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REVIEW

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Tyramine, a biogenic agent in cheese: amount and factors affecting its formation, a systematic review

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Abstract

Tyramine is one of the most important biological amines in food, which leads to food poisoning if consumed in high amounts. In addition to food poisoning, tyramine leads to drug interactions. Foods high in tyramine can cause high blood pressure and migraines in people taking monoamine oxidase (MAO) inhibitors. Therefore, people taking MAO inhibitors should avoid foods high in tyramine. Cheese provides ideal conditions for the production of tyramine. Some cheeses contain high amounts of tyramine and lead to unwanted effects in people taking MAO inhibitors. These unwanted effects are called the cheese effect or tyramine interaction. Considering the importance of the subject, a systematic study was designed with the aim of determining the amount of tyramine in cheeses and the effect of effective factors on the amount of tyramine production. The search was done in three databases, including Scopus, PubMed, and Science Direct. The study was conducted in two phases. In the first stage, the amount of tyramine reported in cheeses, the analytical method, measurement, and characteristics of cheese were discussed. In the second phase, the influencing factors in its formation were investigated. Based on the extracted data, tyramine levels ranged from 3.23 to 1398 mg/kg. The most analytical method for measuring tyramine in the studies was the HPLC method. According to a detailed review of the literature, the influencing factors included bacterial species, animal species, the effect of storage conditions (time and temperature), pH, moisture, salt, and the number of somatic cells. Basically, by identifying the factors affecting the amount of tyramine in cheeses, it is possible to control the production of tyramine.

Keywords Tyramine, Cheese, Bacterial species, Storage condition

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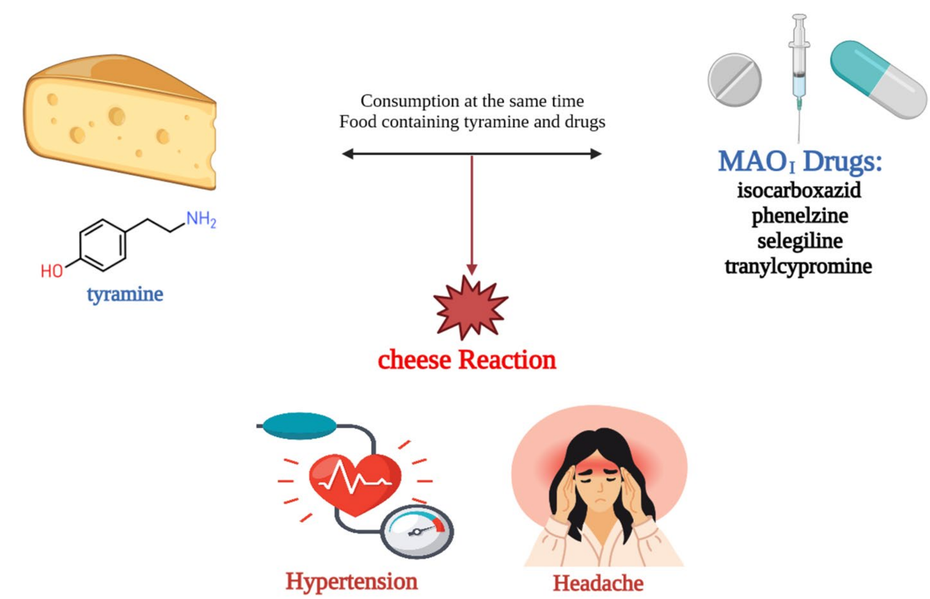
Graphical Abstract



Introduction

Biological amines are low molecular weight compounds that are produced following metabolic activities in microorganisms, animals and plants (Andic et al. 2010; Arlorio et al. 1998). These compounds do not cause problems in small amounts. But in high amounts it leads to migraines, headaches, salivation, fever, and increased blood pressure (Andic et al. 2010; Draz et al. 2021). In some cases, pulmonary edema and heart failure have also been observed (Dadáková et al. 2009). In cell cultures, it leads to necrosis and cell death (Gama & Rocha 2020). Also, when nitrites are present, they are combined with these biological amines and become carcinogenic nitrosamines (Torracca et al. 2015). The evaluation of biological amine in food, in addition to food safety, is also an indicator of food quality (Draisci et al. 1998).

There are different types of biological agents. One of the most important biological amines in relation to food poisoning is tyramine (Wasi Ahmad et al. 2023). Tyramine poisoning occurs in most cases in connection with the consumption of cheese (Andic et al. 2010; Ščavničar et al. 2018). Cheese is a desirable food product all over the world. It has a high nutritional value and is included in the food basket of most countries (Campos-Góngora et al. 2023). A dose of 800 mg/kg for tyramine in cheese is considered a toxic dose (Forzale et al. 2011).

Tyramine stimulates the sympathetic nervous system and leads to the release of noradrenaline, increased blood pressure and tachycardia (Draz et al. 2021). Subsequently, it leads to migraine, headache, and fever (Draz et al. 2021). Furthermore, if a person taking a Monoamine oxidase inhibitors (MAOI) drug receives 6 mg of tyramine, it will lead to cheese reaction or hypertensive crisis (Andic et al. 2010; Edinoff et al. 2022). MAOI drug such as isocarboxazid and phenelzine prevent the activity of monoamine oxidases. Subsequently, following the use of these drugs, the breakdown of some of neurotransmitters such as serotonin decreases. This class of drugs is used to treat depression (Van den Eynde et al. 2023). The presence of tyramine in small amounts in cheese does not create a problem because it is broken down by enzymes in the digestive system (Campos-Góngora et al. 2023). But in some cases, the amount of tyramine may be too much, which can be dangerous for some users who take MAOI drug. In these patients, complications such as hypertension are observed following the consumption of cheeses with high tyramine content (Seong et al. 2022).

Tyramine produced in cheese is the result of the metabolism of microorganisms (Beatrice et al. 2018). In cheese, lactic acid and enterococci bacteria produce relatively high amounts of tyramine (Beatrice et al. 2018). Especially *Enterococcus faecium* plays a major role in tyramine production (Beatrice et al. 2018). Furthermore, molded cheeses such as Gorgonzola contain higher amounts of tyramine than other cheeses (Beatrice et al. 2018). The production of tyramine in cheeses is very complex and depends on many factors. In addition to the

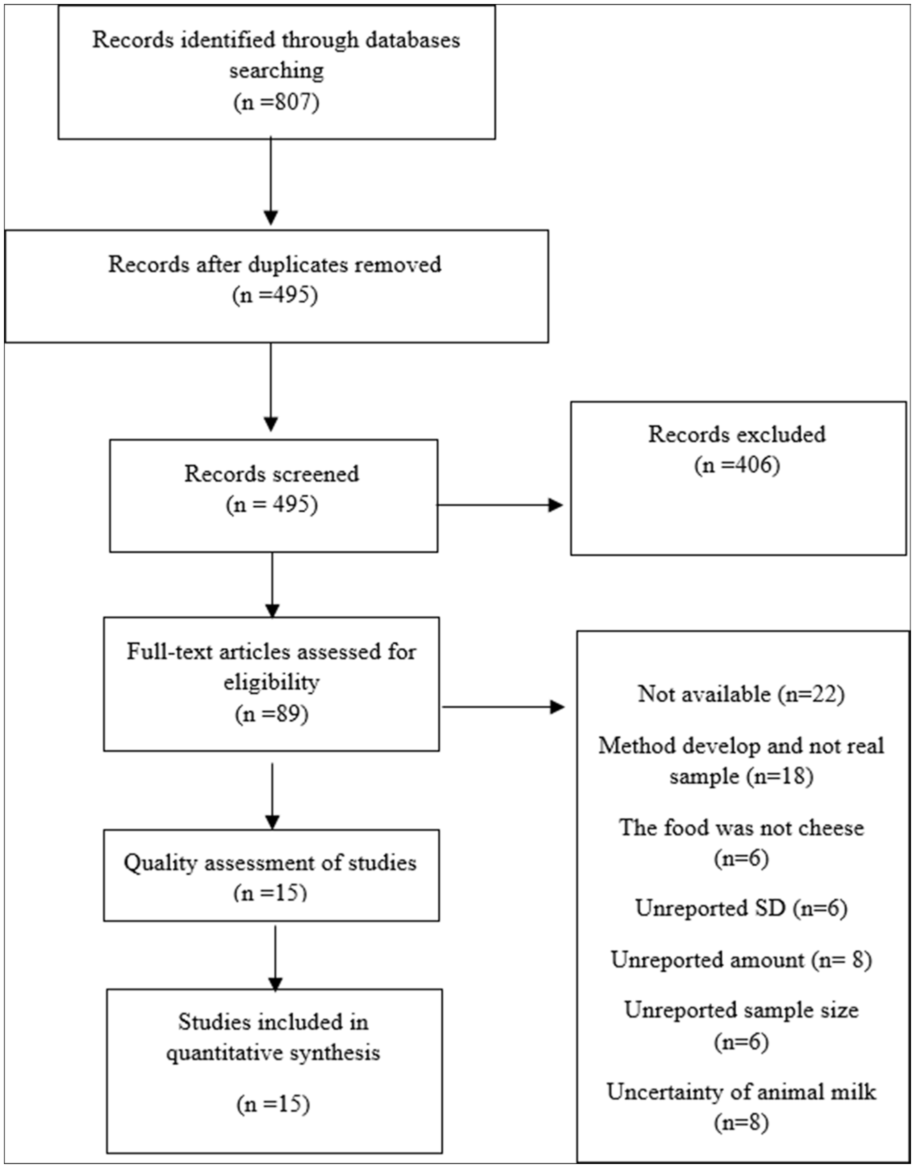


Fig. 1 The diagram of study

bacterial strain, it depends on the duration of storage, temperature and salt concentration during storage (Beatrice et al. 2018). In recent years, food poisoning caused by tyramine has increased (Dala-Paula et al. 2023). It is necessary to pay special attention to this issue. Furthermore, people taking MAOI drug should avoid cheeses with high levels of tyramine. herefore, it is necessary to identify the cheeses with high tyramine content and the factors affecting the amount of tyramine. In this systematic study, in addition to identifying these types of cheeses, factors affecting the amount of tyramine are also discussed.

Method

The search strategy

The search for this study was carried out on January 26, 2023 with two keywords including tyramine and cheese in PubMed, Scopus and Science Direct databases. The search was done by two authors independently (P.S and S.A). Both of their search results were the same.

Inclusion and exclusion criteria

Before searching the databases, the inclusion and exclusion criteria were determined for this systematic review. Inclusion criteria included articles that measured

Table 1 The investigated parameters affecting the formation of tyramine

Parameters	Statement	References
Bacterial species	Bacteria species *Enterococcus faecium, E. durans, E. faecalis, Lactobacillus curvatus, Citrobacter freundii, Esch. coli, Lactobacillus helveticus, Lactobacillus lactis, and Raoultella ornithinolytica* lead to increase production of tyramine. Bacteria species *Lactobacillus paracasei* lead to decrease tyramine.	(Perez et al. 2017), (Guarcello et al. 2016), (O'Sullivan et al. 2015), (Maifreni et al. 2013), (Burdychova & Komprda 2007), (Brindani et al. 2002)
Animal species	The difference between cheeses prepared from the milk of various animals is observation. But more experimental studies are needed in this regard.	(Evans et al. 1988), (Pachlová et al. 2017)
Effect of storage conditions (time and temperature)	The amount of tyramine has a direct relationship with increasing storage time and increasing temperature.	(Ivanov et al. 2021), (Cwiková & Franke 2019), (Soodam et al. 2017), (Komprda et al. 2012), (Pinho et al. 2001), (Valsamaki et al. 2000), (Pachlová et al. 2016)
pH	The optimal pH for tyrosine decarboxylase enzyme activity is 5 to 6.5 in cheeses in various studies.	(Custódio et al. 2007; Fernández et al. 2007a, b; Valsamaki et al. 2000)
Moisture	There is a direct relationship between the amount of tyramine and moisture.	(Kebary et al. 1999)
Salt	The amount of salt is directly related to the amount of tyramine in cheeses.	(Anderegg et al. 2020), (Kebary et al. 1999)
Somatic cell count	There is a direct relationship between the somatic cell count of primary raw milk and the amount of tyramine in cheeses.	(Ubaldo et al. 2015), (Ivanova et al. 2021)

tyramine in cheeses by valid methods. Review studies, chapters of book, and articles in non–English language were excluded from the study. Manuscripts that presented the amount of results in the form of figures instead of numbers were also excluded from the study.

Result

The result of search

The search in Scopus, PubMed and Science Direct databases was done by two of the authors. 807 articles were obtained with the specified keywords (Fig. 1). Duplicate articles were removed. The title and abstract of each article were reviewed. Animal studies, pharmacology and microbiology topics were also excluded from the study. After initial screening, 89 articles were selected for full-text review. 5 points were considered for qualitative evaluation of articles. Articles that received a score of three or more were selected for final review (Sadighara et al. 2023). Valid measurement method, declaration of mean and standard deviation, declaration of the number of samples, identification of the type of cheese and the type of animal milk used in production were among the evaluated criteria.

The data extracted for table

In this systematic study, the country, the amount of tyramine reported in cheeses as mean and standard deviation, analytical method, number of samples and type of animal species were extracted from the manuscripts. In the second stage, simultaneously with data extraction and data interpretation, the influencing factors in the amount of tyramine were investigated and discussed. The results can be seen in Table 1. Based on the extracted data, three countries, including Czech Republic, Italy and Turkey, had the most studies in this regard. The most milk used to produce cheese was sheep's milk. HPLC was the most used analytical method to identify tyramine in cheeses (Table 2).

Discussion

The interaction of tyramine in cheese with drugs is known as the cheese effect (Beatrice et al. 2018). People using monoamine oxidase inhibitors should avoid food products containing high tyramine. Therefore, these people should control their diet. The most important food item with high tyramine content is aged cheeses. The main goal of this systematic study, in addition to investigating the amount of tyramine in cheeses, is to identify the factors affecting the formation of tyramine in cheese.

According to several studies, the maximum limit of tyramine in cheeses is 100 to 800 mg/kg (Kandasamy et al. 2021). According to the data in Table 2, only two studies were more than this limit (Table 2). The highest amount of tyramine was reported as 1300 mg/kg in Soft smear–ripening acid cheese (Pleva et al. 2014). These types of cheeses were stored at 18°C. It is possible that this is one of the reasons for the high tyramine.

Based on the extracted data, the lowest amount of tyramine was observed in Lighvan cheeses at the rate of 3.23 mg/kg (Mohammadi et al. 2017). That study was for developing a method for measuring tyramine in cheeses. The sample size of real samples was low. This type of cheese is made from sheep's milk and has a high percentage of fat (20%) (Mohammadi et al. 2017). The storage time of these types of cheeses is not mentioned.

Table 2 Data extracted based on the research objectives of the study

Name of study	Country	Type and age of cheese	Sample size and Amount /unit	Animal species	Analytical method
(Andic et al. 2010)	Türkiye	Herby cheese/12 Months	$N=30$ 360.3 ± 46.3 (SE) mg/kg	Sheep	HPLC–DAD
(Bozkurt & Altun 2021)	Türkiye	Dry-salted Van herby cheese Brine-salted	Dry-salted ($N=49$): 419.4 ± 330.7 Brine-salted ($N=48$): 228.7 ± 340.3 mg/kg	Sheep	HPLC–DAD
(Forzale et al. 2011)	Italy	Soft pecorino cheeses (SP) semi-hard pecorino cheeses (SHP)	SP ($N=8$): 27.13 ± 37.58 SHP ($N=7$): 125.64 ± 114.54 mg/kg	Sheep	HPLC–UV
(Grootveld et al. 2020)	UK	Soft cheese	$N=5$ 69.4 ± 42.5 mg/kg	Cow	LC–MS/MS
(Kandasamy et al. 2021)	Korea	Semi-hard Gouda	$N=4$ 59.3 ± 70.77 mg/kg	Cow	HPLC–DAD
(Mohammadi et al. 2017)	Iran	Lighvan cheese	$N=3$ 3.23 ± 0.16 mg/kg	Sheep	GC–MS
(Laleye et al. 1987)	Canada	Cheddar cheese	$N=18$ 0.32 ± 0.12 (se)	-	GC–FID
(Pachlová et al. 2016)	Czech Republic	Lyophilised cheese	$N=2$ 22.9 ± 1.34 mg/kg	Cow	HPLC–UV
(Pleva et al. 2014)	Czech Republic	Soft smear-ripening acid cheese	$N=6$ 1398 ± 76.9 mg/kg	-	HPLC–UV
(Poveda et al. 2016)	Spain	Goat cheese	$N=3$ 8.6 ± 1.2 mg/kg	Goat	HPLC–UV
(Pekcici et al. 2021)	Türkiye	Cottage cheese	$N=3$ 54.45 ± 0.17 mg/kg	-	HPLC–fluorescence detector
(Buňková et al. 2013)	Czech Republic	Pasteurised ewe's milk cheeses: 1/114.7 ± 8.0 ($N=2$) Goat's milk cheeses: 1/10.7 ± 0.5($N=6$) cow's milk cheeses (Pasta): 1/25.8 ± 1.5 ($N=5$)			HPLC–UV
(Spizzirri et al. 2013)	Italy	Parmigiano Reggiano	$N=3$ 124.5 ± 4.1 mg/kg	Cow	LC–ELSD
		Pecorino Romano PDO (Brunelli)	$N=3$ 116.7 ± 4.1 mg/kg	Sheep	
		Ripened goat cheese (San Lorenzo)	$N=3$ 10.1 ± 1.8 mg/kg	Goat	
(Standarová et al. 2010)	Czech Republic	Olomouc curd cheese	$N=6$ 6week: 243 ± 17.0 7week: 190 ± 90.3 mg/kg	Sheep	HPLC–UV
(Zazzu et al. 2019)	Italy	Fiore Sardo cheese	$N=36$ 350 ± 300 mg/kg	Sheep	RP–HPLC–DAD

In this systematic study, the influencing factors on the amount of tyramine were reviewed. Identifying the causative factors in the production of tyramine is effective to prevent the formation of tyramine in cheeses. The ripening process of cheese is complex and is influenced by enzymes and microorganisms (Bozkurt & Altun 2021).

One of the influencing factors is bacteria species. Some bacteria have the enzyme tyrosine decarboxylase and lead to the production of tyramine from tyrosine (Perez et al. 2017). In the studies, high amounts of tyramine were observed in sheep's cheeses contaminated with *Enterococcus faecium* and *Enterococcus faecalis* (Beatrice et al. 2018; O'Sullivan et al. 2015). Also, *E. durans* is also able to produce tyramine (Tittarelli et al. 2019). In the studies, it was observed that two types of *Lactobacillus paracasei* and *Lactobacillus curvatusare* isolated from pasteurized milk play a major role in tyramine production. (Beatrice et al. 2018). Furthermore, *Lactobacillus helveticus*, which is separated from the starter, also produces tyramine (Burdychova & Komprda 2007). In another study, two species of bacteria, *Pediococcus acidilactici* and *Enterococcus malodoratus*, played a major role in the production of tyramine in cheeses produced in Italy (Bonetta et al. 2008). Moreover, *Citrobacter freundii, Esch. Coli,* *Lactobacillus lactis* and *Raoultella ornithinolytica* are able to produce tyramine (Brindani et al. 2002; Maifreni et al. 2013). On the contrary, some species of lactic acid bacteria have amine oxidases and are able to break down tyramine (Guarcello et al. 2016). *Lactobacillus paracasei* has the ability to decompose biological amines, so it can be used as a starter. It was observed that tyramine decreased when used as a starter in Caciocavallo cheese (Guarcello et al. 2016). Also, once *Lactobacillus casei* was used as a starter in cheese making, less tyramine was produced (Tittarelli et al. 2019).

The effect of the role of bacteria on the amount of tyramine production has been confirmed with a positive correlation between the use of raw milk and the amount of tyramine. Cheese makers tend to use raw milk for cheese making rather than pasteurized milk due to the better taste of cheese made from raw milk (Schirone et al. 2013). The amount of tyramine in cheeses made from raw milk is higher than pasteurized milk. Gram-negative bacteria are responsible for the production of tyramine. As a rule, their number is less in pasteurized milk (Fernández et al. 2007a, b). Of course, although pasteurization plays an important role in reducing the amount of tyramine, it is not a 100% guarantee (Torracca et al. 2015). A study was conducted on two cheeses made from sheep's milk in Italy. Semi-hard pecorino cheeses (SHP) were prepared from raw milk, and soft pecorino cheeses (SP) were prepared from pasteurized milk. The amount of tyramine in SHP cheese was much higher than that of SP cheese (Forzale et al. 2011). As a rule, the number of tyramine-producing bacteria is sensitive to heat and decreases during pasteurization (Forzale et al. 2011). The amount of protein in cheeses also affects the amount of tyramine. As a rule, following more protein, the amino acid tyrosine and subsequently tyramine will also increase (Bozkurt & Altun 2021; Ivanova et al. 2021).

The amount of tyramine in cheese made from milk of different species and animal breeds is different. For example, the cheeses of Churra breed sheep are more than those of Assaf breed sheep (Combarros-Fuertes et al. 2016). Tyramine is more in cheeses made from goat's milk than from cow's milk (Evans et al. 1988). In another study, the amount of tyramine in cheeses made from goat's milk was higher than that of cow's milk (Pachlová et al. 2017). In a controlled study, it was observed that the amount of amino acids in goat's milk was higher than that of cow's milk, and this issue can affect the amount of tyramine in the prepared cheeses (Pachlová et al. 2017). Furthermore, there is a positive correlation between somatic cell count and tyramine. With the increase of somatic cell count of primary raw milk, the proteolytic activity increases, so tyramine will be produced more in cheeses (Ubaldo et al. 2015). These cells contain enzymes that are released during the production of dairy products (Darbaz et al. 2023). Also, studies indicate the difference between somatic cells in goat milk and cow milk. Due to apocrine secretion, goat milk has more somatic cells than cow milk (Gautam et al. 2023, Kuchtik et al. 2023). Therefore, this may be one of the reasons for the difference between goat cheese and cow cheese.

In the study of Buňková et al. (2013), the amount of tyramine in cheeses made from sheep's milk was much higher than that of cow's milk (Buňková et al. 2013). However, in this regard, it should be noted that the cheese made from sheep's milk was a flavored cheese. The type of flavoring is not mentioned. It has been observed that Herby cheeses have higher amounts of tyramine (Andic et al. 2010). The authors of this manuscript consider the reason for this difference to be the unsanitary production and preparation of herbal cheeses (Andic et al. 2010). Moreover, in another study, herbal cheese prepared from wild plants had relatively high amounts of tyramine (Bozkurt & Altun 2021). The main reason for the increase of tyramine in these cheeses is not mentioned, but it is possible that it is due to microbial contamination before the cheese is made.

Temperature, storage time, pH, salt and humidity are effective for reactions (Combarros-Fuertes et al. 2016). The decarboxylase enzyme activity depends on optimum pH, salt and temperature (Novella-Rodríguez et al. 2000). In an experimental study, the highest amount of tyramine production and tyrosine decarboxylase activity occurred at pH 5 (Fernández et al. 2007a, b). Most fermented foods provide the pH necessary for the activity of the tyrosine decarboxylase enzyme (O'Sullivan et al. 2015). The pH of cheeses is in the range from 5 to 6.5 and provides conditions for the activity of the tyrosine decarboxylase enzyme (Custódio et al. 2007). As a rule, changes in pH outside the mentioned optimal range lead to a decrease in enzyme activity. Furthermore, increasing the salt concentration from 0 to 1.5% leads to an increase of tyramine up to 87% (Anderegg et al. 2020). Storage time and storage temperature are the most important influencing factors in the amount of tyramine (Komprda et al. 2005). During cheese ripening, casein is hydrolyzed to amino acids. Amino acids are decarboxylated and become biological amines (Combarros-Fuertes et al. 2016). Storing cheese at refrigerator temperature inhibits the formation of tyramine (Ivanov et al. 2021). In a study of cheese storage at 6 degrees Celsius for 28 days, the amount of tyramine was less than the permissible limit of 100 mg/kg (Cwiková & Franke 2019). In another study, the amount of tyramine in cheeses stored at two temperatures of 20 and 5 degrees Celsius was detected as 1332 and 353 mg/kg, respectively (Komprda et al. 2012). Increasing the temperature during the storage of cheeses has significantly increased the amount of tyramine (Cwiková & Franke 2019). As mentioned, the highest amount was observed in soft smear cheeses at the rate of 1398 ± 76.9 mg/kg in the Czech Republic. The data of this research was analyzed in detail. The mentioned study was an experimental study in which the cheeses were kept at 18°C instead of being kept at refrigerator temperature (Pleva et al. 2014). A longer period of time has also increased the amount of tyramine, but it has been observed in some evidence that storage may decrease the amount of tyramine. It is possible that some microorganisms have tyramine oxidase enzyme and break down tyramine (Cwiková & Franke 2019). In a study, it was observed that the amount of tyramine decreased after 5 weeks of storage. Probably some microorganisms such as *Brevibacterium linens* can degrade tyramine (Cwiková & Franke 2019). In this study, cheeses were stored for 35 days and 49 days at 6 ℃. The amount of tyramine after 49 days was lower than cheeses stored for 35 days (Cwiková & Franke 2019).

In the review of the literature, most of the tyramine measurement methods are done through HPLC method It is due to the fact that biological amines cannot be identified by UV detector(Ščavničar et al. 2018). These components have low UV absorption (Liu et al. 2018). They need to be derivatized (Ščavničar et al. 2018). The derivatization of these compounds is done in order to make them chromogenic or have fluorescence properties (Compagnone et al. 2001). Derivation is usually done by compounds 5-dimethylaminonaphthalene-1-sulfonyl chloride, fluorescamine, o-phthalaldehyde, benzoylchloride, (Komprda et al. 2005; Mayer et al. 2010). In this systematic study, 86% of detection methods were based on liquid chromatography and 14% were based on gas chromatography. GC is not a common method in determining the amount of tyramine in food because it requires derivatization and tailing problems (Dadáková et al. 2009). But, the MS detection is more reliable and can detect a very small amount of tyramine (Ščavničar et al. 2018). To measure tyramine, HPLC–MS/MS method with cation exchange column does not require derivatization (Reinholds et al. 2020).

Conclusion

In this systematic study, the amount of tyramine in cheeses from around the world was investigated based on the literature. The amount of tyramine was acceptable in most studies. Furthermore, factors affecting the amount of tyramine in cheeses were investigated. Among the reviewed texts, the main bacteria producing tyramine is *Enterococcus faecalis*. Storage time and temperature are also major factors. The duration of storage has a direct relationship with the amount of tyramine, but after long storage, this relationship is reversed due to decomposition by the enzymes of some bacteria. It is necessary to control the temperature. Cheeses must be kept at the temperature of the refrigerator. Regarding the determination of tyramine, although the HPLC method for measuring tyramine in cheese requires derivatization, this method has been used in most studies and this analytical method is well developed. The relationship between animal species and tyramine level was observed. Goat cheeses had more tyramine than cow cheeses. Of course, more extensive studies are needed in this regard. The difference between the physicochemical factors affecting the amount of tyramine in the milk of different animals should be investigated.

Ethical responsibilities of authors

All authors have read, understood, and complied as applicable with the statement on "Ethical responsibilities of Authors" as found in the Instructions for Authors.

Authors' contributions

The search and collecting of data was performed by SA, HS. The manuscript was written by BB, PS and MS.

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Availability of data and materials

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors of this article declare that they have no conflict of interests.

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