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Toxicity of Nutmeg (Myristicin): A Review

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Abstract*— In this paper a detailed review of myristicin is reported. Numerous literatures report that myristicin is responsible for hallucinogenic effects, which induced by the consumption of nutmeg due to its metabolism structure of 3-methoxy-4,5-methylendioxyamphetamine (MMDA). Minimum dosage of nutmeg that can cause psychogenic effect is 5 g (ground nutmeg) with 1 to 2 mg myristicin content and this dosage is considered as 'toxic dose'. At higher dosage of myristicin death may occur. Additionally, Myristicin poisoning can lead to many health problems that related to brain problem. Those symptoms usually occur 3 to 6 hours after ingestion of myristicin or foodstuffs containing it, and effects may persist up to 72 hours. California Poison Control System (CPCS) electronic database 72.3% exposures between 1997 and 2008 that were intentional for recreational purposes (between ages 13 and 20 years old). The remaining considered as unintentionally exposed. Between 1998 to 2008, Texas Poison Center Network (TPCN) received seventeen nutmeg poisoning and 64.7% from that cases involved abuse, and the rest was unintentional exposure. Most of the nutmeg exposures were via the oral route and minor cases of nutmeg exposure occurred through insufflated nutmeg, unintentional dermal and ocular exposures. Nutmeg also has been misused by mixing it with other drugs in order to get "high". For intoxication cases, treatments like decontamination (cathartic, charcoal, dilution, fresh air, IV fluids) and supportive care (benzodiazepines) will be provided to reduce the effects.

***Keywords*— Nutmeg; Myristica fragrans; Myristicin; Toxicity; Intoxication**

I. INTRODUCTION

Nutmeg or its scientific name Myristica fragrans is an aromatic fruit from Myristiceae family that are mainly cultivated in several countries, including Indonesia (Mollucas Of Spice Island and Eastern Java), Caribbean Island (Grenada and Trinidad), Malaysia (Penang) and India. The Nutmeg fruit provides a tropical spice with pleasant aromatic fragrance and strong taste, while its special ability is to enhance the taste of food hence widely used as a flavoring agent in cakes, puddings, beverages, meat and sausages [19], [13].

Besides, Nutmeg been reported to possess many distinct advantages, some of them are: anti-diarrheal activity, antidiabetic, stimulant, antifungal, carminative and anti-inflammatory properties [3], [17]. The nutmeg and mace are also used in Asia as traditional medicines treating stomach cramps, diarrhea and rheumatism. Nutmeg contains volatile oils that comprise of alkyl benzene derivative called myristicin. The characteristics of Myristicin acid is that it act as a weak monoamine oxidase inhibitor and some portion of myristicin have structures similar to serotonin agonist. Myristicin may be metabolized to exhibit compounds similar to amphetamine with hallucinogenic effects similar to lysergic acid diethylamide [9].

Myristicin (5-allyl-1-methoxy-2,3 (methylenedioxy benzene) is a flavoring plant constituent and has been known to produce significant psychopharmacological responses as well as insecticidal activity [16]. The metabolism of myrsiticin resembles that of safrole. Apart from natural sources, myristicin can be produced synthetically, where it has been considered as cheap drug due to its hallucination effects that resulted in being considered as hallucinogen agent.. The Hallucinogen (psychedelics) agents are basically psychoactive substances that forcefully alter perception, mood, and a host of cognitive processes [18].

Since Myristicin is a Hallucinogen agent, it can be used as a cheap hallucinogenic intoxicant, however frequent usage can lead to fatal incidents resulting in organ damages and impact on the cardiovascular systems. Recently, many cases of nutmeg poisoning have been reported, including several fatal myristicin cases [20]. Such poisonings are not solely resulted from toxic effect of myristicin itself, but also from the combined toxic effects of myristicin with other substances. The Chemical Selection Working Group (CSWG) reviews myristicin closely due to prevent the potential widespread human exposure through foods and beverages and the associated negative effects. In order to understand

myristicin and its harmfulness to the human body, this paper will provide the complete review of information on chemical and physical characteristics of myristicin; its metabolism rate; nutmeg (myristicin) dosage; its clinical effect and reactions; reports on its intoxication; misuse of nutmeg and treatment to cure nutmeg intoxication.

II. MYRISTICIN

As mentioned earlier, it is widely believed that myristicin is the major component that is responsible for intoxication. However, when consumed in large portions, myristicin becomes toxic and causes fatty degeneration in the liver [14]. Apart from nutmeg, myristicin is also available in carrots, parsley, celery, dill, parsnip and black pepper [12]. Figure 1 depicts the chemical properties and structure of myristicin.

- Chemical name: 1-allyl-5-methoxy-3,4 methylene-dioxy-benzene
- CAS No: 607-910-0
- Empirical formula: $C_{11}H_{12}O_3$
- Molecular weight: 192.22 [12]

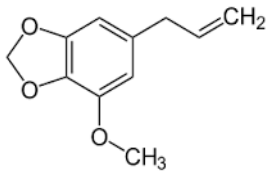

Fig. 1: Properties and chemical structure of myristicin.

A. Metabolism of Myristicin

Myristicin were extensively metabolized by rats and human [5]. The possible cause for the psychoactivity of nutmeg seeds could be due to the metabolic conversion of elemocon and myristicin into amphetamine-like compounds. Myristicin is observed to metabolize to 3-methoxy-dioxy amphetamine (MMDA), which are amphetamine derivatives. Moreover, myrisicin is a weak inhibitor or monamine oxidase, while other components of myristicin (linalool, safrol, isoeugenoland uegenol) are structurally similar to serotonin agonist, which could be responsible for some cardiovascular symptoms [11],[7]. Figure 2 represent chemical structure of myristicin before and after metabolisation.

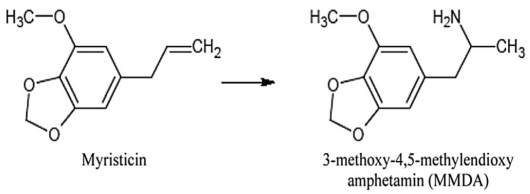

Fig.2: Metabolism of myristicin into 3-methoxy-4,5-methylendioxyamphetamine (MMDA) after ingestion. MMDA are major compounds that are responsible for hallucinogenic effects [11]

B. Nutmeg (Myristicin) Dosage

One to three nutmegs or 5-30g of the ground nut can induce psychogenic effect, while a minimum 5 g of nutmeg powder is considered as toxic dose. One tablespoonful of ground nutmeg spice is approximately equal to 7 g, or one grated nutmeg. A mild cerebral stimulation in human brains caused by 400 mg of myristicin is equivalent to 15 g of nutmeg powder [21]. In 400 mg doses (corresponding to 6-7 mg/kg b.w), myristicin produces “mild cerebral stimulation” in 4 out of 10 humans subjects. However, several intoxications have been reported after the ingestion of approximately 5g of nutmeg corresponding to approximately 1-2mg myristicin/kg b.w. The reason for such occurence is due to the combined effects between myristicin and other compounds of nutmeg [12].

C. Clinical Effects and Reactions

Majority of nutmeg exposures were via the oral route, in some minor cases, nutmeg exposure occurs through insufflated nutmeg, unintentional dermal and ocular exposures [6]. The most significant symptoms experienced with acute intoxication involves the cardiovascular and central nervous systems.

Consumption of nutmeg seeds in large quantity has been reported to lead to facial flushing, tachycardia, hypertension, dry mouth, blurred vision, psychoactive hallucinations, feelings of euphoria (unreality) and delirium. Symptoms usually begin about 3 to 6 hours after ingestion, and resolves by 24 to 36 hours [11]. Lee *at al.* (2005) have reported that myristicin (1-allyl-3,4-methylenedioxy-5-methoxybenzene), a naturally occurring alkyl benzene derivative found in nutmeg induces neurotoxicity in human neuroblastoma SK-N-SH cells by an apoptotic mechanism. Neurotoxicity can be defined as adverse changes in nervous systems due to the toxic chemical exposure, where can result in traumatic brain damages and other neurological diseases. The term neurotoxicity is synonymous with chemical-induced brain damage or drug induced toxicity in nervous system [10]. It was observed that a dose-dependent reduction in cell viability occurred at myristicin concentration for > or = 0.5 mM in SK-N-SH cells. The apoptosis triggered by myristicin was accompanied by an accumulation of cytochrome-c and by the activation of caspase-3. Methanolic extract of *M.fragrans*, even 10µg/ml, induces apoptosis of Jurkat leukemia T cell line through SIRT1 mRNA down regulation.

D. Reports on Nutmeg Intoxication

It is unclear when nutmeg was first began to be abused for its purported hallucinogenic. According to Stein et al. (2011), the first case of nutmeg poisoning was described in 1576 by Lobel [21]. who reported the ingestion of 10-12 nutmegs (approximately 70-84g) by a pregnant English lady to induce inebriety. The same case of nutmeg poisoning was reported by Carstairs and Cantrell (2011) involving two young adult males who had ingested about 14 g powdered nutmeg [6]. Due to its euphoric and hallucinogenic effects, nutmeg has a long history of abuse as a low-cost substitute for other drugs. From the first report of nutmeg hallucinogenic effects, numerous medical literature have described patients who intentionally ingested nutmeg in order to experience psychotropic effects.

As of now in literature, only two nutmeg-associated fatalities have been described. The first, reported in 1887, describes an 8 year old boy who reportedly ingested two nutmegs and was found semi-comatose; he was administered with an emetic “disffusible stimulants”, followed by

"hypodermic injections of brandy, ammonia, and small doses of sulphate of atropia", however he died the following morning. In this case, it can only be speculated that the ingested nutmeg dose may have been between 560 and 840 mg/kg (39-59 g per 70 kg). The second case As of now in literature, only two nutmeg-associated fatalities have been described. The first, reported in 1887, describes an 8 year old boy who reportedly ingested two nutmegs and was found semi-comatose; he was administered with an emetic "disffusible stimulants", followed by "hypodermic injections of brandy, ammonia, and small doses of sulphate of atropia", however he died the following morning. In this case, it can only be speculated that the ingested nutmeg dose may have been between 560 and 840 mg/kg (39-59 g per 70 kg). The second case involves a 55 year old woman that was found dead with a postmortem blood flunitrazepam level of 0.072 mcg/ml (considered within toxic range). The stomach contents of the aforementioned patient smelled strongly of nutmeg; subsequently, myristicin was identified in postmortem blood samples and was quantified as 4.0 mcg/ml [6],[11].

In terms of intoxication, Abernethy and Becker (1992) reported an incident involving a 23 years old college student [1]. He was sent to emergency department after experiencing palpitations, severe anxiety, feelings of dread and described several visual hallucination. The student admitted to ingest approximately 4 tablespoons (28g) of powdered nutmeg mixed with coffee, with the intention of getting "high" 6 hours prior to his presentation. He denied of consuming any other drugs except for occasional alcohol, with no significant past medical or psychiatric history.

Cases related to nutmeg exposures can be categorized into two groups, namely abuse (intentional abuse and misuse) and non-abuse (all other exposures). According to the report by Carstairs and Cantrell (2011), a total of 119 cases of nutmeg exposure were reported to the California Poison Control System (CPCS) electronic database between 1997 and 2008. The intentional exposures were 72.3% for recreational purposes (between ages 13 and 20 years old). The remaining 27.7 % involving patients under 13 years old were considered as unintentional exposures.

Some other incidents involving intoxication occured in Texas between the year 1998 and 2004 were reported by Forrester (2005). During that period, Texas Poison Center Network (TPCN) attended seventeen cases of nutmeg poisoning, where 64.7% from that cases involved abuses, while the rest were unintentional exposures. According TPCN reports, all of the nutmeg abusers were men.

E. Misuse of Nutmeg

Recently, several cases of nutmeg seed ingestion have been reported within the adolescents age group, in particular, all of whom were attempting to achieve a euphoric state at a low cost. Most of toxic based nutmeg ingestions are carried out by prisoners, college students, and adolescents. This is usually done as an experiment or as a deliberate attempt to "get high", especially when ethanol or other recreational drugs are not readily available [1].

The effects of nutmeg that provides hallucination attract teenagers to use it as a cheap recreational drug. Having almost the same effects as marijuana, nutmeg has been chosen as the substitute. In fact the pain relieving capacity of nutmeg has been historically utilized to ward off pain, and therefore commonly used to substitute morphine narcotic drugs. As mentioned earlier, the reputed psycho-activity of nutmeg has always been associated with the hypothesis of potential metabolic activation of nutmeg constituents to amphetamine-like compound [3],[11].

Nutmeg also being misused intentionally by combining with other drugs. Nutmeg abuse can be polypharmacy overdoses. These patients exhibit more serious symptoms and toxicity than nutmeg exposures without other substances. Patients that intentionally exposes to nutmeg will have combined drug intoxication. Popular drugs that being combined with nutmeg is cannabis, amphetamines, lisdexamfetamine, benzodiazepines, diphenhydramine, duloxetine, clonazepam, benzodiazepines, acetaminophen, K2, cough syrup, acetaminophen and antihistamine [8].

F. Treatments

The presence of hemodynamic instability suggests the presence of other toxins or illnesses. Decontamination measures are usually unnecessary because of the presence of vomiting or delayed contact (ie, > 1 to 2 hours after ingestion) by the health care facility. There are no clinical data to guide the treatment of nutmeg intoxication. The use of standard antiemetic (prochlorperazine, trimethobenzamide, odansetron, metoclopramide) and intravenous (IV) fluids may be required to treat protracted nausea and vomiting. Sedatives (diazepam, haloperidol) should be used with caution due to the alternating periods of delirium and abtundation during nutmeg intoxication [4]. Other treatments consisted of decontamination (cathartic, charcoal.dilution, fresh air, IV fluids) and supportive care (benzodiazepines)[9].

III. CONCLUSIONS

In general, excessive consumption of nutmeg exceeding "toxic level" can give negative effects to health because it can induce neurotoxicity in brain. To present, no holistic treatment was develop to prevent nutmeg intoxication. Thus, consuming nutmeg in higher amount should be avoided.

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