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## Selected toxicological aspects of honey

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### Abstract

The aim of the present review was to analyze grayanotoxin and its healthy and poisoning effect to human health according to available resources of literature. Plants contain many compound components which can be categorized as "medical" or "poisonous" depending on their effects to human body. There are also secondary products derived from plants, such as honey, which can contain many chemical compounds with medicinal or poisonous effects depending on their concentration and application. Many plants of the *Ericaceae* family, *Rhododendron*, *Pieris*, *Agarista* and *Kalmia*, contain diterpene grayanotoxins. The consumption of grayanotoxin containing leaves, flowers or secondary products as honey may result in intoxication specifically characterized by dizziness, hypotension and atrial-ventricular block.

## 1. Introduction

There are a lot of information about the nutritional and medicinal properties of honey. Honey is well known as a product with nutritional and health-promoting properties. Honey on the other side can contain compounds which tend to be toxic. Nevertheless, it is important to take into account the aspect of health safety of honey in terms of the potential contaminants presence, mainly plant toxins (Bencko *et al.*, 2017; Kromerová and Bencko, 2017-2020). There are several studies about this issue.

The aim of the present review was to analyze the selected plant toxins in honey, especially grayanotoxin and their health effects including poisoning.

## 2. Selected plant toxins in honey

The secondary plant metabolites such as plant toxins or phytotoxins may have acute or chronic toxic effects or anti-nutritional effects. Consequently bees can contaminate honey if they are fed on these toxic plants flowers. Pyrolizidine alkaloids and grayanotoxins (GTX) belong to the most important plant toxins in honey (Kromerová and Bencko, 2018).

Grayanotoxin is a plant toxin which can be found in the leaves, flowers, and in nectar of some *Rhododendron* species and other members of the *Ericaceae* botanical family. There were some names used for this toxic chemical in the past such as andromedotoxin, acetylandromedol, and rhodotoxin. Grayanotoxin can be also found in honey from pollen and nectar of certain plants mainly *Rhododendron* plants. There is a specific type of grayanotoxin compounds depending on plant species such as diterpenes, polyhydroxylated cyclic hydrocarbons which contain no nitrogen (FDA, 2012a).

A lot of representatives of *Ericaceae* family, *Rhododendron*, *Pieris*, *Agarista* and *Kalmia* are typical for their diterpene grayanotoxins content (Jansen *et al.*, 2012). There were more than 25 grayanotoxin (GTX) isoforms isolated from the *Rhododendron* family. There are three members (GTX-I, GTX-II, and GTX-III) from the large grayanotoxin family which can be labeled as the major toxins. First two toxins GTX-I and GTX-II occur in smaller amounts. The last third GTX-III isoform is the principal toxin of "mad honey" (Qiang *et al.*, 2011).

Toxins also occurred in content components of *Rhododendron* species as well as in plants which belong to *Ericaceae* family. They were also identified in honey derived from these plants. The four toxic isomers of grayanotoxin (I, II, III, IV) (Fig. 1) were found in plants belong to *Ericaceae* botanical family (FDA, 2012a) (Figure 1).

One of the methods for grayanotoxins isolation is extraction of naturally occurring terpenes. Another one is thin-layer chromatography (Scott *et al.*, 1971; Froberg *et al.*, 2007; FDA, 2012a).

The content of grayanotoxin in "mad honey" depends on many factors mainly seasonal climatic variations, season production and the maturity of honey (Sahin *et al.*, 2015).

The presence of specific grayanotoxins relates to plant species. There is no production of grayanotoxins in all *Rhododendrons*. There were found five species of *Rhododendron* in Turkey. *Rhododendron ponticum* is typical plant for the mountains of Black Sea area (Terzioglu *et al.*, 2001). There are also other species of *Rhododendron* and other members of the botanical family *Ericaceae*, which can produce the toxins but they are not so often implicated with the disease. Mountain laurel (*Kalmia latifolia*) and sheep laurel (*Kalmia angustifolia*) are probably the most important sources of the toxin too. It was found that

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Grayanotoxin I (andromedotoxin) occurs only in *Ericaceae* plants and it contains the compounds which are in charge of poisoning. These compounds are diterpenes, polyhydroxylated cyclic hydrocarbons without nitrogen presence. They are extracted directly from the leaves and flowers of *Rhododendron* species by bees (Goldfrank's Toxicologic Emergencies, 2002; U.S. Food and Drug Administration, 2020).

The sources of "mad honey" used in the studies were: Turkish honey (Von Malottki and Wiechmann, 1996; Gössinger et al., 1983), Eastern Black Sea (Biberoglu et al., 1987; Dilber et al., 2002; Kumral et al., 2005), Western Black Sea (Özhan et al., 2004), Central Black Sea (Yavuz et al., 1991), Black Sea (Sutlupinar et al., 1993).

Honey from the Black Sea region of Turkey occasionally contains grayanotoxin and it causes poisoning. The poisoning mainly occurs regarding to the consumption of honey from the eastern part of the Black Sea region. This honey is known as "mad honey". The cases of poisoning are often in the east of the Black Sea region but some cases were observed all over the eastern Black Sea region of Turkey too (Gunduz et al., 2006).

Beekeeping belong to common activities for the people who live in the eastern Black Sea area. *Rhododendrons* are typical long-lived plants. Beekeepers from this region are experienced and know which honey is "mad". Honey produced in springtime is more toxic and it sometimes contains higher concentrations of grayanotoxin than honey produced in other seasons (Dilber et al., 2002).

### 3. Health effects

Honey intoxication means the principal poisoning as the result of the exposure to grayanotoxin. The main reason of this fact is the consumption of honey produced from *Rhododendrons* pollen and nectar. Adverse reaction(s) are the consequence of toxic concentrations of grayanotoxin. There are some other names for this toxicity such as *Rhododendron* poisoning, "mad honey" intoxication, and grayanotoxin poisoning.

It seems that there can be a presence of grayanotoxin in honey, which is poisonous to human, from pollen and nectar of some *Rhododendron* flowers. Grayanotoxin can also be a part of honey from other *Rhododendron* family plants mainly in the Eastern part of the U.S.A. including mountain laurel and sheep laurel. "Mad honey" poisoning is the name for disease which is the consequence of eating honey containing grayanotoxin. This disease occurred in the U.S.A. in the past, nowadays its occurrence is very rare.

There is honey imported mainly from Turkey which has recently caused "mad honey" sickness. The symptoms of poisoning are visible in a few minutes or a couple of hours, but on the other side they are gone within a day. This honey can have brown color and bitter and may cause burning feeling in throat. In case of honey which is produced by large factories in the U.S.A., this honey consists of different pollen and variety of sources, so toxins presence is very low and not harmful as well (FDA, 2012a)

Consumption of honey which contain grayanotoxin can cause intoxication with typical symptoms such as dizziness, hypotension and atrial - ventricular block. These symptoms are result of inability to inactivate neural sodium ion channels and consequently increase of vagal tone.

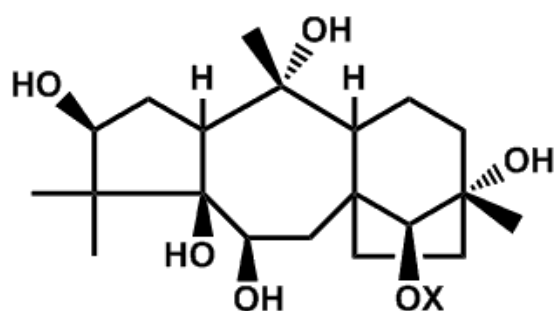
Products which contain grayanotoxin are available only online and this fact increase possible risk. Intoxication in humans in comparison with cattle and pet cases is rarely lethal. There is almost no scientific evidence for medical properties of preparations containing grayanotoxin such as honey or herbal preparation used in folk medicine and it this use could be harmful (Jansen et al., 2012).

Bradycardia, hypotension and syncope belong to symptoms which can be caused by grayanotoxin poisoning. In addition, mortal cardiac rhythms such as complete atrioventricular block and asystole have also been reported (Gunduz et al., 2008).

Grayanotoxin intoxication from the "mad honey" causes dizziness, hypotension, and bradycardia, and in high doses, impaired consciousness, seizures, and atrioventricular block (Gunduz et al., 2006).

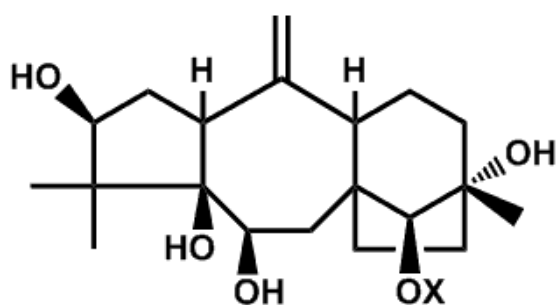
Sahin et al. (2015) determined grayanotoxin (GTX-III) toxin level in "mad honey" from Düzce city locations in the West Black Sea region of Turkey. They examined the dynamic changes of certain biochemical parameters in blood serum of rats that consumed "mad honey". According to results, the quantity of GTX-III found in the honey sample as  $39.949 \pm 0.020 \mu\text{g GTX-III/g honey}$ , and the biochemical analysis of the tested parameters (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, creatine kinase, and creatine kinase muscle and brain) showed a significant elevation with increasing concentration of honey. In conclusion, the use of increasing concentrations of *Rhododendron* honey was seen as a source of enzymatic symptoms.

Especially, "mad honey" intoxication is the most current poisoning, caused by the consumption of honey produced from the nectar of *Rhododendrons*. Cardiac rhythm disturbances such as bradycardia or atrioventricular block, convulsions, vomiting, sweating, blurred vision, chills, and cyanosis can occur after consuming this honey due to grayanotoxins (GTXs) (Dilber et al., 2002; Akinci et al., 2008; Bittmann et al., 2010). There



Grayanotoxin G I (X=Ac)

Grayanotoxin G III (X=H)



Grayanotoxin G II (X=H)

Grayanotoxin G IV (X=AC)

Figure 1. Grayanotoxin Structure (FDA, 2012b)

were some cardiac disturbances observed in patients such as bradyarrhythmia, sinus bradycardia, nodal rhythm, Wolff-Parkinson-White (**Gunduz et al., 2006**).

**Gunduz et al., 2008** found out that "mad honey" from the Black Sea region of Turkey causes cardiac complication such as GTX poisoning by blocking sodium channels in the cell membrane.

The main symptoms of GTXs are believed to be caused by continued sodium channel activation, cell depolarization, and hence stimulation of the vagal nervous system (**Jansen et al., 2012**). The voltage-gated sodium channels of the neurons are a prominent target for grayanotoxins. In general, bradycardia occurs after the administration of GTXs and consumption of its source in foods (**Gunduz et al., 2008**).

The functional disorders can be seen by overdose consumption of *Rhododendron* honey on cardiac side effects such as bradycardia and severe hypotension. Modification of Na<sup>+</sup> and K<sup>+</sup>-ATPase channel is also the most common cause of these disorders. The most important result of Na<sup>+</sup>/K<sup>+</sup> modification, also called "cardiotoxicity", can be measured by blood serum biomarker levels such as AST (aspartate aminotransferase), ALT (alanine aminotransferase), LDH (lactate dehydrogenase), CK (creatinine kinase), CK-MB (creatinine kinase muscle and brain), troponin T, troponin I. Many "mad honey" intoxication cases have been reported, especially cardiac effects of human and experimental animals. Definitely, grayanotoxin forms also act directly on the serum biomarker parameters generally related to cardiac enzymes (**Sahin et al., 2015**).

LDH is the specific heart muscle cells enzyme. The abnormal elevation of this enzyme in the blood stream will occasionally be the marker if a heart attack (myocardial infarction) occurs. There is also a high level of LDH in some case of hypoxia. Exposure of hypophysectomized rats to hypoxia produced a proportional loss of body and heart weight with an equal decrease in both LDH subunits, H (heart) and M (muscle). Growth hormone and/or ACTH (adrenocorticotrophic hormone) did not reverse cardiac atrophy. The adaptive changes in LDH isoenzymes induced by hypoxia could be abolished with hypophysectomy, and partly restored by giving growth hormone and ACTH, but this restoration was not coupled with cardiac growth (**Kaaja and Are, 1996**).

Typical and common signs of grayanotoxin poisoning are nausea and vomiting. Burning, tingling and numbness around the mouth are less common or rare symptoms. The grayanotoxin badly affects nerve cells in brain as well as the heart and muscles. The results are not only dizziness, weakness, confusion, vision disturbance, heavy sweating and saliva flow but also irregular or slow heartbeat, low blood pressure and fainting. Although this poisoning is fatal only in isolated cases, sometimes medical treatments are necessary to insure normal blood pressure and heart rate (**FDA, 2012a**).

It was said that the lowest toxic dose is in range between 5 g to 30 g up to 300 g. The most common symptom of exposure to grayanotoxin is vomiting and this fact could alter the actual dose and the amount of absorbed toxin.

There was no connection between the importance of honey poisoning and the amount of investigated honey according to the studies which were focused on evaluation of this relationship (**Yilmaz et al., 2006; Gunduz et al., 2006**) although there were some references which can indicate some relationship. Significant factor can be the concentration of grayanotoxin in honey (**FDA, 2012a**).

Mad honey intoxication's symptoms are dose-related (**Koca and Koca, 2007**). The symptoms can be visible in a few minutes or more hours. There is a presumption that the latent period for symptoms depends on dose of grayanotoxin (**Gunduz et al., 2006**) but there is no association between amount of eaten honey and symptom onset (**Yilmaz et al., 2006**).

There is also adverse reaction caused by grayanotoxis which includes nausea and vomiting, dizziness, weakness, mental confusion, impaired consciousness; excessive perspiration and/or salivation, cloudy or blurred vision; chest pain or compression; paresthesias in the extremities or perioral area. These symptoms occur immediately after toxic honey eating. The accompanying signs are fainting, low blood pressure or shock, bradyarrhythmia (slow, irregular heartbeat), sinus bradycardia (regular heart rhythm, but with rate slower than 60 beats per minute), and abnormalities in the heart's pacemaker/conduction pathways (e.g., nodal rhythm, second degree or complete atrioventricular block). There are also some evidence of other cardiac issues such as acute myocardial infarction (with normal coronary arteries) due to coronary hypoperfusion.

Patients typically feel better and experience an alleviation of grayanotoxin-induced symptoms along with a return to normal cardiac function, as seen in measures such as heart and blood pressure, within a relatively brief duration. In mild poisonings, the duration of adverse effects are typically a few hours; in severe cases, the duration of the effects can be 1 to 5 days. This fact is because grayanotoxins are metabolized and excreted rapidly.

Grayanotoxins belong to neurotoxins and cardiotoxins. It seems that recovery generally become within 2 hours up to 8 hours without needed intervention. The therapy with vasopressors is seems to be important for cases of adverse reactions which are followed low blood pressure. Atropine therapy can cause sinus bradycardia and conduction effects. Recovery becomes within one day in these cases. There are some cases where care and monitoring in intensive-care units and in some cases using of a temporary pacemaker are necessary. However "mad honey" intoxication is rarely fatal as well as food poisoning if appropriate medical treatment is immediately done on time.

**Gunduz et al. (2006)** have not noticed any cases of death in their study although it is generally known that grayanotoxin causes adverse effects on the cardiovascular and respiratory systems so it is important take these facts in account.

The effect of grayanotoxin on the cell membrane has the impact on the skeletal and heart muscle, peripheral nerves and the central nervous system. Firstly this toxin is bound to voltage-gated sodium channels in cell membranes which cause that the channels open at lower - than - normal membrane potentials and then they remain open more that is usual. The increase in sodium influx and sustained depolarization then cause hyperexcitability of the cell and involving calcium into the cells should be facilitated at this time. There are no blood or urine test available now so possible diagnosis is done according to signs and symptoms of grayanotoxin intoxication and consumption habits. There can be some cases of grayanotoxin poisoning after honey consumption although these cases are very rare. These cases can be connected with people with pre - existing cardiovascular disease or blood - pressure issues. All cases which occurred in Germany, Austria and Korea have been connected with honey from Turkey. There are also some studies in which "mad honey" was used as an alternative medicinal or "natural" therapy or as a folk cure (**FDA, 2012a**).

Mad honey is used in the Black Sea region as an alternative medicine for the treatment of gastric pains, bowel disorders, and hypertension, and it is also believed to be a sexual stimulant (**Sutlupinar et al., 1993**). Given these uses, there has been no decrease in grayanotoxin intoxication cases in spite of this awareness of mad honey (**Gunduz et al., 2006**). The grayanotoxin poisoning has been observed in livestock as well as sheep and goats. These farm animals were fed with feed containing young leaves and flowers from *Rhododendron* species (**FDA, 2012a**).

It seems that maybe appropriate fluid replacement and atropine should be sufficient for the treatment of poisoning in general. Hypotension usually responds to the appropriate fluids, and correction of bradycardia and conduction defects, which usually respond to atropine treatment. Because of this fact complete recovery after hospital admission is normal.

There are some clinical and experimental studies, case series and case reports in the medical literature about grayanotoxin poisoning although the grayanotoxin ("mad honey") poisoning has not been known so far. The great majority of the cases have been reported from Turkey. There are 58 cases of "mad honey" poisoning which have been reported in the studies. One study comes from Germany, one is from Austria, and the rest of studies are from Turkey, in 8 unpublished papers. However, we do not know whether there have been any deaths due to "mad honey" poisoning before the patient reached the hospital (**Gunduz et al., 2008**). There are eight cases of "mad honey" poisoning described in the study from **Gunduz et al. (2008)**.

**Akinci et al. (2008)** presented a case of a patient who was admitted to the hospital because of acute myocardial infarction with normal coronary arteries after "mad honey" ingestion.

The case study by **Gunduz et al. (2006)** represents series of cases of patients (6 women, 2 men) aged between 35 and 75. All of the patients' physical examinations revealed hypotension; 4 patients had sinus bradycardia, 3 had nodal rhythm, and 1 had complete atrioventricular block. The heart rate and blood pressure returned to normal limits within 2 to 6 hours in all patients, except for the patient with atrioventricular block. Two patients were monitored in the coronary intensive care unit.

**Dilber et al. (2002)** reported a pediatric case of honey intoxication, in which the parents were aware that the honey was "mad honey". An eight-year-old previously healthy boy was admitted to the hospital with suddenly developed nausea, vomiting, weakness, dizziness and impaired consciousness. The symptoms began within 1 h of drinking three spoons of honey in the form of sherbets for his abdominal pain. He was sweating diffusely. Body temperature was 36.4 °C, heart rate 45 beats/min, and arterial blood pressure 85/45 mmHg. All routine biochemical tests were within normal limits. The electrocardiogram showed sinus bradycardia. Parenteral fluid was administered, and atropine and dopamine were given for symptomatic treatment of hypotension and bradycardia. Honey poisoning should be kept in mind in any patients admitted with unexplained hypotension, bradycardia and other rhythm disturbances, and patients eating honey from the Black Sea region must be examined carefully.

Therefore is very important to share the experience and call attention to the wide use of honey in nutrition and alternative therapy.

### 3. Conclusion

Medicinal use of grayanotoxin is not well known so the care should be taken when consuming grayanotoxin containing bee product. Honey can be potentially therapeutic or toxic depending on its dose. Though various animal studies have been conducted to elucidate the mechanism by which grayanotoxins act, the dose-response relationship in both animal and human systems has not been well established. Lower doses of honey could have potentially therapeutic short-term antiarrhythmic and long-term cardiovascular benefits. As the old adage goes, "One man's poison is another man's cure". More research is definitely warranted in this area to throw light on the therapeutic and toxic dose-dependent properties of honey.

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### Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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