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Review on The Hidden Potential Health Risks of Natural Toxins in Honey Bees (Apis mellifera) "Honey" in Tigray, Ethiopia.

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Abstract

Honeybees (Apis mellifera) are eusocial golden insects renowned for their ability to produce honey, a natural and nutritious food widely appreciated by humans. They collect nectar and pollen from a variety of wild flowering plants, each contributing unique sugar concentrations that bees process into mature honey using enzymatic secretions. Beyond honey production, honeybees play a crucial role in pollination services, significantly supporting biodiversity and contributing to environmental conservation and climate change mitigation. Through pollination services, bees ensure the survival of numerous plant species, making them essential to the ecological balance of the planet. While honey is regarded as a natural and healthy food, it carries hidden dangers. Consumers often believe that "natural food sources" like honey are inherently safe, but research reveals that honey may contain naturally occurring toxins. These toxins are influenced by multiple factors, including the botanical origin of the nectar, environmental conditions, geographical location, bee races, and beekeeping practices. Such toxins not only pose health risks to consumers but also result in significant economic losses for the honey industry due to contamination and rejection of products. To address these concerns, it is essential to understand the sources of natural toxins in honey and their potential risks to human health. Careful inspection of honey is necessary to identify these contaminants and minimize their presence. To reduce risks and ensure safe consumption, honey producers must adopt proper processing and handling techniques. The use of advanced technologies, such as liquid chromatography-mass spectrometry (LC-MS), is highly recommended. LC-MS is favored for its precision, wide applicability, and ability to accurately detect toxins at low concentrations. Implementing such advanced methods and technologies will help maintain the quality of honey, protect consumer health, and promote sustainable honey production practices.

Keywords: *Clostridium Botulinum, Grayatoxins, Health Risks, Natural Toxins.*

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Introduction

(Background and Justification)

It is well known that honey, a wholesome nutritious and with higher medicinal values originated and collected by eusocial golden insects from nectars of various floral and plant discharges and has been consumed by human beings for eras in the world. It is not only a delicious food but also has a rich history in traditional medicine due to its high levels of AAs, Vitamins B6, riboflavin, and pantothenic & phenolic acids which prevent from fermentation and spoilage. However, recent research highlights that, honey has potential dangers due to the presence of natural toxins that may pose health risks. That is due to the honeybees' foraging range extending up to several km and produced from wide varieties of plant species while they collect nectars from those flowers that produce natural toxins and/or poisonous substances, these toxins can be transferred to the honey, potentially posing health risks to consumers (Danila Cianciosi, 11 Sep 2018). The specific amounts depend on the honey's floral origin and quality. The physiochemical composition varies based on the determinant factors including the botanical origins foraged by the honeybees, the geographical location, the environmental condition of the site, and the specific bee species and races as well as beekeeping practice*s* (Vîjan, 25 May 2023). The typical and well-identified poisonous plant species are grayanotoxins, *rhododendron barnatum* & *Andromeda polifolia L.* & mountain laurel species (Turkish & Italian honey), Tripterygium wilfordii (thunder god vine) produces triptolides (Chinese honey), tutin produced by tutu plant (New Zealand's honey) and pyrrolizidine alkaloids (Australian honey), neem tree *(Azadirachta indica), T*ilia species like (*Tilia cordata)* which have been identified in toxic *(Yan. 15 Feb, 2022)*.

Objectives

General Objective:

This review aims to give comprehensive information about the natural toxins in honey.

Specific Objectives

1) To give highlights on the most common sources of natural toxins found in honey.

2) To review the potential health risks and economic losses by both the consumers and producers.

3) To develop regulatory measures and public health guidelines related to natural toxins in honey.

Literature Review (Discussion)

Sources of natural toxins in honey

Derived From flowering plant species/Food:

Nectar or honey: Honeybees can live longest when they are fed sucrose, the sugars **fructose, glucose, maltose, melezitose, and trehalose** are safe for bees to consume. **In contrast**, the monosaccharides mannose, and galactose and oligosaccharides containing galactose (melibiose, raffinose, stachyose, and lactose) reduce the life span of adult bees at concentrations as low as 2% in syrup or nectar. Can't be hydrolyzed directly but by using enzymes (invertase and glucose oxidase). For instance, the nectar of linden trees **(*Tilia* spp.)** contains mannose and may cause paralysis in bees because they lack the enzyme **phosphor-mannose** isomerase & hexokinase, which is needed to metabolize/synthesize mannose unless it is accommodated in the midgut and create toxins. While most plants provide harmless nectar, some species produce toxins that can accumulate in honey.

From phytotoxins (plant toxins) the most popular known and found in honey is grayanotoxins (GTXs) which are produced from Andromedaspp, rhododendrons, Ericaceae family, tutin, etc which they are sparky/inflorescence

types of flowers, stems, leaves, twigs or branches, nectars and pollen of plants have toxic properties with a bitter flavor. For instance, the consumption of grayanotoxins-contaminated honey is “mad honey poisoning”. The health effects typical the clinical poisoning symptoms include: **Gastrointestinal distress** (vomiting, nausea, sweating & less commonly diarrhea), **Neurological** issues (dizziness, weakness, tingling or numbness), **Cardiovascular problems** & **hypotension** (low blood pressure, and abnormal heart rhythm cases), **Paralysis** limbs & diaphragm, **blurred vision & atrial-ventricular block** and **Coma & death (tutin)** but, in some cases, human beings may develop intoxication symptoms after consuming toxic honey. Thus, the symptoms last no more than 24 hours. Another concern is the presence of **pyrrolizidine alkaloids (PAs)** in honey. These plant-derived toxins, found in certain wildflowers identified over 6000 species and have been linked to liver damage in animals, and potential risks for humans are being investigated (Lorena Lucatello & . Yan, June 2022; 15 Feb, 2022).

Propolis (bee glue): as we know this type of product collects from the resinous and gummy substances collected by honey bees from plants and is used for the construction and maintenance or protection of their hives due to having antimicrobial, anti-inflammatory, antioxidant, and cytotoxic activities (Miguel MG, 2011), despite of, Propolis is consumed as a constituent of beeswax and honey, it highly accumulated with toxic trace elements or heavy metals such zinc, iron,(Zn, Cu, Pb, As and Cd) in multiflowered honey and propolis collected by honeybees or colonies. (A d a m Roman, November, 2011)**.**

Pollen (Bee Bread): pollen is the most mycotoxin-producing product because spoils quickly due to the presence of moisture content, water activity (aw), and pH value, pollen is an ideal medium for the development of different microorganisms such as bacteria, mold, and yeast. As a result of the aspergillus fungi growing on the stored pollen (bee bread) within the hive and producing the mycotoxins (aflatoxins and ochratoxins), this leads to some disorders and diseases. (Aleksandar Ž. Kosti´c, 24 January 2019). Besides pollen contains pectins (derived from galactose), and polysaccharides containing galacturonic acid, in the pollen wall which is toxic and difficult to metabolize by microorganisms of the honeybees. Therefore, immediately after harvesting should be dried properly to prevent moldiness and extend its shelf life. As well as place in a dry, dark, and cool place to retain its good properties.

Derived from honeybees:

The honey bees themselves secrete specific substances (invertase enzymes like glucose oxidase & phospho-mannose isomerase) which convert nectar into honey before storing in honeycombs for maturity. And also contains trace amounts of **melittin**, which is a component of bee venom. Melittin is not a health threat for most people, it’s a localized reaction that causes pain and allergies, swelling, and redness at the sting site. **Propolis** is also secreted from honey bees and added/mixed to the resinous & gummy plant sources (Roman, 2011 & 2019)

Chemical hazards

Modern agricultural practices pose another threat – **environmental toxins** such as heavy metals and pesticides. Honeybees can inadvertently collect nectar contaminated with these pollutants from surrounding environments. While regulations aim to minimize this risk, concerns remain regarding the potential long-term health effects of chronic exposure to these contaminants through honey consumption. These chemical contaminants and residues include: heavy metals, pesticides, toxic elements, drugs and antibiotics, and so on.-(Sha Yan, 15 February, 2022)

Heavy metals and pesticides:

These chemicals toxins or the acidic nature of honey are released from industrial process pollution, from containers, and processing equipment contaminations. These minerals & heavy metals, pesticides, and fertilizers are possible sources that can accumulate into honey as a residual effect from the flowering plant species contaminated with soil and/or water like Lithium, Aluminum, Lead, Cadmium, Mercury, and Copper and so on. (Razzagh Mahmoudi, 7 June 2016).

Health effects of heavy metals *(cadmium/lead/mercury)*: the hazardous nature of cadmium (Cd), mercury (Hg), and lead (Pb) cannot be overstated. All three heavy metals are linked to bodily disorders. Cadmium at abnormal levels causes renal problems (Jeffrey *et al*., 1980); Pb is associated with neuro disorders (Rosen, 1995) and

mercury in the organic form is carcinogenic (Ratcliffe *et al*., 1996). The permissible dietary intake of these metals is less than 1 µg/g. (AE Pillay, June 2017) ***Lithium*** *at raised* levels in the human body could lead to hypothyroidism and kidney disorders (Marcus, 1994). ***Aluminum***: it is widely acknowledged that abnormal intake of aluminum could result in Alzheimer's disorder (Cooke and Gould, 1991). So that, for healthy growth in bread and cheese requires typical mean values are about 5 µg/g.

Modern agriculture relies on **pesticides** to control pests and weeds, but these agrochemicals can contaminate nectar and pollen, finding their way into honey. Therefore, to ensure that it's safe for consumption honey should be tested for pesticide residues by the regulatory body. Though, Honey should be tested for a variety of pesticide and heavy metal contaminants residues to ensure that it is safe for consumption (Hang Zhao, November, 2022)

Adulteration/Fake or Synthetic product:

Adulteration refers to the sophisticated addition of substances to honey either directly or indirectly that alters and deteriorates of its natural physiochemical composition and nutritional value and reduce its quality because, it contains contaminated toxins that mask the natural taste of honey and make it difficult to detect. A value of 200 mg/kg is considered as suspected, while of 500 mg/kg is considered conclusive evidence of the presence of inverted sugar from acid hydrolysis. Some most commonly used adulterants in Ethiopia are: sugar, ripened bananas, water, molasses, sugar syrup/inverted sugars, syrup of maize/wheat flour, and sweet potato flour/syrup etc.

Diseases and pests:

Diseases:

The diseases may transmit vertically from the diseased mother colony's brood into other colonies during splitting and swarming. While the horizontal diseases can occur from neighboring colonies by contamination. For example, during merging/uniting two weak colonies, drifting and robbing when there is a heavy weather condition especially windy and so on. When beekeepers use antibiotics to treat bacterial like AFD or EFD residual traces of antibiotics in honey can pose health risks to consumers. Fumagillin is a naturally occurring compound isolated from *Aspergillus fumigatus* that is applied by beekeepers in a sugar solution to control the microsporidian gut parasites *Nosema ceranae* and *Nosema apis*.

Pests:

When the beekeepers use drugs such formic acid and oxalic acid to treat varroa destructor this may have higher toxin levels.

Antimicrobial compounds/antibiotics

When the beekeepers apply antibiotics inside the hive to control bacterial pathogens. These antibiotics can remain in the honey, posing a health risk for people with antibiotic allergies or contributing to antibiotic resistance. For example, during merging/uniting two weak colonies, drifting and robbing when there is a heavy weather condition especially windy and so on. When beekeepers use antibiotics to treat bacterial like American foul disease (AFD) or European foul disease (EFD) residual traces of antibiotics in honey can pose health risks to consumers. Fumagillin is a naturally occurring compound isolated from *Aspergillus fumigatus* that is applied by beekeepers in a sugar solution to control the microsporidian gut parasites and drugs such formic acid and oxalic acid to treat varroa destructor this may have higher toxin levels (Yarira Ortiz-Alvarado, 19 Nov, 2020).

Feeding Supplements and HMF effects

During the dearth periods the honeybees can support by homemade syrups as supplementary feeds to synchronize the colony in order to collect nectar and pollen.
Bee bread naturally mixed with glandular secretions as well as commercial diets like soybeans flour which contains approximately 40% of sugars present in soybeans are toxic to bees and invert sugars (HFCS) it becomes to more acidic or toxic to bees (Khem Raj Neupane, April 2005).

HMF levels increase with the longevity storage time and temperature mean that if it has low temperature indicates fresh honey. Unless, if we have poor processing and handling i.e during pasteurizing honey excessive heating and prolonged storage have deteriorated its quality. specify that honey should contain no more than 40 mg/kg of HMF standard limit due to the (Codex Alimentarius Commission, 2001). while honey from tropical regions may have a higher limit due to natural factors (Kate Robertson, The effects of aging and heat treatment of honey)

Microbial hazards

Microorganisms like yeast, molds and spore forming bacteria such *aspergillus fumigatus, Clostridium botulinum, bacillus spp* etc are the major causative agents for mycotoxins in honey.

Honey processing & handling

Before and after harvesting as well as processing the product, starting from the personal hygiene and materials & equipment used will be clean and free from corrosive properties. Besides, improper honey processing and handling techniques can introduce toxins or contaminants into the final product. Here are some key factors to consider during refining honey: Overheating **(>**140˚C**):** during heat treatment or pasteurizing process excessive heating can accelerate the formation of hydroxymethylfurfural (HMF), while the normal thermal values 72 ˚C maintained for 120 seconds. HMF is toxic only in high concentrations that is >40mg/kg except tropical regions with limit <80mg/kg. Overheating can also alter the color, flavor, and aroma of honey. In addition to prolonged storage time and exposure to light can accelerate the breakdown/reduced content of honey enzymes such invertase, glucose oxidase and diastase and increase the risk of HMF toxin formation (foodtechprocess.com, July 27, 2023). www.Refininghoney

The health effects or risks of toxic honey

Allergens risk

Unlike processed honey, raw honey may contain small amounts of pollen grains, propolis and other impurities. There is cases of allergic reactions of coughing and anaphylaxis after ingestion of raw honey that contained pollen. Symptoms could range from itching in the oral mucosa to anaphylactic shock. People who are allergic to pollen or with severe seasonal allergies (hay fever) should be aware of the potential risk of eating raw honey (Md, 11 November 2013).

Infant Botulism risk

Due to the anaerobic Clostridium botulinum endospores forming bacterium present in raw honey that causes a rare but serious gastrointestinal botulism and botulinum neurotoxin (BoNTXs). This is infants don't fight off those bacteria due to their digestive tract have not yet developed well. The early symptoms are **constipation,** followed by tiredness, difficulties in feeding or sucking, generalized muscle weakness or floppiness, sagging eyelids, loss of facial expressions & head control, weak cry and respiratory failure. Hence, infants below the age of 1 year must be kept away from any and all products/supplements containing honey (even if in trace amounts) (Larissa Hirsch, February 2023).

Detection methods

The simplest and accurate method for detection the different toxins in honey especially, grayanotoxins is used by High-performance Liquid Chromatography (HPLC) and Liquid Chromatography coupled with a Tandem Mass Spectrometer (LC/MS), Isotope ratio mass spectrometry (IRMS, NMR, are commonly used to detect toxins. However, there is a need for on-site, rapid and cost-effective detection methods, currently enzyme-linked

immunosorbent assays (ELISAs), Lateral Flow Assays (LFAs) and bio-sensors are becoming popular analytical tools for rapid detection (Muammer Kaplan, 2 June, 2014).

Mitigation strategies

Generally, the main affecting factors in terms of quality and nutritional values of honey, in our country to address and to be safe the product, the government should set guidelines and regulations which limit the levels of certain toxins that are allowed in honey for safety of food products including honey in accordance with the international standards of Codex Alimentarius and EU Directive 101/2001. And public health concerns especially for vulnerable populations such children, pregnant women, and individuals with underlying health conditions (Grigoryan, 2016).

Reducing risk

Obviously, it is important to note that mold which produces aflatoxins and mycotoxins are usually does not grow in properly standardized or processed and stored honey so that properly handling is an effective measure/resolution against mold growth and the production of toxins.
Some advisable key points to minimize the health risk from toxicity are:

- ☑ Inspect regularly the wholesomeness of the products contaminated with aflatoxins for evidence of mold, and discard any that look moldy, discolored, or shriveled mean dried-up;
- ☑ Avoid from giving raw honey to infants;
- ☑ Buy honey as possible as free or with minimal toxins;
- ☑ Make sure that honeys are stored properly and labeled traceably;

Beekeeper Practices:

The beekeepers should responsible & prioritize some biosecurity practices mean hive health by locating their hives away from sources of pollution and agricultural fields that are unwise and heavily sprayed with pesticides. As well as the beekeepers should transit to the organic beekeeping practices. This enable them to minimize the synthetic interventions and toxin hazards and creates a trust and market.

Testing and Certification:

Look for honey that has been third-party tested for purity and contamination. If the government set a legislations and regulation on honeybee products by encouraging to produce organic honey and recognized by traceability with certification awards.

Conservation flowering plant Varieties or species:

Consider consuming honey from a variety of monofloral and multifloral sources to reduce the risk of exposure to any one type of toxin. To minimize the risk effects in honey, planting the best honey bee floras which are available locally as a native flowering plant species. Example, Manuka honey is a toxic product

Research on Toxin Mitigation:

Scientists are actively researching ways to mitigate the impact of toxins in honey. This includes studying the natural detoxification processes within beehives and developing methods for beekeepers to identify and manage toxin risks.

Conclusion

Based on the review, naturally honey is not considered as a "completely safe and nutritious food" because it contains several toxic compounds that can have adverse health effects on human consumption. These toxins may derive from wild flowering plants, genetics, diseases & pests, microbials, chemicals and environmental contaminants.

Therefore, to address these drawbacks: using advanced detection techniques such rapid field testing, Refractive index, sensitive & specific assays, and biosensors, Spectrometry and natural sensory properties or testing techniques like color, aroma, and flavor, are important factors.

Finally, we have to develop an evidence-based polices, guidelines and controlling mechanisms to enhance our safety protocols during honey harvesting and processing practices through creating knowhows about the complexity interplay between bees, flowering plants and toxins is crucial by both the producers and consumers. As a result, it promotes trusty, marketing and consumption of the product sustainably.

Recommendations forwarded

☑ As several studies indicated that, countries of the world have been published on honey toxicity like Europe, Turkey or Nepal, New Zealand, China, Australia, and Latin America, however, as a continent Africa especially in Ethiopia & Tigray there is no reports done on toxic honeys so that, this will be our future task.

☑ My review suggests that, Promoting and supporting research in developing a simple, rapid, cost-effective and reputable field (on-site) testing portable devices to detect toxins, which making it easier for the producers and consumers to assess and promote honey quality in market trustable.

☑ In Ethiopia, to minimize the potential health risks of natural toxins in honey and promoting safe consumption practices; the National Food and Drug Administration (FDA), Ministry of Health & Nutrition, Food Safety and Regulations should strictly set a clear and informative legislations & regulations but, not as a blue print it should applicable as control mechanism.

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Conflicts of interest

I declared that I have no personal competing or conflicts of interest or plagiarism issues in my review manuscripts which I attached to be publish to your institution. It is my original work.

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