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Presence of kynurenic acid in alcoholic beverages – Is this good news, or bad news?

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ABSTRACT

Kynurenic acid (KYNA) is a metabolite of tryptophan formed enzymatically along kynurenine pathway in bacteria, fungi, plants and animals. It was suggested that yeast may produce KYNA during the fermentation process. Since KYNA was found to interact with alcohol metabolism by inhibition of aldehyde dehydrogenase activity the aim of this study was to measure the content of KYNA in selected alcoholic beverages of various type, beer, wine, mead and spirits. Moreover, the absorption and elimination rate of KYNA administered as a beverage was investigated in humans. Twelve healthy volunteers (6 female and 6 male) were studied. Fifty six samples of alcoholic beverages were of commercial origin. KYNA was determined by means of high-performance liquid chromatography method with fluorometric detection. KYNA was identified in all studied beverages. The amounts of KYNA found in various types of beverages differed significantly: mead 9.4–38.1 μg/100 ml, wine 1.4–10.9 μg/100 ml, beer 0.1–5.2 μg/100 ml, spirits 0.01–0.1 μg/100 ml. In human, it was found that KYNA is rapidly absorbed from digestive tract reaching its maximal concentration in blood 30 min after administration. Thus, the potential interaction between KYNA and alcohol occurring in human body after ingestion of alcoholic beverages was proven.

Introduction

Recently, it was suggested that yeast may produce kynurenic acid (KYNA) during the fermentation process and its presence in fermented food including beer and wine was evidenced [1]. KYNA is a metabolite of tryptophan formed enzymatically along kynurenine pathway in bacteria, fungi, plants and animals [2–6]. Its pharmacological properties and potential role in human physiology arouse continuing researchers' interest. Initially, the neuroprotective activity of KYNA resulting from its antagonism at glutamate receptors in the brain was discovered [7–9]. Unfortunately, it does not penetrate to the brain from periphery due to poor penetrability of the blood-brain barrier [10,11], what practically excludes its neuroprotective action after exogenous load. More recently, the discovery of KYNA agonistic action on G protein-coupled receptor (GPR35) and aryl hydrocarbon receptor (AHR) [12,13] located mainly outside the brain tissue has focused research on its peripheral activity. It was evidenced that peripheral administration of KYNA showed anti-ulcerative [14], anti-inflammatory [15], antioxidant [16], analgesic [17] antimigraine [11] and metabolic activities [18]. Moreover, of great importance were the findings that KYNA is present in food and is absorbed from the digestive tract [19] which suggest that KYNA derived from food may affect several processes in the body. Importantly, KYNA was found to interact with alcohol metabolism by inhibition of aldehyde dehydrogenase activity *in vivo* [20]. Thus, its presence in alcoholic beverages may influence alcohol degradation rate and relate to the intensity of negative consequences of alcohol consumption.

Hypothesis

Our hypothesis proposes that KYNA is present in alcoholic beverages and may interact with alcohol in humans (Fig. 1). To test this concept we performed study intended to measure the content of KYNA in selected alcoholic beverages of various type, beer, wine, mead and

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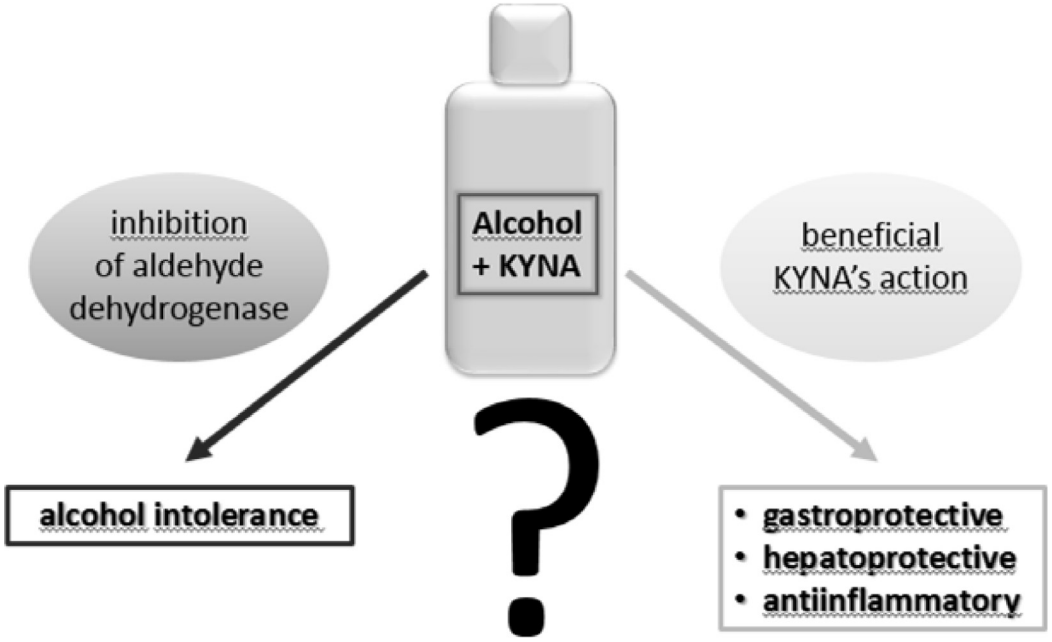

Fig. 1. Graphical illustration of the hypothesis concerning kynurenic acid (KYNA) beneficial or harmful interaction with alcohol.

spirits. Moreover, the absorption and elimination rate of KYNA administered as a beverage was investigated in humans.

Materials and methods

Subjects

The study protocol was approved by the Bioethics Committee of the Medical University of Lublin, Poland (KE-0254/80/2016). Written consent was obtained from each subject under the study. Twelve healthy volunteers (6 female and 6 male) aged 22–25 were studied. All participants did not eat a meal and drank only mineral water six hours before study. On the day of study, the median cubital vein was cannulated with 17G peripheral catheter.

Study protocol

Chestnut honey (Miel de chataignier de Midi-Pyrenees, Naturalim France Miel, France) was dissolved in water with ratio 1:1. Beverage in an amount of 200 ml was consumed over a 5 min period at 8.00 a.m. following an overnight fast. Venous blood samples (5 ml) were drawn from an peripheral venous catheter at specified times after administration of honey beverage: baseline (0), 15, 30, 60, 90, 120 min. Blood samples were centrifuged at 1300 g for 15 min and supernatant serum was frozen in −80 °C for KYNA determination.

Alcoholic beverages

All samples of alcoholic beverages were of commercial origin. The names of producers or suppliers were specified in table legends.

KYNA determination

KYNA was isolated and determined according to the methods described previously [21]. Mead was diluted with distilled water (1:1 v/v). Samples of serum and beverages were acidified with 50% trichloroacetic acid and centrifuged (7800 g, 10 min). 1 ml of supernatant was collected and applied to the columns containing cation exchange resin Dowex 50 (50 W^+; 200–400 mesh) prewashed with 0.1 N HCl. Subsequently, columns were washed with 1 ml of 0.1 N HCl and 1 ml of water. Fraction containing KYNA was eluted with 4 ml of water. Eluate was subjected to high performance liquid chromatography (HPLC) and KYNA was detected fluorometrically (Hewlett Packard 1050 HPLC system: ESA catecholamine HR-80, 3 µm, C_{18} reverse-phase column, mobile phase: 250 mM zinc acetate, 25 mM sodium acetate, 5% acetonitrile, pH 6.2, flow rate of 1.0 ml/min; fluorescence detector: excitation 344 nm, emission 398 nm). KYNA, standard (98.5% purity, determined by HPLC) used for quantitative analysis of KYNA presence in plant extracts was purchased from Sigma (St. Louis, MO, USA). To calculate recovery rate from different matrices, a known amount of a standard solution of an authentic KYNA was added to samples as an internal standard. All HPLC reagents used in the study were obtained from Baker (Griesheim, Germany) and were of the highest available purity.

Statistics

Samples were determined in duplicates. Data was presented as a mean value and a standard deviation (SD) or standard error of the mean (SEM). Statistical analysis was accomplished using one-way ANOVA followed by post hoc Tukey test. A P-value of less than 0.05 was considered significant.

Results

KYNA was found in all studied beverages. The amounts of KYNA found in various types of beverages differed significantly.

Content of KYNA in beer and cider

KYNA was detected in 20 selected beers. The highest concentration was measured in Paulaner Hefe Weissbeer – 5.152 µg/100 ml. A high amount of KYNA was also found in: Schöfferhofer Kaktusfeige – 2.842 µg/100 ml, Grand Imperial Porter – 2.127 µg/100 ml and Grand Imperial Porter Chilli – 2.027 µg/100 ml. The lowest concentration of KYNA was detected in Okocim Jasne – 0.454 µg/100 ml. KYNA is also present in ciders: Pear Cider – 0.323 µg/100 ml and Apple Cider – 0.315 µg/100 ml (Table 1).

Table 1
Kynurenic acid (KYNA) content in beer and cider.

Symbol	Brand	KYNA [μg/100 ml] mean ± SD	P < 0.05 vs
A	Paulaner Hefe Weissbeer	5.152 ± 0.117	B,C,D,E,F,G,H,I,J,K,L,M,N,O,P,R,S,T,U,V
B	Schöfferhofer Kaktusfeige	2.842 ± 0.063	A,C,D,E,F,G,H,I,J,K,L,M,N,O,P,R,S,T,U,V
C	Grand Imperial Porter	2.127 ± 0.170	A,B,G,H,I,J,K,L,M,N,O,P,R,S,T,U,V
D	Grand Imperial Porter Chilli	2.027 ± 0.463	A,B,G,H,I,J,K,L,M,N,O,P,R,S,T,U,V
E	Okocim Porter Mocno Dojrzały	1.727 ± 0.124	A,B,H,I,J,K,L,M,N,O,P,R,S,T,U,V
F	Gniewosz na miodzie akacjowym	1.702 ± 0.091	A,B,I,J,K,L,M,N,O,P,R,S,T,U,V
G	Noteckie	1.465 ± 0.141	A,B,C,D,J,K,L,M,N,O,P, R,S,T,U,V
H	Schöfferhofer Granatapfel + Guarana	1.348 ± 0.065	A,B,C,D,E,L,M,N,O,P,R,S,T,U,V
I	Warka	1.139 ± 0.117	A,B,C,D,E,F,R,S,T,U,V
J	Książęce pszeniczne	0.975 ± 0.165	A,B,C,D,E,F,G,T,U,V
K	Perła Winter	0.936 ± 0.101	A,B,C,D,E,F,G,T,U,V
L	Desperados	0.858 ± 0.199	A,B,C,D,E,F,G,H
M	Żywiec Porter	0.816 ± 0.022	A,B,C,D,E,F,G,H
N	Perła Zielona	0.789 ± 0.081	A,B,C,D,E,F,G,H
O	Perła Non-pasteurized	0.760 ± 0.175	A,B,C,D,E,F,G,H
P	Żubr	0.688 ± 0.050	A,B,C,D,E,F,G,H
R	Kasztelan Niepasteryzowane	0.686 ± 0.069	A,B,C,D,E,F,G,H,I
S	Harnaś	0.600 ± 0.103	A,B,C,D,E,F,G,H,I
T	Okocim Jasne	0.454 ± 0.022	A,B,C,D,E,F,G,H,I,J,K
U	Pear Cider	0.323 ± 0.008	A,B,C,D,E,F,G,H,I,J,K
V	Apple Cider	0.315 ± 0.021	A,B,C,D,E,F,G,H,I,J,K

Beer and cider were obtained from following producers or suppliers: Paulaner, Munchen, Germany – indicated in column 1 as: A; Schöfferhofer Weizenbier, Frankfurt am Main, Germany – B,H; Amber Brewery, Bielkowko, Poland – C,D; Carlsberg, Okocim, Poland – E,S,T; Czarnków Brewery, Poland – F,G; Grupa Żywiec, Warka, Poland – I,L,M; Kompania Piwowarska, Tyskie Browary Książęce, Poland – J; Perła Brewery, Lublin, Poland – K,N,O; Kompania Piwowarska, Dojlidy Brewery, Poland – P; Kasztelan Brewery, Sierpc, Poland – R; Amber, Lublin, Poland – U, V. Data are presented as a mean ± SD. Statistical analysis was performed using one-way ANOVA with Tukey post hoc test ($P < 0.05$) vs respective product. Results presented in column 5, each letter corresponds to one product as indicated in column 1.

Content of KYNA in wine

KYNA was present in all 14 investigated wines. The highest amount of KYNA was found in red wines: Veglio Michelino & Figlio 'Sinfonia' Vino da Tavola Rosso – 10.9 μg/100 ml and Mastroleo Negroamaro Puglia 2009 – 10.0 μg/100 ml. The content of KYNA in white wines was lower: Vino Frizzante Prosecco Done and Kessler-Zink Weisser Burgunder 2009 – 1.7 μg/100 ml, Bordeaux Cellier Yvecourt 2009 – 1.4 μg/100 ml (Table 2).

Content of KYNA in distilled beverages

KYNA was found in all studied distilled beverages and ciders. The highest content of KYNA was detected in Krzeska Herbal Vodka – 1.624 μg/100 ml, Finlandia Cranberry Vodka – 0.119 μg/100 ml and Stock Prestige – 0.066 μg/100 ml. Cognac Maxime Trijol contained 0.056 μg/100 ml and Jack Daniel's Whisky 0.055 μg/100 ml (Table 3).

Content of KYNA in mead

KYNA was present in all 15 investigated different types of meads. The highest amount of KYNA was found in Korzenny mead – 38.08 μg/100 ml. Castellan – 26.74 μg/100 ml, Klasztorny – 24.76 μg/100 ml and Stolnik – 21.07 μg/100 ml were also rich in KYNA. The lowest content was detected in Dominikański – 9.92 μg/100 ml, Piastun – 9.83 μg/100 ml and Piastowski mead – 9.39 μg/100 ml (Table 4). No correlation between KYNA content and mead to water ratio was found (Table 4).

Table 2
Kynurenic acid (KYNA) content in wine.

Symbol	Brand	Colour	KYNA [μg/100 ml] mean ± SD	P < 0.05 vs
A	Veglio Michelino & Figlio 'Sinfonia' Vino da Tavola Rosso	Red	10.9 ± 0.58	B,C,D,E,F,G, H,I,J,K,L,M,N
B	Mastroleo Negroamaro Puglia 2009	Red	10.0 ± 0.47	A,C,D,E,F,G, H,I,J,K,L,M,N
C	Casa De Campo Reserve Malbec – Shiraz 2008	Red	7.6 ± 0.33	A,B,D,E,F,G, H,I,J,K,L,M,N
D	Piccini Selezione Oro Riserva, 2005	Red	5.7 ± 0.29	A,B,C,G,H, I,J,K,L,M,N
E	Cellier du Rhone Cotes du Rhone 2009	Red	5.1 ± 0.27	A,B,C,H,I,J,K,L,M,N
F	Bourgogne Pinot Noir 2008	Red	4.9 ± 0.27	A,B,C,H,I,J,K,L,M,N
G	Rincon del Sol Chardonnay – Chenin 2010	White	4.7 ± 0.22	A,B,C,D,H,I,J,K,L,M,N
H	Kessler-Zink Dornfelder Rotwein-Halbtrocken 2009	Red	3.3 ± 0.18	A,B,C,D,E,F,G,J,K,L,M,N
I	Vecchia Storia Gavi	White	3.1 ± 0.16	A,B,C,D,E,F,G,I,J,K,L,M,N
J	Pasquier Desvignes Chablis 2009	White	1.9 ± 0.12	A,B,C,D,E,F,G,H,I
K	Chateau Fonfroide Bordeaux 2008	White	1.9 ± 0.18	A,B,C,D,E,F,G,H,I
L	Kessler-Zink Weisser Burgunder 2009	White	1.7 ± 0.11	A,B,C,D,E,F,G,H,I
M	Vino Frizzante Prosecco Done	White	1.7 ± 0.10	A,B,C,D,E,F,G,H,I
N	Bordeaux Cellier Yvecourt 2009	White	1.4 ± 0.13	A,B,C,D,E,F,G,H,I

Wine was obtained from following producers or suppliers: Piedmont, Italy – indicated in column 1 as: A; San Bonifacio, Italy – B; Bodegas Santa Ana, Mendoza, Argentina – C; Chianti DOCG, Italy – D; Thorins, France – E; Romaneche-Thorins, France – F; Mendoza, Argentina – G; Flonheim, Germany – H,L; Gavi, Italy – I; Burgundy, France – J; Bordeaux, France – K,N; Soave, Italy – M. Data are presented as a mean ± SD. Statistical analysis was performed using one-way ANOVA with Tukey post hoc test ($P < 0.05$) vs respective product. Results presented in column 5, each letter corresponds to one product as indicated in column 1.

Table 3
Kynurenic acid (KYNA) content in distilled beverages.

Symbol	Brand	Type	KYNA [μg/100 ml] mean ± SD	P < 0.05 vs
A	Krzeska Herbal Vodka	Vodka	1.624 ± 0.338	B,C,D,E,F
B	Jägermeister	Liquer	0.127 ± 0.010	A
C	Finlandia Cranberry Vodka	Vodka	0.119 ± 0.009	A
D	Stock Prestige	Vodka	0.066 ± 0.008	A
E	Cognac Maxime Trijol	Cognac	0.056 ± 0.006	A
F	Whisky Jack Daniel's	Whisky	0.055 ± 0.006	A

Alcohol beverages were obtained from following producers or suppliers: Polmos Siedlce, Poland – indicated in column 1 as: A; Mast-Jägermeister AG, Wolfenbüttel, Germany – B; Finlandia Vodka Worldwide Ltd., Helsinki, Finland – C; Stock Polska, Warsaw, Poland – D; Cognac Maxime Trijol, France – E; Jack Daniel Distillery, Tenessee, USA – F. Data are presented as a mean ± SD. Statistical analysis was performed using one-way ANOVA with Tukey post hoc test (P < 0.05) vs respective product. Results presented in column 5, each letter corresponds to one product as indicated in column 1.

Content of KYNA in human plasma

Mean KYNA concentration in serum before administration of chestnut honey dissolved in water was 0.052 ± 0.004 μM and 0.051 ± 0.014 μM in men and women, respectively. 30 min after administration of chestnut honey dissolved in water content of KYNA reached its maximum - 237% and 308% vs control in men and women, respectively (Fig. 2).

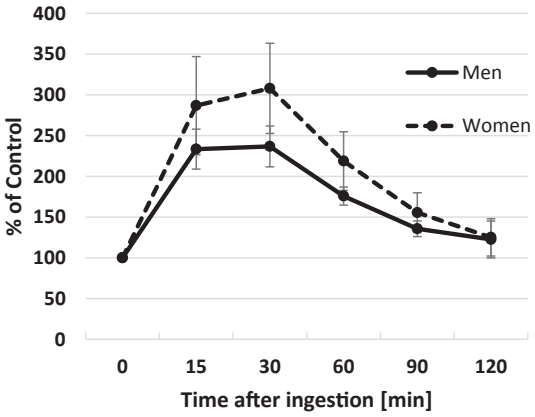

Fig. 2. Content of kynurenic acid (KYNA) in human plasma after ingestion of chestnut honey dissolved in water. Data are presented as a mean ± SEM.

Discussion

It was found that KYNA is present in various beverages in different concentrations. The highest level of KYNA was found in mead, followed by wine and beer, while the lowest in distilled alcoholic beverages. To the best of our knowledge, the content of KYNA in alcoholic beverages has never been comprehensively investigated before. Only recently, presence of KYNA was reported in beer and red wine samples [1].

It was suggested that KYNA found in some foodstuffs is synthesized by yeast during fermentation process [1]. KYNA is produced from kynurenine by kynurenine aminotransferase (KAT). Four isoenzymes were distinguished (KAT I-IV) [22]. In fact, presence of enzymes responsible for KYNA synthesis was demonstrated in yeasts *Hansenula schneggii* [23,24] *and Saccharomyces cerevisiae* [25–27]; the last one is generally used in the beer and wine making process. However, plant derived components of alcohol production process may contain KYNA as well [3].

Apart from yeast, beer is produced from malted cereal grains, barley and wheat. In our study, the highest content of KYNA was found in wheat beer Paulaner Hefe Weissbeer. However, in another wheat beer Książęce pszeniczne KYNA content was considerably lower, thus suggesting that the type of grain used in brewing process is not the critical factor determining the content of KYNA in the final product. Our finding that KYNA level in beer brands which contain ingredients or flavorings such as herbs, fruits or honey was relatively high is in line with this hypothesis. Large differences among beer brands suggest that their recipe and production processes, e.g. yeast used, may affect the content of KYNA in beer beverages.

Apart from yeast, wine is made from fermented grapes or other fruits. As expected, KYNA was present in all studied wine brands, however, its content varied widely. It appears that the level of KYNA is higher in red wine in comparison to white wine. The red color of wine depends mainly on the presence of pigments which are localized in the exocarp of the grape drupe. The content of KYNA in grapes has not been studied yet. Therefore, we can speculatively assume that KYNA is concentrated mainly in the skin of the fruits. This assumption can be supported by a low content of KYNA in ciders which are made from juice extracted from apples and pears.

The content of KYNA in spirits was very low probably due to their distillation process. Herbal vodka Krzeska was an exception. Interestingly, the producer stated that this brand contains seventeen

Table 4
Kynurenic acid (KYNA) content in mead.

Symbol	Brand	Composition mead:water [units]	KYNA [μg/100 ml] mean ± SD	P < 0.05 vs
A	Korzenny	1:3	38.08 ± 0.40	B,C,D,E,F,G,H,I,J,K,L,M,N,O
B	Castellan	1:2	26.74 ± 1.20	A,D,E,F,G,H,I,J,K,L,M,N,O
C	Klasztorny	1:1	24.76 ± 0.27	A,D,E,F,G,H,I,J,K,L,M,N,O
D	Stolnik	1:2	21.07 ± 0.40	A,B,C,F,G,H,I, J,K,L,M,N,O
E	Bernardyński	1:2	19.85 ± 0.80	A,B,C,H,I,J,K, L,M,N,O
F	Podczaszy	1:2	18.71 ± 0.27	A,B,C,D,I,J,K, L,M,N,O
G	Castellan	1:1	18.43 ± 0.40	A,B,C,D,I,J,K, L,M,N,O
H	Jadwiga	2:1	17.20 ± 2.13	A,B,C,D,E,K,L,M,N,O
I	Pearl in the Crown	1:3	15.69 ± 0.27	A,B,C,D,E,F,G,K,L,M,N,O
J	Rex Honestus	2:1	15.03 ± 0.13	A,B,C,D,E,F,G,L,M,N,O
K	Pułkownikowski	1:2	13.23 ± 0.27	A,B,C,D,E,F,G,H,I,M,N,O
L	Kurpiowski	1:1	12.03 ± 0.66	A,B,C,D,E,F,G,H,I,J,O
M	Dominikański	1:1	9.92 ± 0.13	A,B,C,D,E,F,G,H,I,J,K
N	Piastun	1:2	9.83 ± 0.27	A,B,C,D,E,F,G,H,I,J,K
O	Piastowski	1:2	9.39 ± 0.61	A,B,C,D,E,F,G,H,I,J,K,L

Mead was obtained from following producers or suppliers: Apiculture Cooperative APIS, Lublin, Poland – mead indicated in column 1 as: A,C,D,E,F,H,K,L,M,N,O; TiM, Bielsko Biała, Poland – B,G,I,J. Data are presented as a mean ± SD. Statistical analysis was performed using one-way ANOVA with Tukey post hoc test (P < 0.05) vs respective product. Results presented in column 5, each letter corresponds to one product as indicated in column 1.

different herbs. Since KYNA is present in medicinal herbs [3], a relatively high level of this compound in herbal vodka can be attributed to its non-alcoholic ingredients. Similarly, a high level of KYNA ranging from 9.39 to 38.08 μg/100 ml was found in meads which are created by fermenting honey mixed with water. This result was expected since the amount of KYNA is very high in honey [19,28]. Unexpectedly, the content of KYNA did not correlate with the mead to water proportion used in the production process. Lack of such a correlation can be attributed to differences in the content of KYNA in various honey types [28] or to the presence of various ingredients used by producers, e.g. spices, grains, fruits and hop. It was reported previously that culinary herbs and spices contain KYNA at varying concentrations [29]. The high variability of KYNA content in alcoholic beverages suggests that plant derived components and yeast species as well as different manufacturing conditions may have impact on KYNA level in final products.

It was suggested that KYNA applied in beverages may affect receptors present in the digestive tract or affect functioning of internal organs after its absorption [30]. Presence of receptors affected by KYNA in the digestive tract was demonstrated. Wang et al. 2006 reported that GPR35 receptors are located predominately on enterocytes in intestinal crypts [12]. AHR is expressed highly in intestinal epithelial cells and in cells of the gut-associated immune system [31]. Moreover, glutamate receptor subunits α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and N-methyl-D-aspartate (NMDA) were identified on neurons in submucosal and myenteric plexuses [32]. Interestingly, it was found that administration of KYNA significantly inhibits formation of ulcer induced by ethanol and stress in rats [14]. It also protects against gastric and duodenal ulcers, duodenal hyperemia and peritoneal ascites evoked by administration of a poisonous extract from Atlantic mussels in mice [33]. These findings point to the beneficial role of KYNA in gastric and duodenal mucosa protection system. Moreover, KYNA was found to exhibit anti-inflammatory and antispasmodic activity in animal model of colon obstruction [15] and experimental colitis [34,35]. Its hepatoprotective effect in an animal model of liver failure induced by thioacetamide was demonstrated (Marciniak 2018). Thus, in this context the presence of KYNA in alcoholic beverages seems to be favorable. Since the content of KYNA in alcoholic beverages is low and spirits contained only traces of KYNA, it seems reasonable to postulate supplementation of such beverages with KYNA.

However, Badawy et al., 2011 showed that KYNA inhibits rat liver mitochondrial aldehyde dehydrogenase [20], a key enzyme in alcohol metabolism. This resulted in an increase of blood content of acetaldehyde [20]. It is well known that elevated acetaldehyde level makes drinking unpleasant. More importantly, acetaldehyde is a biologically active metabolite, a key generator of free radicals and a known carcinogen [36,37]. It should be underlined that according to the International Agency for Research on Cancer alcohol-drinking-related acetaldehyde was categorized to Group 1 for head and neck and esophageal cancers [38]. Moreover, the recent epidemiological studies have also shown significant positive associations between the aldehyde dehydrogenase ALDH2 (rs671)*2 allele encoding inactive enzyme, which causes elevation of acetaldehyde and gastric, colorectal, lung, and hepatocellular cancers [38]. The pivotal role of acetaldehyde and its adducts was suggested also in the pathogenesis of alcoholic cardiomyopathy [39] and liver damage [40,41]. Thus, the enhancement of acetaldehyde by KYNA present in alcoholic beverages may have harmful consequences.

On the other hand the blood content of ethanol was significantly lowered by acute administration of KYNA [20]. It was also found that administration of KYNA reduced ethanol intake in an aversion model in rats and decreased alcohol preference in mice [20]. In turn, these effects may result in reduction of alcohol intake and may help to control alcohol overuse.

In order to determine whether KYNA might interact with alcohol, when they coexist in a beverage, we performed study to determine the absorption rate of KYNA from honey dissolved in water. Chestnut honey was selected because it contains exceptionally high amount of KYNA among its known natural sources [28]. It was found that in humans KYNA from honey is rapidly absorbed after oral administration; its concentration reached peak in blood 15–30 min after ingestion and slowly declined thereafter. Noteworthy, a very similar time-course of absorption of alcohol after ingestion of beer, wine and spirits was reported by Mitchell et al. [42]. Thus, it can be concluded that an interaction between KYNA and alcohol derived from the same beverage may occur. Such interaction is also probable when alcohol is ingested in the form of drinks or at the same time with food containing KYNA. Therefore, the effect exerted by KYNA on metabolism of alcohol deserve special attention and needs to be furtherly investigated.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2018.11.003.

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