WORLDWIDE DISTRIBUTION AND CLINICAL CHARACTERISTICS OF MAD HONEY POISONING CASES

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SUMMARY

Objectives: Mad honey poisoning is a common public health problem that can be seen in many parts of the world. In this study, the symptoms and clinical findings of mad honey poisoning cases and their distribution worldwide were investigated based on current data.

Methods: PubMed, Scopus, Web of Science and Google Scholar databases were searched. The demographic characteristics of the cases, clinical findings, amount of consumed honey, duration of hospitalization, and data of the region where mad honey was produced were recorded.

Results: 900 cases were identified. The majority of poisoning cases (91.44%) were reported from mad honey produced in Turkey, Nepal (4.67%) came second and Korea (1.56) third. The majority of cases in Turkey were due to honey produced in the Black Sea Region. It was also determined that the mad honey was produced in the west Black Sea Region in most of the cases (35.22%), followed by the east Black Sea Region with a rate of 33.22%. In poisonous cases, it was determined that the mad honey was mostly produced in Rize, followed by Trabzon and Kastamonu, respectively. The most common signs of mad honey poisoning were bradycardia (88.48%) and hypotension (76.04%).

Conclusion: The majority of cases have been reported from Turkey. When examining where the mad honey was produced in Turkey, it was seen that the western Black Sea Region came first, and the eastern Black Sea Region came second. Rize came first among the provinces, followed by Trabzon and Kastamonu. There is a parallelism between the distribution of mad honey poisoning cases and the distribution areas of *Rhododendron* species. However, although *Rhododendron* species show a widespread distribution throughout the world, why the majority of the cases were reported from Turkey draws attention as an issue that needs to be investigated.

Key words: Black Sea Region, Rhododendron, geographic distribution, grayanotoxin, intoxication, mad honey, poisoning, toxicity

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INTRODUCTION

Review of the literature has pointed out that the use of honey as food and a remedy against diseases dates back 8000 years (1). Current literature highlights health benefits of honey in the management of a series of diseases. It has beneficial immune, antioxidant, anti-inflammatory, antibacterial, anti-diabetic, hepatoprotective, antihyperlipidemic, cardiovascular, antitussive, anti-fungal, and anti-tumor effects. It is also useful in treating some respiratory, ophthalmological, cardiovascular, and nervous system disorders (1–3). Additionally, the therapeutic effects of honey in traditional medicine in a variety of diseases including eye diseases, asthma, throat infections, tuberculosis, thirst, hiccups, fatigue, dizziness, hepatitis, constipation, worm infestation, piles, eczema, ulcers, and wounds have frequently been reported (1, 2). Presently, approximately 300 types of honey have been recognized. These varieties are related to different types of nectar that are collected by the honeybees. The main composition of honey are carbohydrates that contribute 95–97% of its dry weight. Furthermore, honey includes proteins, vitamins, amino acids, minerals, and organic acids as main compounds. It also includes phenolics and terpenoid compounds that are responsible for its purportedly beneficial antioxidant capacity (1, 3). Amongst honey types, "mad honey" is well-known for its unusual human toxicity (4, 5).

Numerous reports and reviews have been published in the literature regarding mad honey poisonings. However, the geographic distribution, frequency of various clinical findings, characteristics of the poisoned individuals, and the source plant for the poisonings is unclear.

Distribution of Plant Species Potent in Mad Honey Poisoning

The Ericaceae are a family of perennial, hermaphroditic or dioecious, shrubs and small trees, rarely lianas. Members of the family grow in acid soils, typically in bog, moorland or heathland communities with distributions worldwide in temperate and tropical regions. Their economic importance includes cultivated ornamentals, especially *Rhododendron* and *Erica* (6). *Rhododendron* is one of the largest genera of the Ericaeae including ca. 850

taxa distributed in the northern hemisphere mainly in Asia (7). The genus is represented by five species (*Rhododendron luteum* Sweet, *R. caucasicum* Pall., *R. ponticum* L., *R. ungernii* Trautv., *R. smirnovii* Trautv.) and four hybrids (*Rhododendron x davisianum R*. Milne, *Rhododendron x filidactylis R*. Milne, *Rhododendron x rosifaciens R*. Milne, *Rhododendron x sochadzeae* Charadze & Davlianidze) in Turkey and most of them are in northeast Anatolia (8). They rarely occur in other types of forests or above the tree line. Beekeepers usually place their hives on the hillsides on pastures at these heights consisting mainly of rhododendron bushes (e.g., *R. ponticum,* blue-coloured flowers) or above these heights in highlands near the forest, allowing the bees to collect nectar (personal communication-beekeepers). Beekeepers place their hives in clearings or fields near the rhododendron bushes intentionally to collect honey made from rhododendron nectar.

Table 1. *Distribution of cases according to province where mad honey was produced (N = 529)*

Province	n	%
Rize	121	22.87
Trabzon	120	22.68
Zonguldak	116	21.92
Kastamonu	108	20.41
Ordu	21	3.96
Sakarya	18	3.40
Samsun	12	2.26
İnegöl	7	1.32
Düzce	4	0.75
Kocaeli	1	0.18
Erzurum	1	0.18
Total	529	100.00

MATERIALS AND METHODS

In order to obtain case reports of mad honey poisoning, PubMed, Scopus, Web of Science, and Google Scholar databases were screened. In this screening, "mad honey" and "poisoning" or "grayanotoxin" and "honey" and "poisoning" word groups were used. No year limit was set in the search in order to reach case diversity and English articles published until July 2020, when the study was carried out, included in the research. Scientific articles reporting clinical findings on mad honey poisoning cases were included in the study. Conference papers were excluded from the research. In addition, the references of the gathered articles and the Google search engine were searched. In this search, non-English case reports and poisoning cases who consumed grayanotoxin containing plant parts or products were involved. Finally, 114 articles were included in the study.

The clinical findings collected from the studies gathered from the aforementioned databases include/comprise sex, age, symptoms, systolic and diastolic blood pressure (mmHg), heart rate, and electrocardiogram (ECG) findings. Heart rate less than 60/min was considered as bradycardia, blood pressure less than 90/60 mm/Hg was considered as hypotension. The data are shown as the mean ± SD, and they were obtained quantitatively as numbers and percentages. The frequencies of bradycardia and hypotension were calculated by taking into account the studies in which the number of cases with blood pressure and heart rate were indicated. In the reviewed studies, systolic blood pressure and heart rate findings were available for 384 and 860 cases, respectively. In the present review, *Rhododendron* species the nectar of which was potentially contained in the mad honey from the locations were identified by a plant taxonomist who contributed to the present paper.

RESULTS

The age of the cases studied ranged from 57 days to 89 years, and 77% were males. According to the data obtained worldwide from 900 cases, 8.78% (n = 79) of the total cases had AV block and 6.33% (n = 57) of them had junctional/nodal rhythm. The most common findings were bradycardia – 761 cases (88.48%), hypotension – 292 cases (76.04%), dizziness – 492 cases (54.67%),

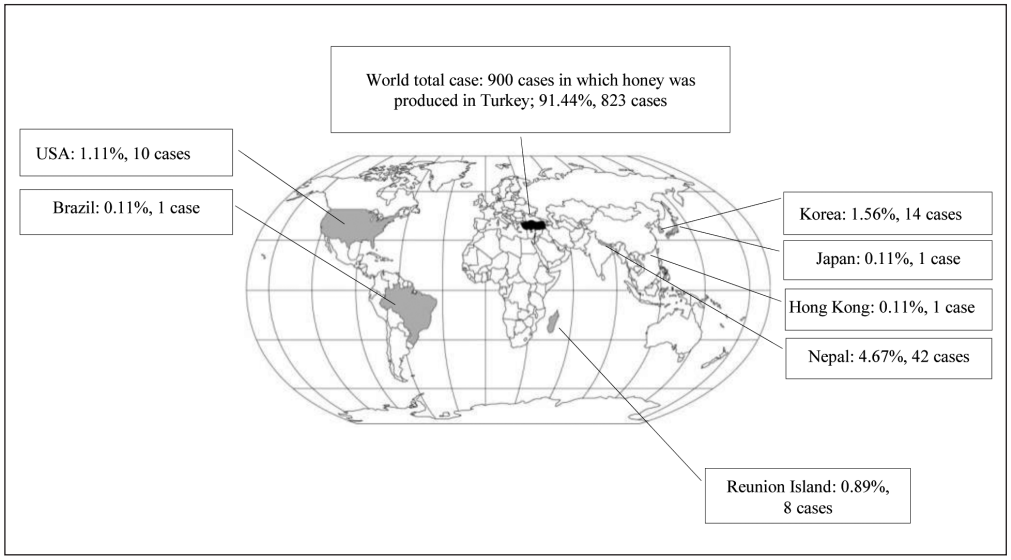

Fig. 1. *Distribution of poisoning cases by countries of origin of mad honey.*

and nausea or vomiting – 427 cases (47.44%). The next most frequent findings were fainting or syncope – 291 cases (32.33%), weakness – 148 cases (16.44%), and diaphoresis – 127 cases (14.11%, 127 cases).

Figure 1 shows a country-based distribution of the mad honey poisonings worldwide. Notably, 90.22% (812 cases) of the world total (900 cases) occurred in Turkey. In the mad honey poisoning cases reported from Austria (9, 10) and Germany (11–18), the mad honey was reportedly obtained from Turkey. The mad honey was produced in Turkey in 823 poisoning cases examined. Oh et al. reported two mad honey poisoning cases from Korea and indicated mad honey was from Nepal and Brazil (19).

Sohn et al. also reported 15 mad honey poisoning cases from Korea and indicated that the mad honey was brought from Nepal (20). In a mad honey poisoning case report from Hong Kong, Chen et al. indicated that the mad honey was brought from the Himalaya Region (21), and for another poisoning case reported from France by Nassibou et al., the mad honey was reported to have been produced in Nepal (22). Consequently, it was determined that the mad honey was produced in Turkey in the vast majority of the cases (91.44%) examined. It was also determined that Nepal (4.67%) came second and Korea (1.56%) third.

The majority of the poisoning cases in Turkey were reported from the Black Sea Region (Fig. 2). In addition, in some of the cases reported from outside the Black Sea Region, it was indicated that the mad honey was brought from the Black Sea Region. A remarkably high number of mad honey poisoning cases were recorded from eastern, middle or western Black Sea Regions – 643 cases (71.44%). When examining the regions where mad honey is produced in the poisoning cases, it was seen that the western Black Sea Region (35.22%) took the first place. The Eastern Black Sea Region (33.22%) came second.

In Turkey, in only one case, the honey was reported to have originated from the Eastern Anatolian Region. In 529 (65.15%) of cases from Turkey, it was clear which city was the source of the mad honey. It was determined that in the poisoning cases the mad honey was mostly produced in Rize (Table 1). Trabzon took the second and Kastamonu the third place. When provinces are analysed by regions, frequency of the cases recorded, the mad honey was from the cities Rize – 121 cases (22.87%), Trabzon – 120 cases (22.68%) and Ordu – 21 cases (3.96%) from eastern Black Sea Region; Zonguldak – 116 cases (21.92%), Kastamonu – 108 cases (20.41%) and Sakarya – 18 cases (3.40%) from the western Black Sea Region; and Samsun – 12 cases (2.26%) in the middle Black Sea Region. In the remaining cases of poisoning, it is not clear where the mad honey was produced.

DISCUSSION

The study determined that the vast majority of the mad honey poisoning cases were reported from Turkey. Following Turkey, most cases were detected in Nepal, Korea, Reunion Island, USA, Japan, Brazil, and Hong Kong, respectively. Looking at the natural habitat of the plants belonging to Ericaceae family, it is seen that these plants are widely grown in North America's east and west parts, the Black Sea and the eastern Black Sea Regions of Turkey, south China, Nepal, and Korea (23). In this respect, it is seen that the spreading areas of the plants belonging to the Ericaceae family coincide with the cases of mad honey poisoning. However, the analysis carried out in terms of the number of poisoning cases shows that the cases are not homogeneously distributed in the expansion area of the plants belonging to the Ericaceae family, and almost all of them are seen in Turkey. These differences in the number of cases may be related to honey production methods as well as the type and concentration of grayanotoxin contained in the plants in the mentioned regions. However, we do not have clear information about which species belonging to the Ericaceae family grow in these countries and regions and which of these plants contain more GTX (GTXI, II and III) varieties.

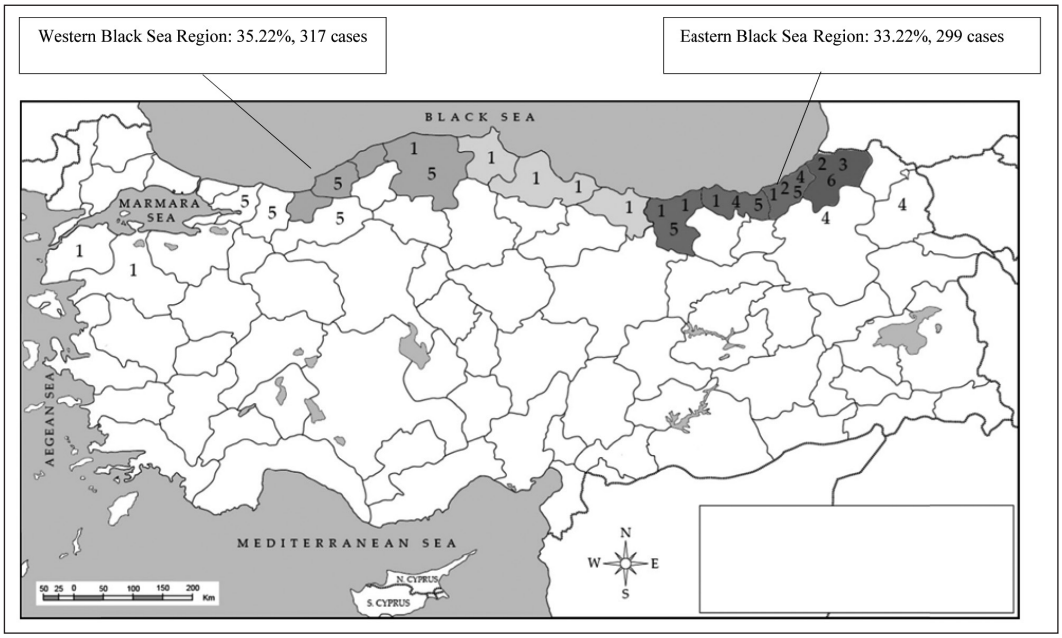

Fig. 2. *Distribution of Rhododendron species – the most common causes of mad honey poisoning in Turkey (1 – Rhododendron luteum, 2 – Rhododendron caucasium, 3 – Rhododendron ungernii, 4 – Rhododendron smirnovii, 5 – Rhododendron ponticum, 6 – Rhododendron sochadzeae)*

Despite North America's east and west parts having a rich flora, the number of cases in Turkey is about 80 times higher than in the United States. At this point, another striking situation arises when historical records are examined. Indeed, American botanist and physician Benjamin Smith (1785) recorded toxic effects in a few people eating wild honey near Barton, Ohio (24). Dr. Coleman (1852) published a mad honey case series in New Jersey in which 14 people were affected, one of which was fatal (25). In addition, cases of mad honey poisoning were reported from Texas, California, New Jersey and North Carolina in the 1800s (26). However, in this study the number of cases reported from the USA between 1981–2020 was only 10. It is thought that this decrease in mad honey poisoning cases in the USA from history to date is due to the technological methods used in honey production.

In Turkey, Ericaceae plants grow along the Black Sea coast and especially in the eastern Black Sea Region. When the case distribution is examined, it is seen that the plants of Ericaceae plants are mostly concentrated in the Black Sea Region in parallel with their spread area. It has been found that the number of cases in the western and eastern Black Sea Regions is similar but slightly higher in the western Black Sea Region. The concentration of the cases in the Black Sea Region can be related to the fact that this region is a natural habitat of Ericaceae plants, as well as the numerous local honey producers and high amount of unprocessed honey sold. In addition, the widespread use of mad honey as an alternative treatment method among the public is considered one of the reasons for this situation. On the other hand, commercial and touristic activities in the regions where mad honey is produced may result in locally produced honey causing poisoning in different regions and different countries. For instance, mad honey poisoning cases were reported in Germany and Austria as a result of consumption of mad honey produced in Turkey (9, 12).

Individual characteristics such as age and gender are factors that can influence prognosis in mad honey poisoning. Yaylacı et al. found that symptoms of mad honey poisoning in geriatric patients appeared earlier and persisted longer (27). In general, it is reported that mad honey poisoning is more common and more severe in males than females (3, 28).

Grayanotoxins cause many of the cholinergic toxidrome findings by acting on the peripheral vagal pathway (29). Gunduz et al. have shown that plasma pseudocholinesterase (BChE) levels are not reduced in mad honey intoxication as opposed to cholinergic intoxication (30). Earlier, Onat et al. have found that grayanotoxins caused cardiac toxicity by affecting M2 muscarinic receptors (31). It has been known that bradycardia and hypotension are leading findings of cardiotoxicity of mad honey poisoning (28). It was determined that 88.48% of cases developed bradycardia and 76.04% of the cases developed hypotension in the studies investigated.

Other important cardiotoxic effects of grayanotoxins are cardiac conduction disorders (32, 33). Grayanotoxins increase sodium permeability in excitable cell membranes. This facilitates the entry of calcium ions into the cell. As a result, the period of depolarization in the excitable cells is prolonged and the activation potential reduced. Decreased activation potential can lead to various pathologies by affecting the central nervous system and cardiac muscle (28, 34). In particular, the effect on sinoatrial node may result in cardiac conduction disorders (35). Furthermore, it has been reported that grayanotoxins affect the central nervous system, causing convulsions, transient ischaemic attack and stroke-like symptoms (36).

Rhododendron species, which are known to be the most important source of mad honey poisoning, have a widespread area throughout the world (37). However, the vast majority of the poisoning cases were recorded in Turkey, especially in the western Black Sea Region. *Rhododendron ponticum* is widely grown in the area and it is well-known that honey produced in arid seasons is more toxic. In the Black Sea Region, amateur beekeeping is practiced by a large number of local people. Also, the honey is used as a source of healing food and widely consumed by the local inhabitants for this purpose (personal communication).

CONCLUSION

This review reveals that the majority of the mad honey poisoning cases are from Turkey. Most of the mad honey which was the cause of the poisoning cases in Turkey was produced in the western Black Sea Region. In the province-based evaluation, it was seen that the honey that causes poisoning is mostly produced in Rize, Trabzon and Kastamonu, respectively. These regions, where mad honey production is common, are the natural habitats of Ericaceae family. In addition, beekeeping activities are carried out locally in these regions and honey is generally offered for sale without processing. The results of the study reveal that mad honey cases are frequently seen in the natural habitats of Ericaceae family and in areas where unprocessed honey sales are common. However, as a result of commercial and touristic activities, mad honey can be dispersed to different parts of the world and mad honey poisonings, the most important toxic symptoms of which are caused by the heart, can be seen all over the world. In this respect, mad honey poisoning is an important public health problem that especially emergency physicians may encounter. There is a need for large-scale studies searching for the reasons why mad honey poisoning cases cluster in the Black Sea Region and comparing the poisoning cases in the Black Sea Region and the toxin concentration in the plants grown there with those in other regions.

Conflict of Interests

None declared

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