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Mushroom (*Amanita phalloides*) Poisoning: Mechanisms, Pathogenesis, Prognosis and Strategies of Treatment

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***Abstract* — Poisoning due to mushroom consumption is uncommon, but it causes death by causing acute liver failure (ALF). The ingestion of Amanita phalloides, is one of the ultimate frequent causes of mushroom poisoning globally. This type has three main categories of toxins: amatoxins, phallotoxins, and virotoxins. From these toxins amatoxins and its metabolite α-amanitin, is the main cause of toxicity in population which cause deterioration in synthesis of protein and consequent cell necrosis and inhibition of RNA polymerase II ,so finally cause cell death. Liver is the chief organ involved in toxicity, kidneys and central nervous system also involved. Latent period has been proceeds the poisoning symptoms, which includes gastrointestinal symptoms followed by liver failure symptoms, coma and ultimately death. Management including supportive cares, gastrointestinal decontamination, special medications (Benzyl penicillin, N-acetyl cyctien, cimetidine, silibinin and others) and, finally liver transplantation if clinical condition deteriorated.**

***Keywords* —: Mushroom , *Amanita pholloides* , Acute liver failure , α-amanitin.**

I. INTRODUCTION

The nomenclature “mushroom” is associated with the fleshy, spore-having fruiting body of more advanced fungi, naturally spreading over ground, that is their food source (Plage DL *et al* 1981) .The collection and ingestion of wild mushrooms has increased during late years due to their soft consistency in addition to high nutritional value and protein content (Cheung PCK (2010)). Globally, there are relatively 5000 types of mushroom, up to 100 toxic to humans, whereas only 200–300 are edible (Arora D,1098). Death due to mushroom poisonings, is resulting from amanitin-containing species. Poisoning due to these species represent a real problem in clinical toxicology because there is no specific and effective antidote is available yet (Jan Magdalan *et al*,2010).The best seasons of the year for A. phalloides fructification are spring, late summer, and autumn, therefore the majority of the intoxication cases occur in these seasons (Bonnet *et al* ,2002).Similarity in shape and color among the poisonous (Amanita pholloides) and edible mushroom cause misidentifying between these species by farmer who collect mushroom this leads to toxicity worldwide(Vetter J (1998)). Figure (1 a and b) show the similarity between Toxic and edible mushroom respectively.

FIGURE (1 a): *Amanita Polloides* (Toxic mushroom) FIGURE (1b) : Edible mushroom

Amanita phalloides contains three categories of cyclic peptide toxins, which can be grouped into amatoxins, phallotoxins, and virotoxins. All groups of toxins contain a tryptophan residue substituted at position 2 of the indol ring by a sulfur atom. Amatoxins are highly toxic causing death within 2–8 days, on the other hand phallotoxins and virotoxins are less toxic but act faster, causing death within 2–5 h (Vetter J (1998)).The high mortality rate of A. phalloides poisoning depends on its containing of potent toxin which is amatoxins, and α-amanitin is usually responsible for the hepatic and renal damage after ingestion because these are the most metabolically active tissues(Becker C *et al* 1976 and Reichl F *et al* X2011). Histological investigations of liver cells showed aberrant presence of lipids and carbohydrates within the nucleus (Becker C *et al* 1976).

II. MECHANISM OF TOXICITY

Toxicodynamic of α-amanitin depends upon inhibition of RNA polymerase II, Consequently, it leads to inhibition of transcription process (Wieland T (1983). Furthemorer, other toxic mechanisms have been supposed , mainly generation of reactive oxygen species (Zheleva A *et al* (2007), Zheleva A(2013) .In addition , α-amanitin may also act co adjuvant with endogenous cytokines (e.g., tumor necrosis factor-α) to induce apoptosis (Leist M et al 1997) . The decrease in of mRNA concentration resulting in inhibition of the protein synthesis and finally lead to cell death(Wieland T (1983)), furthermore apoptosis also play central role in amanitin causing sever hepatic damage (Magdalan 2010b), accumulation of amanitin in liver cells causing p53-and caspase3-dependent apoptosis(Figure. 2)(Magdalan *et al* 2011), concentration required for promotion of p53 was related with the concentration required to decrease mRNA production, supposing g a relationship between these two effects (Ljungman *et al* 1990). Oxidative stress can also acts as a contributor in amanitin toxicity that cause changing in mitochondrial membrane permeability by way of formation of p53 complexes with protective proteins (Bcl-xL and Bcl-2) (Figure.2) (Magdalan *et al* 2011) and transferring of p53 from cytoplasm to mitochondria, and discharge of cytochrome c to cytoplasmic space (Arima *et al* 2005). High hepatic amanitin concentration lead to the generation of free radicals and other reactive species ,an increment of superoxide dismutase (SOD) concentration and malondialdehyde products, further more lead to decrease of catalase concentration (Zheleva A *et al* 2007). Lipid peroxidation also play an important role in the extensive necrosis and massive liver damage (Zheleva A *et al* (2013), Zheleva A *et al* 2007)phenoxyl free radicals that might be involved in ROS generation (Zheleva A *et al* (2013) as in Figure 2.

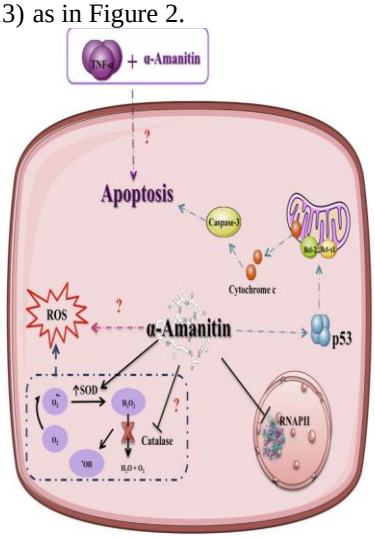

FIGURE (2) : Signaling pathways involved in α-amanitin-induced toxicity. The main toxicity mechanism of α-amanitin is the inhibition of RNA polymerase II. Other mechanisms have been suggested and include the formation of reactive oxygen species (ROS) leading to oxidative stress related damage. Generation of ROS may also be induced by increase of superoxide dismutase (SOD) activity and inhibition of catalase activity. Amatoxins may act synergistically with tumor necrosis factor (TNF), to induce apoptosis, though the underlying mechanisms are not yet known.

III. TOXICOKINTICS

Amatoxn is a bicyclic octapeptides, formed by at least nine different compounds: α-amanitin, β-amanitin, γ -amanitin, εamanitin, amanin, amaninamide, amanullin, amanullinic acid, and proamanullin (Vetter J *et al* 1998). There is an assumption that virotoxins are derived from the same phallotoxin precursor (Brossi *et al* 1991, Derelanko *et al* 2001), so the chemical structure and bioactivity of virotoxins are resemble to that of phallotoxin. Both phallotoxins and virotoxins have no considerable toxicity after ingestion.

These toxins are heat stable and water soluble, this make them very toxic and cannot be devastated by cooking or dehydrating processes. Furthermore, amatoxins cannot be destroyed or deactivated by the acidic media and enzymatic activity of gastrointestinal tract (Wieland *et al* 1978). These toxin are readily absorbed after oral ingestion(Homann *et al* 1986) , and be in free form in blood stream and not bind with any plasma protein such as albumin (Faulstich *et al* 1985) then distributed from the blood to the kidney and liver within 48 hours (Jaeger *et al* 1993) Amatoxins toxicity targeting the liver primarily and the cause of death is due to liver failure (Karlson-Stiber *et al* 2003). Actually due to oral ingestion and the gastrointestinal absorption of amatoxins, it is expected that the liver is the main and first organ of entrance of the high concentrations of those toxins. Amatoxins transports to the hepatic cells by organic anion transporting octapeptide OATP transporter situated in the sinusoidal membrane of hepatocytes (Figure. 3) (Letschert *et al* 2006) identified OATP1B3 as the main human uptake transporter for amatoxins. Amatoxins excreted unchanged in high concentration in the urine (Jaeger *et al* 1993). So the kidneys exposed to high concentration of toxin that lead to nephrotoxicity (Mydlik *et al* 2006) . Low concentrations can be excreted by bile and may undergo enterohepatic circulation, which prolong the duration of action (Faulstich *et al* 1985). Intestinal elimination can contribute in the elimination (Jaeger *et al* 1993).

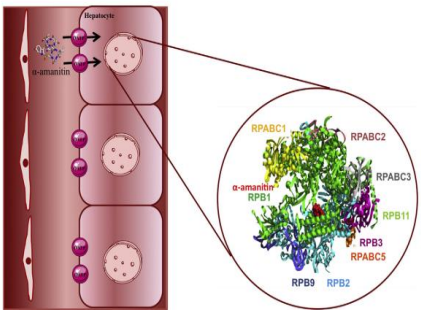

FIGURE 3 (Letschert *et al* 2006) : Simplified model of α-amanitin transport and main toxic mechanism in hepatocytes. α-Amanitin accumulation occurs in the liver upon uptake via an organic aniontransporting octapeptide (OATP1B3) located in the sinusoidal membrane of hepatocytes. Once in the hepatocyte, α-amanitin binds to RNA polymerase II causing inhibition of its activity. The α-amanitin binding site is located in the interface of Rpb1and Rpb2 subunits.

VI. SYMPTOMS

There is long latent period (10 hours) (an asymptomatic) which precedes the gastrointestinal

symptoms (abdominal cramps, nausea, vomiting and diarrhea) .This period occurs because the amanitin doesn't causing direct irritation to mucous membrane of gastrointestinal tract. This period followed by hepato-renal involvement symptoms(jaundice, hepatitis and renal shut down) finally fulminant liver failure and then death if management late or liver transplantation failed or late (Anant Parasher *et al* 2020).

VII. CIINICAL PRESENTATION OF TOXICITY

Amatoxin has been well studied and occurs in four phases:

1.The first phase is quiescent period prolong 6 to 24 hours after eating , where the amatoxin is actively damaging the liver and kidneys cells. During this stage the patient usually does not complains of any symptoms (Becker C *et al* 1976, NAMA 2014). This phase averages ten hours (Santi L *et al* 2012) .

2. The Second stage in this phase patients commonly experience diarrhea. Escudie et al. have found that diarrhea begin within 8 hour represent a bad prognosis (Escudie L *et al* 2007, Allen B *et al* 2014). Abdominal cramps, nausea, emesis , and diarrhea occur during the second phase of poisoning. These symptoms may occur with other symptoms such as hyperpyrexia , palpitation , decrease the blood sugar concentration, decrease blood pressure, dehydration and acute electrolyte imbalance (Becker C *et al* 1976, NAMA 2014). This gastrointestinal phase commonly accompanied by bloody diarrhea and vomiting. Renal and liver function test usually within normal range during this phase (Santi L *et al* 2012) .

3.The third phase : a 24- hour period in which the patient look to be recover , despite of kidneys and liver damage which proven by renal, hepatic function. Elevated Serum transaminases and lactic dehydrogenase and jaundice will be developed and became apparent (Santi L *et al* 2012). If the patient discharged without evaluation of liver and kidneys functions, this may lead to death (NAMA 2014) .

4.The fourth phase is hepatic failure stage, or fulminant hepatitis, is represent by a massive increase of transaminases level, coagulopathy, delirium, headache, hyperbilirubinemia, oliguria, uremia, hepatic encephalopathy, hepatorenal syndrome and acute renal failure (Becker C *et al* 1976, NAMA 2014, Santi L *et al* 2012, Haard R *et al* 1977) . Multi-organ failure, disseminated intravascular coagulation, seizures and death may occur one to three weeks after ingestion. The common factor in patients who will recover is rapid improvement in both symptoms and liver function tests, leading to full recovery (Santi L *et al* 2012).

VIII. PATHOPHYSIOLOGY OF INTOXICATION BY AMATOXIN :

1. Liver

Hepatic failure is the main pathophysiological outcome of mushroom poisinoning. Hepatic histopathological examination has revealed massive centrilobular hepatic necrosis (Pond *et al* 1982-1983). Hepatitis may elaborate abruptly then develop to liver failure and coma (Mydlik *et al* 2006). Hepatic cells show massive necrosis and fatty degeneration (Kucuk *et al* 2005). Hepatic failure could cause disseminated intravascular coagulation because of decrease of elimination of clotting factors and excretion of pro-coagulants from degenerated hepatic cells all these events lead to multi-organ failure (P. *et al* 1988, Soysal *et al* 2006).

2. Kidney

Amanita phalloides poisoning may cause acute tubular necrosis and renal shut down((Mydlik *et al* 2006). Post- Fanconi-type renal tubular acidosis also can occur (Barceloux *et al* 2008).

3. Central nervous system

Accumulation of ammonia(by product of protein catabolism) due to hepatorenal failure, as the renal system is responsible for conversion of ammonia to urea and excreted by kidney. This increases the ammonia blood level which can pass the blood brain barrier and causing encephalopathy Consequently, the process leads to the primary neurological manifestation that associated with *Amanita phalloides* (Bonnet *et al* 2002). Liver and renal failure combined with the drop in blood pressure and leads to secondary neurologic manifestations (Barceloux *et al* 2008).

IX. STRATIGIES OF TREATMENT

1. PRIMARY ASSISSMENT AND INTIAL CARE

2. GASTRIC LAVAGE and activated charcoal inhibit the gastrointestinal absorption of amatoxin but this measure is effective when the patients arrive the emergency department early after ingestion(Yongzhuang Ye *et al* 2018, Vale JA 1997). This approach loss its effectiveness as the patient delayed in reaching to the hospitals due to latent phase that occurs directly after mushroom ingestion and persist for approximately 6 hours after(Vale JA *et al* 2004).

3. MULTIPLE DOSES OF ACTIVATED CHARCAOL

After gastric lavage, were potentially effective to reduce the gastrointestinal absorption when administered early after ingestion (Albertson TE *et al* 2011). When delay occurs in administration of activated charcoal, however, the goal of this measure was to interrupt the enterohepatic circulation of amatoxins (Garcia J *et al* 2015).

4. REHYDRATION

As the poisoning by amanita pholloides mushroom cause vomiting and diarrhea which leads to dehydration, sometimes severe dehydration causing reduction of the renal blood flow and then renal insufficiency. In addition this dehydration leads to metabolic acidosis and an increase in lactic acid level. Therefore, intravenous fluid administration is essential to correct this biochemical abnormalities, this intervention is very important to maintain and inhibit irreversible hepatic failure (Escudie L *et al* 2007 , Sese TJ *et al* 1985).

5. DIURESIS

As amatoxin excreted renally, therefore forced diuresis have an important role in increasing the elimination of toxin(Madhok M *et al* 2006).

6. BILIRY DRINAGE

Amatoxin undergoes enterohepatic circulation, percutaneous biliary drainage contributed in decreasing of amatoxin absorption. As a result the reducing the hepatic injury. Biliary drainage interrupt of enterohepatic circulation and attenuate amatoxins induced liver injury by reducing amatoxins absorption (Koppel C *et al* 1993).

7. HEMODIALYSIS AND HEMOPERFUSION

When amatoxin transfers to the blood and detected in plasma , hemodialysis and hemoperfusion show beneficial effect in spite of they didn't affect on final prognosis (Jaeger *et al* 1993, Koppel C *et al* 1993). However, the other studies show that is beneficial impact on the patients survival (Jander S *et al* 2000).

8. PLASMAPHERESIS

The other detoxification technique is plasmapheresis, despite it cannot eliminate a sufficient concentration in compassion with renal excretion (Jaeger *et al* 1993), but it can provides the albumin immunoglobulins, coagulation factors, and fibrinolytic proteins and mineral salts which are essential for hepatic cells resuscitation (Jander S *et al* 2004) .

X. ANTIDOTES

No specific antidote is available for amatoxin some drugs to enhance the excretion of the amatoxins, some of these effective antidotes involving benzylpenicillin, N-acetylcysteine, and silymarin they have a beneficial effect in case of A. pholloides poisoning .

1) PENECILLIN G OR BENZYL PENOCILLIN

Its mechanism of action is performed by the competition with amatoxin on binding site on plasma protein especially albumin (Baniasad N *et al* 2014, Magdalan J *et al* 2010, Nici A *et al* 2011).The second mechanism inhibit uptake of amatoxin by hepatocyte by inhibition the OATP1B3 receptors (Baniasad N *et al* 2014, Nici A *et al* 2011 , Poucheret *et al* 2010). Ultimaetly , normal flora in intestinal mucosa synthesizes gamma-aminobutyric acid (GABA), amatoxin causes degradation of this compound by the liver so benzylpenicillin by killing the intestinal normal flora decreasing the GABA level and prevent encephalopathy (Patowary BS *et al* 2010).

2) N-ACETYLCYSTIEN (NAC)

As amatoxin causing state of oxidative stress that is leading to GSH depletion, so administration of NAC will acts as glutathione precursor (Baniasad N *et al* 2014, Nici A *et al* 2011). Another antioxidant agent having a role in the management of toxicity is ascorbic acid which protects the hepatic cell from injury and apoptosis by free radical (Poucheret *et al* 2010). Second, the reactive oxygen species produces lipid peroxidation of cell membranes, oxidation of proteins, oxidation of nucleic acids and damage to all components within the cell, leading to cell death and glutathione depletion. NAC scavenges free radicals in a non-specific manner, preventing cell destruction by these means (Poucheret *et al* 2010). NAC has been shown to increase non-transplant survival and has been proven to be beneficial in grade I–II encephalopathy (Craig DG *et al* 2013).

3. CIMITIDINE

Cytochrome P450 enzyme converts amatoxin to active form amanitin which active form of toxic amatoxin. Cimetidine inhibits this enzyme and prevents this toxic biotransformation (Nici A *et al* 2011).

4. SILIBININE

When the consumption of mushroom was since two days , extract of silymarin, a flavolignan derived from the seeds of the milk thistle (Silibinin) can be helpful (Santi L *et al* 2012) Its mechanism of action by inhibition of OATP1B3 receptor systems prevent uptake of amanitin by liver and intestinal cells (Mengs U *et al* 2012). It is improve the prognosis by decreasing the rate of mortality by exhibiting protective effect (Garcia J *et al* 2015).

XI. BIOLOGICAL REPLACEMEMT THERAPY

1. HEMODIALYSIS : Medically, dialysis is a procedure of get rid of metabolic product and excessive fluids and toxic substances form the general circulation, It acts as artificial renal system (Pendse S *et al* 2008 ، Zainab Ali Kadhem 2014) . Multiple-dose activated charcoal should be considered only if a patient has ingested a life threatening amount of carbamazepine, dapsone, phenobarbital, quinine, or theophylline. (Kivisto JE *et al* 2006 , Raid Kareem Dehiol (2017). Hemodialysis although it doesn't have a beneficial effect in mushroom toxicity but can improve the encephalopathy that accompanied with amanitin poisioning (Fauser U *et al* 1973).

2. POLYMIXIN B: It acts by binding to the binding site of amanitin on RNAP II, so it prevents the binding of amantin to RNAP II, it considerably decreases the liver and kidneys damage caused by toxin .Moreover it improves the long term prognosis by decreasing the mortality rate (Garcia J *et al* 2015).

3. LIVER TRANSPLANTATION : If the patient is late in arrival to the hospital or didn't treat in an appropriate way, fulminant liver failure will develop , hepatic transplantation will save the patient and improve the state of patient with bad prognosis (Craig DG *et al* 2010, Larson AM *et al* 2010).

XII. PROGNOSIS

The prognoses of patients poisoned with *Amanita polloides* depends upon time of initiation of treatment and time of ingestion as earlier as the best prognosis and survival increased significantly (Garcia J *et al* 2015). Liver transplantation is the last option of management; it has a significant effect in decreasing mortality rate and improve survival and final prognosis(Larson AM *et al* 2010, Craig DG *et al* 2010, Garcia J *et al* 2015 , Ganzert M *et al* 2005) . Poisoned people that enter to an intensive care unit will usually improve because of availability of devices and medical staff that monitor the biological activity and vital signs and initiate medical intervention immediately(Wang DW *et al* 2003, Mas A 2005), patient with other disease like those with cardiovascular, respiratory defects or complication and various infection, those patients have poor prognosis (Mas A 2005). Patients who need liver transplantation due to acute liver failure have bad prognosis than those who receive liver transplantation due to chronic

liver failure; however, one-year survival rate ranges from 65–80% (Craig DG *et al* 2010).

XIII. CONCLSION

Amanita phalloides is one of the most toxic mushrooms and is involved in the majority of human fatal cases of mushroom poisoning. When *Amanita phalloides* poisoning occurs, most patients are admitted to hospital at a late stage, and often no appropriate tools for analyzing amatoxins or corroborate the poisoning are available. The presumed diagnosis of amatoxin poisoning is often suggested based on a gastrointestinal syndrome preceded by a latent period and a history of mushrooms ingestion. Treatment often aims decontamination, control of fluid and electrolyte balance and prevention of multiple organ failure, especially liver failure. The optimal management of the *Amanita phalloides* poisoning remains to be determined, which makes difficult the establishment of a worldwide standard treatment. In fact, this can explain the therapeutic differences between the different poisons centers analyzed throughout the globe. Some options have been employed and include detoxification measures, chemotherapy, and liver transplantation as the last resort. Retrospective analysis of the applied therapy, specifically using benzylpenicillin, silybin, and Nacetylcysteine, has revealed contradictory results regarding to their clinical effectiveness.. Despite the mortality rate being below 10%, the patients' prognosis largely depends on the prompt recognition and treatment. Even so, more clinical studies and in vivo experimental data are needed to prove its use in the clinical practice. Emergency liver transplantation is the only intervention with recognized survival benefits in acute liver failure patients with a poor prognosis. Nevertheless, liver failure may develop rapidly within days, hindering timely hepatic transplant. Inhibition of the RNAP II has been postulated to be the main toxic mechanism of α-amanitin. Other mechanisms have been pointed but need further investigation. A more detailed understanding of the above mechanism will aid in the development of effective and more powerful drugs for treating amatoxins poisoning. An important approach would be to develop an antidote that competes with amatoxins and displaces them from RNAP II. In fact, an optimal agent should be able to bind to RNAP II protecting against amatoxins while not disturbing the normal transcription process.

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