Kynurenic Acid in the Digestive System—New Facts, New Challenges

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Abstract: This review provides information on the most recent findings concerning presence, origin, and role of kynurenic acid (KYNA), a tryptophan metabolite, in the digestive system. KYNA is an antagonist of both the ionotropic glutamate receptors and the alpha7 nicotinic acetylcholine receptor, as well as an agonist of G-protein coupled GPR35 receptor. Since the GPR35 receptor is mainly present in the gastrointestinal tract, researchers have concentrated on the digestive system in recent years. They have found that KYNA content increases gradually and significantly along the gastrointestinal tract. Interestingly, the concentration of KYNA in the lumen is much higher than in the wall of intestine. It has been documented that KYNA may have a positive influence on the number of pathologies in the gastrointestinal tract, in particular ulcers, colon obstruction, or colitis. Future studies might determine whether it is advisable to supplement KYNA to a human organism.

Keywords: kynurenic acid, digestive system, pathophysiology, food, herb

International Journal of Tryptophan Research 2013:6 47–55
doi: 10.4137/IJTR.S12536

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**Introduction**

Kynurenic acid (KYNA) is a metabolite of tryptophan formed enzymatically along the kynurenine pathway. The first step in the pathway is catalyzed by tryptophan 2, 3-dioxygenase (TDO) and indoleamine 2, 3-dioxygenase (IDO), enzymes responsible for tryptophan degradation to formylkynurenine. TDO is primarily expressed within the liver and IDO is an extrahepatic cytokine inducible enzyme. The next step in the synthesis of kynurenine is catalyzed by formylkynurenine formamidase. The main end product of kynurenine catabolism is nicotinamide adenine dinucleotide (NAD$^+$). An another biologically active product, KYNA, is generated from kynurenine by kynurenine aminotransferase.$^{1,2}$

KYNA presence was first demonstrated in urine by Liebig.$^3$ Nevertheless, the compound was not thoroughly analyzed until the 1980’s and 1990’s when researchers indicated that KYNA is an antagonist of ionotropic glutamate receptors.$^4$–$^8$ Subsequently, researchers presumed that KYNA is present in the human brain.$^9$,$^{10}$ Numerous studies were conducted to investigate the role of KYNA in the physiology and pathology of the central nervous system (CNS). Since both the concentration of KYNA in the human brain and penetration of KYNA through a blood-brain barrier are low, studies of peripheral KYNA gained popularity.

**Mechanisms of Action**

Table 1 presents a summary of receptors affected by KYNA, quantities of KYNA necessary to exert action, and further comments regarding its mechanism of action. KYNA is widely known as an antagonist of ionotropic glutamate receptors.$^4$–$^8$,$^{11}$ receptors present mainly in the brain. Research conducted over the last two decades of the 20th century, therefore, focused on the role of KYNA in the physiology and pathology of the CNS. Since both the concentration of KYNA in the human brain and penetration of KYNA through a blood-brain barrier are low, studies of peripheral KYNA gained popularity.

**Content of KYNA in the CNS and Periphery**

The concentration of KYNA in cerebrospinal fluid and the brain lies within the range of 0.001–0.032 µM and 0.001–1.58 µM, respectively (Table 2), and is lower than the concentration necessary to affect glutamate or cholinergic receptors (Table 1). The concentration of KYNA in peripheral tissues ranges from 0.090 µM in the wall of the intestine to 0.815 µM in the kidney. The lowest concentration of KYNA in body fluids was found in saliva (0.003 µM) while the highest was found in mucous from ileum (16.1 µM). The content of KYNA in urine ranges from 4–40 µM (Table 2).

It should be emphasized that the concentration of KYNA high enough to interact with glutamate, alpha-7 cholinergic, and GPR35 receptors in vitro was detected in lumen of ileum. Also of note, the GPR35 receptor is mainly present in gastrointestinal tissues.$^{12}$

**KYNA in CNS**

Glutamate receptors are mainly located in the CNS. According to electrophysiological studies, KYNA exerts a modulatory effect on neurotransmission in the brain.$^{11}$,$^{16}$ Several papers review the action and the potential role of KYNA in the brain.$^{17}$–$^{19}$

**KYNA in Periphery**

Initially, KYNA was found in urine in 1853.$^3$ More recently, presence of KYNA in urine was described in numerous papers (Table 2).$^{20}$–$^{26}$

It was evidenced that KYNA is present in serum where its concentration varied from 0.004–0.06 µM (Table 2). Additionally, KYNA was found in synovial$^{27}$ and amniotic fluid.$^{28}$

Furthermore, numerous reports concentrate on KYNA content outside of the CNS, specifically focusing on its presence in the digestive system.

**KYNA Content in Digestive System**

Table 3 presents the most recent findings of KYNA concentration in the lumen of the digestive system. The lowest concentration of KYNA was found in human saliva (0.003 µM) and human gastric juice (0.01 µM), while the highest content of KYNA was detected in the rat’s middle ileum mucus (8.08 µM) and the rat’s distant ileum mucus (16.10 µM). It is worth noting that the concentration of KYNA increases gradually
along the gastrointestinal tract, reaching its highest value at the very end of it. It is also noteworthy that KYNA content in the distant ileum of the rat mucus is nearly 5400 times higher than in human saliva. The physiological significance of such remarkable gradation of KYNA concentration in the digestive system is currently unknown.

Interestingly, a much lower concentration of KYNA was found in the wall of the gastrointestinal tract. According to Kuc et al, the concentration of KYNA in the wall of a rat’s duodenum, jejunum, and ileum was 0.29 µM, 0.21 µM and 0.28 µM, respectively. Pawlak et al reported a concentration of 0.09 µM of KYNA in rat intestine. The content of KYNA in the wall of a rat’s duodenum, jejunum, and ileum was, therefore, 19%, 6%, and 3% of the content of KYNA in the lumen of the appropriate part of a rat’s intestine, respectively. As a result, the supposition that KYNA is produced in the wall of the intestine and then secreted to the intestinal fluid in such a high amount seems rather unlikely.

The remarkable content of KYNA amounting to 0.31–0.83 µM and 1.11 µM was found in bile of human and pig, respectively. Unexpectedly, KYNA was detected in the pancreatic juice of pigs with a relatively high concentration (0.76 µM). However, the distribution and activity of kynurenine transaminases in pancreatic tissue, and thus the mechanism

### Table 1. Receptors affected by kynurenic acid.

| Receptor/binding site                      | Concentration [EC_{50}, µM] | Comment                                      | Reference |
|-------------------------------------------|-----------------------------|----------------------------------------------|-----------|
| NMDA autoreceptors                        | 0.03                        | On glutamatergic nerve terminals             | 48        |
| Strychnine insensitive glycin/NMDA receptor | 8                           |                                              | 5         |
|                                           | 41                          |                                              | 6         |
|                                           | 15                          |                                              | 7         |
|                                           | 15                          |                                              | 11        |
|                                           | 24.4–195.4                  |                                              | 8         |
| NMDA                                      | 187                         |                                              | 6         |
|                                           | 200–500                     |                                              | 7         |
|                                           | 235                         |                                              | 11        |
| AMPA/kainate                              | 101                         | AMPA                                         | 6         |
|                                           | 400                         | GLUR6                                        | 4         |
|                                           | 432.5–595.7                 |                                              | 8         |
| α7 nicotinic                              | 7                           | Ineffective                                  | 11        |
| GPR35                                     | 7                           | 1000–3000 µM                                 | 8         |
|                                           | 11                          | Rat                                           | 12        |
|                                           | 39                          | Mouse                                         |           |
|                                           | 2.9–4.9                     | Mouse Sult1b1                                 | 49        |
|                                           | 18.8–22.0                   | Human SULT1A1                                 |           |
|                                           | 19.6–45.8                   | Human SULT1B1                                 |           |
| Aryl hydrocarbon receptor (AHR)           | 1.4                         | Human AHR-expressing mice                     | 50        |
| Organic anion transporting polypeptides (OATP1B1/3) | ~20                      | Rat and human hepatocytes                     | 51        |
| Pol(ADP)ribose                           | 670                         |                                              | 52        |
| Arachidonic acid-induced platelets aggragation | 900                      | Guinea pig                                    | 53        |
| Adenosine diphosphate-induced platelets aggragation | 1100               | Guinea pig                                    |           |
| GABA\_                                      | 2900                       | 34% inhibition                                | 8         |
| Styrchnine-sensitive glycin receptor p75   | >3000                      | NGF binding to p75 receptor in PC12 cells     | 54        |

Abbreviations: AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; GABA, γ-aminobutyrate; GPR35, G protein-coupled receptor; NMDA, N-methyl-D-aspartate.
of KYNA formation in exocrine acinar cells of the pancreas, have not been elucidated to date.

Based on the data concerning the KYNA absorption in the intestine\cite{31,32} and its presence in bile and pancreatic juice,\cite{29} the hepatic-pancreatic-intestinal secretion-absorption functional cycle creating a high concentration of KYNA in intestinal fluid can be suggested. Furthermore, it is highly probable that activity of colon microbiota participates in the main maintaining of KYNA in the gastrointestinal content especially in their distal part as well.\cite{29}

**Table 2.** KYNA content in tissues and body fluids.

| Tissue       | KYNA content [µM]\* | Comment                        | References |
|--------------|---------------------|--------------------------------|------------|
| Brain        | 0.14–1.58           | Human                          | 9,55,56    |
|              | 0.001–0.05          | Rat                            | 57–59      |
|              | −0.002              | Hamster                        | 60         |
|              | 0.16                | Gerbil                         | 61         |
| Kidney       | 0.815               | Rat                            | 30         |
| Liver        | 0.161               | Rat                            | 30         |
| Lung         | 0.172               | Rat                            | 30         |
| Intestine    | 0.090–0.29          | Rat                            | 29,30      |
| Ileum (lumen)| 8.08–16.1           | Rat                            | 29         |
| Spleen       | 0.129               | Rat                            | 30         |
| Muscle       | 0.197               | Rat                            | 30         |
| Plasma       | 0.004–0.060         | Human                          | 62–66      |
|              | 0.016               | Human, pregnant women          | 23         |
|              | 0.066               | Human, umbilical cord blood    | 28         |
|              | 0.122               | Monkey                         | 67         |
|              | 0.028–0.065         | Rat                            | 68         |
|              | −0.02               | Hamster                        | 60         |
| Cerebrospinal fluid | 0.001–0.005 | Human                          | 63,64,69–72 |
|              | −0.005              | Human, 7 months old            | 73         |
|              | 0.006               | Monkey                         | 67         |
|              | 0.032               | Gerbil                         | 61         |
| Saliva       | 0.003               | Human                          | 44         |
| Amniotic fluid| 1.132              | Human                          | 28         |
| Synovial fluid| 0.016               | Human; rheumatoid arthritis    | 27         |
| Urine        | 4–40                | Human                          | 20–25      |
|             | 11.7                | Human, pregnant women          | 23         |

Notes: \*For the sake of a comparison, the content of KYNA in wet tissue was calculated as follows: \(\eta\) mol/g = µM.

**Table 3.** Content of KYNA in the lumen of digestive system.

| Species            | KYNA content [µM] | Reference |
|--------------------|-------------------|-----------|
| Saliva             | 0.003             | 44        |
| Gastric juice      | 0.01              | 74        |
| Bile               | 0.31–0.84         | 74        |
| Pancreatic juice   | 1.11              | 74        |
| Jejunum—mucus      | 0.76              | 74        |
| Proximal ileum—mucus| 1.49             | 29        |
| Middle ileum—mucus| 3.30              | 29        |
| Distal ileum—mucus| 8.08              | 29        |
|                    | 16.10             | 29        |

**Properties of KYNA in Pathological States of the Gastrointestinal Tract**

Numerous researchers have analyzed properties of KYNA in the pathology of the gastrointestinal tract. According to Glavin et al, KYNA protects against gastric and duodenal ulceration caused by a poisonous Atlantic shellfish.\cite{33} Furthermore, Glavin and Pinsky found that KYNA attenuates stress- and ethanol-induced ulcers in rats.\cite{34} KYNA was also found to inhibit intestinal hypermotility and xanthine oxidase activity during experimental colon obstruction in dogs.\cite{35} Moreover, Varga et al pointed out that KYNA decreases motility and inflammatory activation in the early phase of acute experimental colitis in rats.\cite{36}
Interestingly, the KYNA level in serum was found to be higher in inflammatory bowel disease patients\(^{37}\) while it was found to be lower in irritable bowel syndrome patients, in comparison with healthy subjects.\(^{38}\) The second finding was confirmed by Christmas et al who found that KYNA levels in serum tends to decrease in irritable bowel syndrome patients.\(^{39}\) Finally, a high concentration of KYNA was detected in mucus aspirated from the coecum or ascending colon of patients suffering from colorectal cancer adenomas.\(^{40}\) A summary of the findings is presented in Table 4.

All in all, scientific reports suggest that KYNA may have a positive influence on the number of pathologies of the gastrointestinal tract, especially regarding ulcers, colon obstruction or colitis. There is some dispute as to whether KYNA exerts a positive or negative action in bowel diseases since an increased level of KYNA in colon neoplasia cannot be interpreted either in favor of or against KYNA, as its mechanism of action in the mentioned diseases is yet unknown. Recently, KYNA’s enhancement of the expression of cyclin-dependent kinase inhibitor, p21 Waf1/Cip1, and inhibition of cell proliferation and DNA synthesis in colon adenocarcinoma HT-29 cell line were described.\(^{41}\)

### Table 4. KYNA and pathology of gastrointestinal tract.

| Pathology                     | Effect of KYNA                                                                 |
|-------------------------------|-------------------------------------------------------------------------------|
| Gastroduodenal ulceration     | KYNA protects against gastric and duodenal ulceration induced by extract from poisonous Atlantic shellfish in mice. | 33 |
| Gastroduodenal ulceration     | KYNA blocks restraint-cold stress ulcers, ethanol ulcers and basal, non-stimulated gastric acid secretion in rats. | 34 |
| Experimental colon obstruction| KYNA inhibits intestinal hypermotility and xanthine oxidase activity during experimental colon obstruction in dogs. | 35 |
| Colitis                       | KYNA decreases motility and inflammatory activation in the early phase of acute experimental colitis in rats. | 36 |
| Inflammatory bowel disease    | Serum level of KYNA is elevated in inflammatory bowel disease patients.        | 37 |
| Irritable bowel syndrome      | Serum level of KYNA is reduced in irritable bowel syndrome patients.           | 38 |
| Diarrhea-predominant irritable bowel syndrome | Trend to decrease in KYNA content in serum of diarrhea-predominant irritable bowel syndrome patients. | 39 |
| Colon carcinoma, Adenoma tubulovillosum, Adenoma tubulare | High KYNA concentration is detected in mucus aspirated from caecum or colon ascendens of patients diagnosed with colon carcinoma, Adenoma tubulovillosum or Adenoma tubulare. | 40 |

### KYNA and the Gut Flora

Most recently, it was indicated that *Escherichia coli* is able to produce KYNA and liberate it to extracellular milieu.\(^{29}\) Similarly, KYNA production was shown in cell-free extracts of *E. coli*.\(^{42}\) Furthermore, there is allusion to positive correlation between microflora concentration and KYNA content in jejunum and ileum.\(^{29}\) These findings suggest that gut flora may participate in forming the common pool of intestinal KYNA.

On the other hand, it has also been demonstrated that KYNA affects bacterial growth. Interestingly, low and medium concentrations of KYNA stimulate growth of certain probiotics while KYNA in high concentrations possesses antibacterial properties.\(^{43,44}\)

### Metabolism of KYNA

KYNA is present in the lumen of rat small intestine in micromolar concentrations,\(^{29}\) which is sufficient to affect the GPR35 receptor. The sources of KYNA in the gastrointestinal tract are not known, although it seems that, in this instance, KYNA was either produced from tryptophan or delivered with food and other dietary products.

The pathway for KYNA creation in humans was most recently investigated by Hiratsuka et al in young Japanese women who consumed tryptophan in amount of 0.7 g (3328 µmol) per day with subsequent analyzes of various tryptophan metabolites.\(^{20}\) KYNA production was reported near 10 µmol/day, indicating that transformation of tryptophan to KYNA occurs with an effectiveness of 0.3%.\(^{20}\) Leklem reported a slightly higher effectiveness of the reaction at 0.42%.\(^{26}\)

The expert report created by the World Health Organization (WHO), Food and Agriculture Organization...
(FAO), and United Nations University (UNU) recommends a tryptophan dose of 4 mg/kg/day.\textsuperscript{45} Therefore, assuming an adult’s weight to be 70 kg, a recommended dose of tryptophan per person is 280 mg/day. It can be estimated that either 0.84 mg (effectiveness of 0.3%) or 1.18 mg (effectiveness of 0.42%) of KYNA is created in the human body along the kynurenine pathway from tryptophan.

Therefore, the research suggests that KYNA might be synthesized in the human body along the kynurenine pathway from its precursor, tryptophan. However, there was no analogous research on KYNA synthesis from its immediate precursor, kynurenine, and there is no data regarding the presence of kynurenine in either food or herbs.

Despite some previous research indicating that KYNA might be metabolized to quinaldic acid,\textsuperscript{46} we did not observe its formation from KYNA in rat brain slices and liver homogenates (unpublished observation). Nevertheless, there is no data on KYNA accumulation in the body. Numerous scientific papers report that KYNA is present in human urine and hence excreted with it.\textsuperscript{20–26} Reports of excreted KYNA concentrations vary from 1143.9 µg per day to 5376.6 µg per day (Table 5). Based on the results shown in Table 5, and bearing in mind the fact that estimated production of KYNA from tryptophan in human organism is either 840 µg per day or 1160 µg per day, it could be assumed that KYNA is also absorbed from the digestive system. In fact, there is indication that KYNA can be absorbed from the digestive system into blood circulation.\textsuperscript{31}

Literature data suggests that the majority of KYNA content in human organisms likely comes from exogenous sources. Therefore, it is important to review the studies of KYNA content in food and herbs.

**KYNA in Food**

According to research by Turski et al, KYNA is present in various kinds of food and, therefore, is a constituent of a human diet.\textsuperscript{31,32} Interestingly, the concentration of KYNA varies significantly among analyzed food products. As can be seen in Table 6, content of KYNA in a majority of analyzed vegetables is higher in comparison to content of KYNA in various kinds of meat. Nevertheless, it is honey that contains the highest concentration of KYNA among all analyzed food products. It is also worth noting that KYNA content in broccoli is very high. Both honey and broccoli are believed to possess pro-health properties. On the other hand, high concentration of KYNA was found in potato and potato related food products, such as French fries or crisps, which are not commonly thought of as healthy food. Further research by Turski et al.\textsuperscript{27} indicated that the content of KYNA in potatoes may depend on variety of a potato.

**Table 5. Excretion of KYNA in urine.**

| KYNA content in urine | Reference | KYNA excretion [µg/day]* |
|-----------------------|-----------|--------------------------|
| 9.97 µmol/day         | 20        | 1884.3                   |
| 4.035 µmol/L          | 21        | 1143.9                   |
| 2.54 µg/mL            | 22        | 3810                     |
| 11.7 µmol/L           | 23        | 3317                     |
| 18.965 µmol/L         | 24        | 5376.6                   |
| 13 µmol/L             | 25        | 3683.5                   |
| 15.9 µmol/day         | 26        | 3005.1                   |

*The assumption behind the calculations is that a human being excretes 1.5 liters of urine on a daily basis.\textsuperscript{75}

**Table 6. Content of KYNA in food products.**

| Food products | KYNA [µg/g wet weight] | Average consumption* [g wet weight] | KYNA intake [µg/day] |
|---------------|------------------------|-------------------------------------|----------------------|
| Red paprika   | 0.001                  | 100                                 | 0.1                  |
| Apple         | 0.002                  | 150                                 | 0.3                  |
| Sunflower oil | 0.003                  | 100                                 | 0.3                  |
| Beef          | 0.003                  | 100                                 | 0.3                  |
| Pork          | 0.004                  | 100                                 | 0.4                  |
| Cucumber      | 0.004                  | 100                                 | 0.4                  |
| Sweet potato  | 0.005                  | 100                                 | 0.5                  |
| Egg           | 0.005                  | 70                                  | 0.35                 |
| Rice          | 0.006                  | 100                                 | 0.6                  |
| Tomato        | 0.006                  | 150                                 | 0.9                  |
| Carrot        | 0.007                  | 50                                  | 0.35                 |
| Wheat flour   | 0.007–0.008            | 100                                 | 0.7–0.8              |
| Hard cheese   | 0.008                  | 50                                  | 0.4                  |
| Pea           | 0.009                  | 100                                 | 0.9                  |
| Corn (maize)  | 0.016                  | 100                                 | 1.6                  |
| Milk          | 0.017                  | 200                                 | 3.4                  |
| Onion         | 0.023                  | 50                                  | 1.15                 |
| Cauliflower   | 0.047                  | 100                                 | 4.7                  |
| Crisps        | 0.060–0.157            | 30                                  | 1.8–4.7              |
| French fries  | 0.035–0.160            | 100                                 | 3.5–16.0             |
| Broccoli      | 0.418                  | 100                                 | 41.8                 |
| Potato        | 0.040–0.648            | 100                                 | 4.0–64.8             |
| Honey         | 0.179–0.877            | 10                                  | 1.79–8.77            |

*All data on KYNA content in food products are from ref.\textsuperscript{31,32} Average consumption stands for a hypothetical quantity of a certain product that an average human being consumes in one day.
An average KYNA intake from food was calculated based on KYNA content in a gram of wet weight of a certain food product multiplied by an average consumption of a certain food product. The summary of results is shown in Table 6. Based on our estimation, the highest amount of KYNA delivered to the human body with food comes from broccoli. It should be noted, however, that the boiling procedure lowered KYNA content in broccoli by 88%. High amounts of KYNA can be delivered with potatoes. Conversely, consumption of rice and maize delivers remarkably lower amounts of KYNA.

**KYNA in Herbs**

Research conducted by Turski et al indicates that analyzed herbs contain significant amounts of KYNA. Interestingly, herbs seem to contain more KYNA than ordinary food products (Tables 6 and 7). Bearing in mind the fact that the use of herbs is beneficial for health, it might be suggested that KYNA may be partially responsible for their beneficial effects. As can be seen in Table 7, St. John’s wort, nettle leaf, birch leaf, elderberry flower, and peppermint leaf contain the highest concentrations of KYNA among all analyzed herbs. All of them are regarded as herbal medicines when it comes to the digestive system. They are believed to possess protective and healing properties.

**Summary**

Reviews of available data suggest that KYNA is present in the lumen of the digestive system in high concentration. Furthermore, KYNA is both produced in the human body from tryptophan as well as absorbed by it from various food and herbs. It can be also produced by gut flora. Numerous researchers suggest that KYNA may play a significant role in the functioning of the digestive system. Interestingly, recent studies indicate that KYNA may possess therapeutic properties when used to treat diseases of the gastrointestinal tract.

Nevertheless, numerous questions still need to be answered. No scientific data exists detailing KYNA excretion levels with feces. Furthermore, the ability of intestinal bacteria to produce KYNA and its subsequent production levels must be investigated. Moreover, existence of KYNA enterohepatic circulation also requires study as KYNA is excreted in bile and can be absorbed from the intestine. Specifically, the effectiveness of absorption in various parts of the digestive system deserves further elucidation.

There is no clear data concerning an optimal daily intake of KYNA by humans and their daily demand for it. Consequently, no data details whether there is the possibility of KYNA shortage in the human organism and, if so, the outcome generated by such shortage. We recommend gastrointestinal tract diseases and states of malnutrition be thoroughly analyzed, as daily exogenous KYNA supply may not be sufficient to cover its losses through, for example, urine.

KYNA’s influence on enterocytes also warrants further investigation. And finally, the role of KYNA in tumor development needs to be studied.

Future studies may determine whether it is advisable to supplement KYNA to a human organism.

**Acknowledgements**

M.P. Turski and M. Turska are students, volunteers in the Department of Toxicology, Institute of Rural Health and the Department of Experimental and Clinical Pharmacology, Medical University, respectively.
Author Contributions
Analyzed the data: MPT, MT. Wrote the first draft of the manuscript: MPT. Contributed to the writing of the manuscript: MT, PP, JPT, GO. Agree with manuscript results and conclusions: MPT, MT, PP, JPT, GO. Jointly developed the structure and arguments for the paper: MPT, MT, PP, JPT, GO. Made critical revisions and approved final version: MPT, MT, PP, JPT, GO. All authors reviewed and approved of the final manuscript.

Funding
Author(s) disclose no funding sources.

Competing Interests
Author(s) disclose no potential conflicts of interest.

Disclosures and Ethics
As a requirement of publication the authors have provided signed confirmation of their compliance with ethical and legal obligations including but not limited to compliance with ICMJE authorship and competing interests guidelines, that the article is neither under consideration for publication nor published elsewhere, of their compliance with legal and ethical guidelines concerning human and animal research participants (if applicable), and that permission has been obtained for reproduction of any copyrighted material. This article was subject to blind, independent, expert peer review. The reviewers reported no competing interests.

References
1. Schwarz R, Bruno JP, Muchowski PJ, Wu HQ. Kynurennines in the mammalian brain: when physiology meets pathology. Nat Rev Neurosci. 2012;13:465–77.
2. Adams S, Braidy N, Bessede A, et al. The kynurenine pathway in brain tumor pathogenesis. Cancer Res. 2012;72:5649–57.
3. Liebij, J. Über Kynurensäure. Justus Liebigs Ann Chem. 1853;86:125–6.
4. Alt A, Weiss B, Ogden AM, et al. Pharmacological characterization of glutamate agonists and antagonists at recombinant human homoceric and heteroceric kainate receptors in vitro. Neuropharmacology. 2004;46:793–806.
5. Ganong AH, Cottam CW. Kynurenic acid and quinolinic acid act at N-methyl-D-aspartate receptors in the rat hippocampus. J Pharmacol Exp Ther. 1986;236:293–9.
6. Kemp JA, Foster AC, Leeson PD, et al. 7-Chlorokynurenic acid is a selective antagonist at the glycine modulatory site of the N-methyl-D-aspartate receptor complex. Proc Natl Acad Sci U S A. 1988;85:6547–50.
7. Kessler M, Terramani T, Lynch G, Baudry M. A glycine site associated with antagonists at the glycine modulatory site of NMDA receptors: characterization and identification of a new class of antagonists. J Neurochem. 1989;52:1319–28.
8. Mok MH, Fricker AC, Weil A, Kew JN. Electrophysiological characterisation of the actions of kynurenic acid at ligand-gated ion channels. Neuropharmacology. 2009;57:242–9.
9. Turski WA, Nakamura M, Todd WP, Carpenter BK, WhetSELL WO Jr, Schwarz R. Identification and quantification of kynurenic acid in human brain tissue. Brain Res. 1988;454:164–9.
10. Moroni F, Russi P, Lombardi G, Beni M, Carla V. Presence of kynurenic acid in the mammalian brain. J Neurochem. 1988;51:177–80.
11. Hilmås C, Pereira EF, Alkondon M, Rassoulpour A, Schwarz R, Albuquerque EX. The brain metabolite kynurenic acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications. J Neurosci. 2001;21:7463–73.
12. Wang J, Simonavičius N, Wu X, et al. Kynurenic acid as a ligand for orphan G protein-coupled receptor GPR35. J Biol Chem. 2006;281:22021–8.
13. Albuquerque EX, Schwarz R. Kynurenic acid as an antagonist of alpha7 nicotinic acetylcholine receptors in the brain: facts and challenges. Biochem Pharmacol. 2013;85:1027–32.
14. Szalardy L, Zadori D, Toldi J, Fulop F, Kliviényi P, Vecsei L. Manipulating kynurenic acid levels in the brain—the on the edge between neuroprotection and cognitive dysfunction. Curr Top Med Chem. 2012;12:1797–806.
15. Moroni F, Cozzi A, Sili M, Mannaioui G. Kynurenic acid: a metabolite with multiple actions and multiple targets in brain and periphery. J Neural Transm. 2012;119:133–9.
16. Scharfman HE, Goodman JH, Schwarz R. Electrophysiological effects of exogenous and endogenous kynurenic acid in the rat brain: studies in vivo and in vitro. Amino Acids. 2000;19:283–97.
17. Wonodi I, Schwarz R. Cortical kynurenine pathway metabolism: a novel target for cognitive enhancement in Schizophrenia. Schizophr Bull. 2010;36:211–8.
18. Vamos E, Pardutz A, Kliviényi P, Toldi J, Vecsei L. The role of kynurenines in disorders of the central nervous system: possibilities for neuroprotection. J Neurol Sci. 2009;283:21–7.
19. Erhardt S, Olsson SK, Engberg G. Pharmacological manipulation of kynurenic acid: potential in the treatment of psychiatric disorders. CNS Drugs. 2009;23:91–101.
20. Hiratsuka C, Fukuvatari T, Shibata K. Fate of dietary tryptophan in young Japanese women. Int J Tryptophan Res. 2012;5:33–47.
21. Zhao J, Chen H, Ni P, et al. Simultaneous determination of urinary tryptophan, tryptophan-related metabolites and creatinine by high performance liquid chromatography with ultraviolet and fluorometric detection. J Chromatogr B Analyt Technol Biomed Life Sci. 2011;879:2720–5.
22. Crow B, Bishop M, Paliakov E, Norton D, George J, Bralley JA. Analysis of urinary aromatic acids by liquid chromatography tandem mass spectrometry. Biomed Chromatogr. 2008;22:1346–53.
23. Milart P, Sikorski R. Kynurenic acid concentration in blood and urine during normal pregnancy. Ginekol Pol. 1998;69:968–73.
24. Furlanetto S, Tognini C, Carpenedo R, La PE, Pinzaüti S. Set-up and validation of an adsorptive stripping voltammetric method for kynurenic acid determination in human urine. J Pharm Biomed Anal. 1998;18:67–73.
25. Mawatari K, Iinuma F, Watanabe M. Fluorometric determination of urinary kynurenic acid by flow injection analysis equipped with a “bypass line”. Anal Biochem. 1990;190:88–91.
26. Leklem JE. Quantitative aspects of tryptophan metabolism in humans and other species: a review. Am J Clin Nutr. 1971;24:659–72.
27. Parada-Turski J, Rzeski W, Zgrajka W, Majdan M, Kandefer-Szerszen M, Turski W. Kynurenic acid, an endogenous constituent of rheumatoid arthritis synovial fluid, inhibits proliferation of synoviocytes in vitro. Rheumatol Int. 2006;26:422–6.
28. Milart P, Urbanska EM, Turski WA, Paszkowski T, Sikorski R. Intrapartum levels of endogenous glutamate antagonist—kynurenic acid in amniotic fluid, umbilical and maternal blood. Neurosci Res Com. 1999;24:173–8.
29. Kuc D, Zgrajka W, Parada-Turska J, Urbank-Sypniewska T, Turski WA. Micromolar concentration of kynurenic acid in rat small intestine. Amino Acids. 2008;35:503–12.
30. Pawlak D, Tankiewicz A, Matys T, Buczko W. Peripheral distribution of kynurenine metabolites and activity of kynurenic pathway enzymes in renal failure. J Physiol Pharmacol. 2003;54:175–89.
31. Turski MP, Turska M, Zgrajka W, Kuc D, Turski WA. Presence of kynurenic acid in food and honeybee products. Amino Acids. 2009;36:75–80.
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53. ElTahir KEH, Bakheet BM. Kynurenic acid as an additional endogenous anti-aggregatory factor. *Satdhi Pharmaceut J.* 2007;15:135–9.

54. Jaen JC, Laborde E, Busch RA, et al. Kynurenic acid derivatives inhibit the binding of nerve growth factor (NGF) to the low-affinity p75 NGF receptor. *J Med Chem.* 1995;38:4439–45.

55. Jaech D, Urbanska EM, Guidetti P, et al. Dysfunction of brain kynurenic acid metabolism in Huntington’s disease: focus on kynurenic acidaminotransferases. *J Neurol Sci.* 1995;130:39–47.

56. Baran H, Cairns N, Lubec G. Increased kynurenic acid levels and decreased brain kynurenic acid transferase I in patients with Down syndrome. *Life Sci.* 1996;58:1891–9.

57. Miranda AF, Boegman RJ, Beninger RJ, Jhamandas K. Protection against quinolinic acid-mediated excitotoxicity in nigrostriatal dopaminergic neurons by endogenous kynurenic acid. *Neuroscience.* 1997;78:967–75.

58. Cannazza G, Chiarugi A, Parenti C, Zanoli P, Baraldi M. Changes in kynurenic, antranillic, and quinolinic acid concentrations in rat brain tissue during development. *Neurosom Res.* 2001;26:511–4.

59. Erhardt S, Oberg H, Engberg G. Pharmacologically elevated levels of endogenous kynurenic acid prevent nicotine-induced activation of nigral dopaminergic neurones. *Naunyn Schmiedebergs Arch Pharmacol.* 2001;363:21–7.

60. Richter A, Loscher W, Baran H, Gramer M. Increased levels of kynurenic acid in brains of genetically dystonic hamsters. *Brain Res Dev Brain Res.* 1996;92:111–6.

61. Salvati P, Umar G, Dhlo L, et al. Brain concentrations of kynurenic acid after a systemic neuroprotective dose in the gerbil model of global ischemia. *Prog Neuropscyhoparmacol Biol Psychiatry.* 1999;23:741–52.

62. Amirkhani A, Heldin E, Markides KE, Bergquist J. Quantitation of tryptophan, kynurenic acid and kynurenic acid in human plasma by capillary liquid chromatography-electrospray ionization tandem mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci.* 2002;780:381–7.

63. Illezaki J, Kokki T, Stelmaszak Z, Turski WA. Endogenous protectant kynurenic acid in amyotrophic lateral sclerosis. *Acta Neurol Scand.* 2003;107:412–8.

64. Kepplinger B, Baran H, Kainz A, Ferraz-Leite H, Newcombe J, Kalina P. Age-related increase of kynurenic acid in human cerebrospinal fluid—IgG and beta2-microglobulin changes. *Neurosignals.* 2005;14:126–35.

65. Hartai Z, Klivenyi P, Janaky T, Penke B, Dux L, Vecsei L. Kynurenic metabolism in plasma and in red blood cells in Parkinson’s disease. *J Neurol Sci.* 2005;239:31–5.

66. Urbanska EM, Luchowski P, Luchowska E, et al. Serum kynurenic acid positively correlates with cardiovascular disease risk factor, homocysteine: a study in stroke patients. *Pharmacol Rep.* 2006;58:507–11.

67. Jaech DA, Sethy VH, Weick BG, Chase TN, Schwarz R. Intravenous administration of L-kynurenine to rhesus monkeys: effect on quinolinate and kynurenic bases in serum and cerebrospinal fluid. *Neuropharmacology.* 1993;32:467–72.

68. Moroni F, Rusi P, Karri V, Lombardi G. Kynurenic acid is present in the rat brain and its content increases during development and aging processes. *Neurosci Lett.* 1989;94:145–50.

69. Swartz KJ, Matson WR, MacGarvey U, Ryan EA, Beal MF. Measurement of kynurenic acid in mammalian brain extracts and cerebrospinal fluid by high-performance liquid chromatography with fluorometric and coulometric electrode array detection. *Anal Biochem.* 1990;185:363–76.

70. Rejdak K, Bartosik-Psujek H, Dobosz B, et al. Decreased level of kynurenic acid in cerebrospinal fluid of relapsing-onset multiple sclerosis patients. *Neurosci Lett.* 2002;321:63–5.

71. Erhardt S, Schwieler L, Engberg G. Kynurenic acid and schizophrenia. *Adv Exp Med Biol.* 2003;527:155–65.

72. Nilsson LK, Linderholm KR, Engberg G, et al. Elevated levels of kynurenic acid metabolism in Huntington’s disease: focus on kynurenine aminotransferase I in patients with Down syndrome. *J Med Chem.* 2005;48:111–9.

73. Yamamoto H, Murakami H, Horiguchi K, Egawa B. Studies on cerebrospinal fluid kynurenic acid and 2,3-dioxygenase activation in a male cohort. *Adv Exp Med Biol.* 1989;254:365–72.

74. Paluszkiewicz P, Zgrajka W, Saran T, et al. High concentration of kynurenic acid in human bile and pancreatic juice. *Am J Clin Nutr.* 2002:72:409–15.

75. Boron WF, Boulaop EL. Medical Physiology: A Cellular And Molecular Approach. Philadelphia, PA: Elsevier/Saunders; 2005.

76. Zgraja W, Turski M, Rajter G, Majdan M, Parada-Turska J. Kynurenic acid content in antihemuric herbs. *Ann Agric Environ Med.* 2013; accepted.