinarius orellanus* Fr. and *C. orellanoides* (Current name: *Cortinarius rubellus* Cooke). The effects of orellanine on the digestive system are seen on average 36-48 hours. Its effect on the kidneys is seen after 7-17 days (Beuhler and Graeme, 2005; Wessely et al., 2007). Symptoms include anorexia, headache, dry mouth,

burning in the tongue and lips, vomiting, diarrhea, chills, joint and muscle pain. It is not understood that the symptoms are due to mushroom poisoning, since the duration of symptoms is long. If kidney impairment has occurred, kidney transplantation is required. Complete recovery may take a long time (Eigler et al., 1997; Tegzes and Puschner, 2002; Karimi and Razavi, 2014).

Gyromitra syndrome

Syndrome-causing species are mushrooms containing Gyromitrin, such as *Gyromitra esculenta* (Pers.) Fr. and *G. californica* (W. Phillips) Raitv.. Symptoms appear between 6-48 hours after consumption (Michelot and Toth, 1991; Azzolina et al., 2011). The first symptoms are gastrointestinal symptoms such as vomiting, abdominal pain or diarrhea. Clinical symptoms include vertigo, sweating, dysarthria, coordination disorder, seizures, hemolysis, methemoglobinemia, rhabdomyolysis, myalgia and hypoglycemia abnormalities. If it is used for a long time, it may cause liver damage. Treatment is symptomatic (Brooks and Graeme, 2005; Goldfrank, 2009; Karimi and Razavi, 2014).

Phalloides syndrome

Amanita phalloides (Vaill. ex Fr.) Link, *A. verna* (Bull.) Lam., *A. virosa* Bertill. and *Galerina* Earle species are fungi that cause this syndrome. Symptoms appear on average between 6-24 hours following consumption. The first symptoms are nausea, vomiting, severe abdominal pain and bloody diarrhea. These symptoms persist for an average of 1 day. It then enters the 1-2-day process called pseudo-healing. During this period, the symptoms disappear (Vogel et al., 1984; Alves et al., 2001; Vanooteghem et al., 2014). Although the patient looks clinically well, enzymes rise rapidly in the blood test. In the next process, necrosis begins in the liver and kidneys. As a result, jaundice, stomach and intestinal bleeding and hepatic coma are seen. If early diagnosis and treatment is not made, the patient die within an average of 6-16 days. (α, β, γ,) amanitins and phallotoxins are compounds responsible for poisoning (Mas, 2005; Unverir et al., 2007). Activated charcoal use may be useful in adsorbing toxic compounds in the gastrointestinal tract. Hemoperfusion is required within 48 hours of consumption to remove toxin from the blood. For this reason, with the onset of symptoms, the treatment should be started immediately. However, continuous monitoring, fluid supplementation, and penicillin therapy are essential parts of the treatment of Phalloides syndrome. In addition, liver transplantation can be successfully applied in cases of severe poisoning and inadequate treatments (Donnelly and Wax, 2005; Karimi et al., 2011; Karimi and Razavi, 2014).

Rhabdomyolysis syndrome

The mushrooms responsible for the syndrome are *Tricholoma equestre* (L.) P. Kumm. and *Russula subnigricans* Hongo. Symptoms begin to appear within an average of 24-72 hours after consumption (Azzolina et al., 2011; Karimi and Razavi, 2014). Symptoms appear as diarrhea, nausea and vomiting. In severe cases of poisoning, muscle weakness, fatigue, muscle pain and rhabdomyolysis, kidney failure and metabolic acidosis are observed. Treatment is symptomatic (Karlson-Stiber and Persson, 2003; Beuhler and Graeme, 2005; Karimi and Razavi, 2014).

Cardiogenic effects of poisonous mushrooms

Mycetism cases are generally known to have serious toxic effects on the liver, kidneys and central nervous system. However, the effects of mushroom poisoning on heart functions have not been determined much. In previous studies, several cases of left ventricular systolic functions have been reported with increased cardiac biomarkers with increased cardiogenic shock in the absence of mycardism-related myocardial infarction (Unverir et al., 2007; Nieminen et al., 2008; Faulstich and Wieland, 2019). ECG abnormalities can often be seen in mycetism cases. ECG abnormality frequently seen in mycetism cases is sinus tachycardia. In addition, other ECG abnormalities are sinus arrhythmia, ST / T inversion, 1st degree AV block and QT prolongation. Inflammatory damage in the pericardial space may be the cause of tachycardia in mycetism cases. The cardiotoxic effects of mycetism are still not fully disclosed. The data in the literature are mainly based on several case reports and series. In a study on mice under consumption of *Tricholoma flavovirens* (Current name: *Tricholoma equestre* (L.) P. Kumm), plasma CK and CKMB activities and plasma bilirubin concentrations were higher than those in the control group. In addition, pericardial inflammation was observed from histological samples of long-term mushroom supplemented mice (Nieminen et al., 2008; Azzolina et al., 2011).

In a different study, it was reported that a mycetism case increased the level of troponin I (Avcı et al., 2014).

In another mycetism case, the patient's liver and kidney function tests found high amylase and cardiac levels. Cardiac markers may be elevated due to the fact that amatoxins bind actin filaments in myocardiocytes or kidney cells, or their effects as circulating antitroponin antibodies. Myocardiocytes or amatoxins that bind actin filaments in kidney cells may cause elevated heart markers. In addition, a temporary decrease in systolic function was observed in this reported mycetism case (Altıntepe et al., 2014). In another study, after 5 hours after mushroom consumption, the patient observed an increase in ST in low leads and high cardiac markers. As a result of angiogram, the coronary arteries were found at normal levels. It has been suggested that ECG changes and elevation of biomarkers in mycetism case may be related to temporary vasospasm (Kalcik et al., 2015). In cases of mycetism, hypertension or hypotension may occur. Hypotension can be seen due to its mechanism of action on the renin-angiotensin system. Hypertension may occur as a result of endothelial damage of toxins of vasoconstrictive agents (Kalcik et al., 2015).

C. atramentarius is a type of fungus that causes Coprinus syndrome. When this mushroom is consumed before or during alcohol consumption, erythema of the face and hands, swelling and rash on the hands, tachycardia, hypotension, dyspnea, nausea, vomiting and shock can be seen. The symptoms seen are similar to the symptoms seen when a patient with disulfiram, which is used to treat alcohol, is drinking alcohol. Disulfiram has been reported to be isolated from *C. atramentarius* (Stolman, 2013). In a study, reversible ECG changes were observed in most patients during the controls of patients receiving alcohol therapy. As a result of toxic interactions between disulfiram and alcohol, cardiac arrhythmias and myocardial infarction have been described (Jr Tyler, 1963; Stolman, 2013). Cardiac arrhythmias and myocardial infarction have been described by toxic interactions between disulfiram and alcohol, while in most patients observe reversible ECG changes during controlled reactions (Markham and Hoff, 1953; Wessely et al., 2007). Due to the similarities between these two reactions, it can be expected that disorders of heart function may occur after alcohol consumption of *C. atramentarius*.

Although edible mushrooms constitute a healthy food group for livings, cardiogenic harmful effects of poisonous mushrooms that are have been observed. Studies and observations on this subject are very limited. The number of cases in the case series with the subject is not sufficient. Despite few studies, the harmful effects of some mushrooms are known. In this study, the cardiological effects of poisonous mushrooms are emphasized.

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