Why eating star fruit is prohibited for patients with chronic kidney disease?

Authors
Eduarda Savino Moreira de Oliveira[1]
Aline Silva de Aguiar[1]

[1] Universidade Federal de Juiz de Fora.

Abstract

New studies have shown the mechanism by which the star fruit (*Averrhoa carambola*) becomes toxic to individuals with chronic kidney disease (CKD). The aim of this study was to review the current literature on the topic. This is a review article, with publications from 2000 to 2014 available in scientific database. There are reports that neurotoxicity is due to the presence of oxalate in star fruit, but recent findings show that the neurotoxic effect of the toxin is by caramboxin, which appears to inhibit the GABAergic system which is the major inhibitory system in the central nervous system (CNS), involving changes as sobs and confusion, to more serious conditions such as seizures and death. It is important to multidisciplinary action to alert patients with CKD as the prohibition of the star fruit consumption.

Keywords: food; kidney; neurotoxins; nutritional sciences.

Introduction

Carambola (Averrhoa Starfruit) belongs to the oxalidacea family of fruits. It is a fruit found in tropical regions, originally from Asia.[1,2] Cross-sectional slices have the star shape that gives it its name in English literature: "starfruit". It can be yellow or greenish with flavors ranging from bitter to sweet[1].

The scientific literature has papers published, discussing the toxic effects of carambola. However, the first Brazilian report of these effects was published in 1993[3] and by 2013 we were still unsure of the toxic effects of eating such fruit.[4] Carambola has a neurotoxin capable of causing neurological disorders in patients with Chronic Kidney Disease (CKD), involving changes such as hiccups and mental confusion to severe conditions such as seizures and death.[2,4] This neurotoxin seems to inhibit the GABAergic system,[3] which is the main inhibitory system of the central nervous system (CNS), formed by neurons containing gamma-aminobutyric acid (GABA). The cell membranes of most CNS neurons and astrocytes express GABA receptors, which decrease neuronal excitability via a variety of mechanisms. Because of its widespread distribution, GABA receptors influence many neural circuits and functions.[5]

However, new studies have been carried out to clarify the mechanism by which carambola becomes toxic to individuals with CKD; thus justifying this review paper to discuss and disclose new evidence on the subject. It is important that healthcare professionals know the real effects and mechanisms by which carambola can be lethal to patients in this clinical situation.

The objective of this study was to conduct a review of the toxic effects of starfruit in patients with CKD; given that the fruit-induced neurotoxicity has been reported both in patients undergoing dialysis and in patients not requiring it.

Submitted on: 06/20/2014.
Approved on: 03/09/2015.

Correspondence to:
Aline Silva de Aguiar Nemer.
Universidade Federal de Juiz de Fora (UFJF)/Instituto de Ciências Biológicas (ICB) - Departamento de Nutrição.
Cidade Universitária, São Pedro, Juiz de Fora, MG.
CEP: 36036-900.
E-mail: aline.nemer@ufjf.edu.br
Tel: + 55 (32) 2102-3234.

DOI: 10.5935/0101-2800.20150037

Methods

This is a systematic review containing papers published between the years 2000 and 2014, on the influence of star fruit intake for patients with CKD. The inclusion and exclusion criteria of the papers were previously established. Eligibility criteria encompassed: review papers, case reports and research papers published in Portuguese and English. Exclusion criteria were: papers discussing carambola cultivation, use of starfruit in other diseases, studies with children; treatment and therapeutic approach in poisoning. In addition to these, we also excluded studies not available through the Internet and those that were not in Portuguese or English.

We consulted the following databases: Latin American and Caribbean Health Sciences (LILACS), International Literature on Health Sciences (PubMed), Scientific Electronic Library Online (SciELO) and Google Scholar. We defined keywords by consulting Descriptors in Health Sciences (DeCS). We crossed keywords over such as: starfruit, intoxication; kidney; chronic kidney diseases and neurotoxic, in English; and carambola; intoxicação; rins; doença renal crônica e neurotoxina in Portuguese. We selected 56 papers and excluded 24 duplicate papers. After employing the inclusion criteria 20 papers were excluded, because they addressed the carambola crop (n = 3), use of carambola in other diseases (n = 1), study with children (n = 1), treatment and therapeutic approach in intoxication (n = 7); restricted access through the Internet (n = 7) and not being in Portuguese or English (n = 1). Thus, 13 papers were selected to make up this study. Seven references did not fit the inclusion criteria, but were used for the description of concepts and etiology.

Results

Most of the studies included (67%, n = 8) referred to report cases involving individuals of both genders, two of the papers included are review papers (16%, n = 2) and 25% (n = 3) are Experimental studies in rodents.

Of the 110 patients reported in the study, 75.45% (n = 83) survived and 24.55% (n = 27) died after showing clinical symptoms after consuming carambola, and hiccups and confusion were the most reported symptoms.

Case reports

From the first report of neurotoxicity by carambola in 1980, when the star fruit extract was intraperitoneally injected into normal mice resulting in seizures, there were case reports of neurotoxicity in patients who had eaten the fruit. From there, it was thought that an excitatory neurotoxin was responsible for those symptoms, but still of unknown nature.[3]

The first neurotoxicity outbreak of carambola in uremic patients was described in 1993, when eight patients developed hiccups after eating carambola.[6] In 2002, there were papers reinforcing this correlation between carambola and neurotoxicity.[6,7] Following studies showed that both patients with CKD undergoing dialysis and patients not requiring dialysis developed symptoms of carambola poisoning,[6] and it was reported that the ingestion of carambola causes decline in kidney function regardless of disease stage.[8] More recently, in 2010, other studies also with patients not requiring dialysis, strengthened the idea that there is a poor correlation between the degree of underlying renal function and mortality rate by carambola poisoning; and consumption of the fruit causes rapid deterioration of renal function and death, suggesting the seizure effect of this neurotoxin in the fruit.[3,9]

Hiccups were the most frequently reported symptom presented by the intoxicated patients, often uncontrollable and unresponsive to conventional medications, mental confusion and seizures (Table 1). Seizures are significantly associated with poor patient prognosis.[10]

Only three papers reported cases of persons (n = 7) who, despite having normal kidney function, had symptoms of poisoning after ingesting carambola[11,12] and acute kidney failure.[13] According to Neto *et al.*, Five patients

Table 1 Summary of the cases of carambola-induced intoxication cases

Author	Tempo	Number of patients	Gender	Age	Chronic Kidney Disease (CKD) stage	Dose ingested	Symptoms	Mean time to symptom onset	Results
Chang *et al.*,[14] 2002	10 days	1	M	64	CKD without the need for dialysis	2 carambolas	Back pain, hiccups, nausea, vomit, confusion and agitation	1 day	Improvement after dialysis
Wu *et al.*,[7] 2002	5 days	2	M & F	62 & 75	CKD without the need for dialysis	4 pieces of carambola sweet	Hiccups and altered conscience	12 hours,8 hours	Improvement after dialysis
Tse *et al.*,[6] 2003	10 months	7	M (5) & F (2)	Between 39 and 77	CKD under dialysis (5) and without the need for dialysis (2)	-	Acute confusion and hypercalcemia (4). Ventilatory support (1). Mild symptoms (2).	8 hours	Spontaneous recovery (2). Improvement after dialysis (5).
Hung *et al.*,[8] 2004	5 days	1	F	65	CKD without the need for dialysis	1 carambola	Vomit, hiccups, diarrhea and numbness on lower limbs, progressing to epilepsy.	2 hours	Hemodialysis was carried out but the patient died.
Tsai *et al.*,[10] 2005	7 days and 23 days	2	M & F	84 & 74	CKD without the need for dialysis	3 fruits in three days and 3 fruits in two days.	Hiccups, vomits, confusion and agitation, developing epilepsy.	-	Despite hemodialysis, the patients died.
Neto *et al.*,[11] 2009	-	5	M (4) F (1)	Between 34 and 67	Prior normal kidney function	15 fruits in 7 hours, 1 liter of juice in 3 hours, 1.5 liters of juice in 3 hours, 12 fruits in 1 hour and 300 ml of juice in 30 minutes in an empty stomach.	All the patients had hiccups, back pain, vomits, insomnia and acute renal failure (4).	3-8 hours	Improvement without the need for dialysis.
Martins *et al.*,[9] 2010	5 days	1	F	53	CKD without the need for dialysis	Carambola juice	Nausea, vomits, hiccups, confusion, agitation, seizures, dyspnea and tachypnea.	2 days	Despite hemodialysis, the patient died.
Moreira *et al.*, 2010	4 days	1	M	56	CKD without the need for dialysis	4 carambolas	Malaise, headache, nausea, vomit, followed by seizures.	24 hours	Despite hemodialysis, the patient died.
Yamamoto *et al.*,[12] 2011	31 days	1	M	59	Prior normal kidney function	30 ml of oolong tea mixed with oxalic acid.	Sore throat, tachypnea, heartburn, nausea, acute kidney failure and metabolic acidosis.	4 hours	There was improvement after hemodialysis.
Scaranello *et al.*,[13] 2014		1	F	44	Previous normal kidney function	30 carambolas + juice from 20 carambolas	Diarrhea for 4 days, followed by nausea, vomit, abdominal pain in colic and low urinary volume	24 hours	Improvement after two hemodialysis sessions

M: Male; F: Female.

with normal renal function showed symptoms of hiccups, back pain, insomnia and vomiting after eating the fruit. According to the authors, the amount of carambola intake per person varied, the highest amount was 15 fresh fruits and the lowest amount was 300 ml of juice, but with an empty stomach. This study showed that the ingestion of large amounts of starfruit as well as a small amount on an empty stomach, may cause acute renal failure, formation of oxalate crystals and neurotoxicity, because of the oxalate present in the fruit.[11] Other studies reinforce this issue, reporting that patients with normal renal function had acute kidney failure after drinking tea containing oxalic acid (30 ml of oolong tea)[12] or the very fresh fruit or its juice (30 carambola + juice from 20 fruits)[13]. The two cases reported showed improvement after treatment with hemodialysis sessions.[7,14]

Review paper

The two review papers included in this study discuss case reports on clinical symptoms after CKD patients consumed carambola (Table 2). The authors reported that this neurotoxin has a seizure-causing effect and that the epileptic bout is significantly associated with poor patient prognosis.[6,10]

The oxalate present in the fruit has been mentioned as a possible candidate to cause acute nephropathy and neurotoxicity.[10] According to the review papers, carambola should be avoided because of the complications it causes in CKD patients.[6,10]

Experimental studies

Three experimental studies were selected to compose this paper. The studies were carried out in Wistar and Sprague Dawley rodents, and showed that carambola intake is associated with acute kidney injury and neurotoxicity in patients with CKD (Table 3).

In 2001, Fang *et al.*[15] correlated the high level of oxalate in carambola with the development of acute nephropathy in rats. In 2008, they reproduced the neurological disorders found in patients intoxicated by carambola in nephrectomized rats fed with this fruit extract containing naturally 0.2M oxalate, and groups fed with 0.2M or 0.4M of oxalate solution being administered by gavage at a dose of 2 ml/100 g of body weight.[16] This study clearly showed the role of oxalate in the onset of neurotoxicity, to be noted that those two groups had acute renal injury because of the obstructive effect of the calcium oxalate crystals and apoptosis induced by the kidney epithelial cells.[16]

In a recent study published in 2013, they discovered a toxin that would be responsible for the neurotoxic effects of carambola. In that study the authors isolated the neurotoxin present in the fruit that acts specifically by inhibiting the GABAergic system. The researchers named the neurotoxin: caramboxin, a non-protein molecule, different from oxalate. When mixed with water and stored at room temperature, caramboxin undergoes a reaction that inactivates it. In that study, they ran tests with crude carambola extract in Wistar rats. The crude carambola extract from the fresh fruit was given via gavage to the mice to induce acute kidney injury, and then, the lyophilized crude carambola extract (20 mg/ml) and caramboxin (0.1 mg/ml) solubilized in saline was administered via Intracerebral injection, causing seizures and even deaths.[4]

Discussion

Star fruit intake can be fatal for patients with CKD because it contains a neurotoxin that is not properly eliminated by the kidneys. In patients without nephropathy, the neurotoxin present in carambola is absorbed, distributed and excreted by the kidney, without compromising the body. In CKD patients, the neurotoxin is not properly excreted, its serum levels are elevated, which would allow its passage through the blood-brain barrier and consequent action on the CNS.[2,3,17]

Some studies show that the fruit's neurotoxicity is due to the oxalate action; however, recent findings show that the neurotoxic effect is not only related to the high content of oxalate,

Table 2 Systematic literature review

Author	Objective	Time	Number of patients	Age	Dosage ingested	Symptoms	Treatment	Outcome/ survival
Tse *et al.*,[6] 2003	Report cases of carambola intoxication and discuss evidence for the possibility of neurotoxin.	Papers from 1993, 1998, 2000 and 2001.	35	-	-	Hiccups, vomit, confusion, weakness, dyspnea, insomnia, paresthesia.	Dialysis (34) and without the need for dialysis (1).	Of the 35 patients, 9 died.
Tsai *et al.*,[10] 2005	Clear the relationship between seizures and neurotoxicity and carambola. Check to see whether mortality is associated with	Between 1967 and February of 2005	53	Between39 and 84	Between 300 mL of juice to 4 fruits	Confusion, agitation, hiccups, vomit, paresthesia, headache, insomnia. Epileptic bouts (16).	Dialysis and anti-epileptic drugs.	Among the 16 patients who had epileptic bolts, 12 died.

Table 3 Main results found by the experimental studies that assessed the effects of carambola ingestion in chronic kidney disease (CKD)

Author	Lineage	N	Time (days)	Study goals	Methodology	Results
Fang *et al.*,[15] 2001	Sprague-Dawley male rats	Four groups with 6 to 9 rats (control group, experimental, fasting and water restriction).	5	Establish a connection between the star fruit and acute nephropathy by oxalate, and investigate factors that predispose for its development.	4 mL/100 g of body weight of bitter star fruit juice with 2.46 g/dL of oxalate, about 1 g/kg.	The experimental group had high levels of serum creatinine and calcium oxalate crystals in the kidney. The star fruit, because of the grade of oxalate, may cause acute nephropathy during fasting and water restriction.
Fang *et al.*,[16] 2008	Sprague-Dawley Male rats	Four groups of 8 rats (control group, star fruit group, and two oxalate groups).	-	Investigate the mechanisms through which the star fruit may cause acute nephropathy by oxalate, study the nephrotoxic effect of the star fruit.	Star fruit group: star fruit juice with 0.2 M of oxalate. Oxalate group: 0.2 M or 0.4 M of oxalate solution. The solutions were administered by gavage, at a dose of 2 mL/100 g of body weight.	Star fruit juice, or an oxalate solution induces apoptosis of kidney epithelial cells, calcium oxalate crystals, and acute kidney lesion, which may be caused by the content of oxalate in the fruit.
Garcia-Cairasco *et al.*,[4] 2013	Wistar rats	14-30	30	Identify the star fruit toxin and draw attention to the dangers of CKD patients ingesting it.	Star fruit extract, given by gavage to induce acute kidney lesion and star fruit freeze-dried extract (20 mg/mL) and caramboxin 0.1 mg/mL) solubilized in saline solution injected in the brain.	Intracerebral caramboxin microinjection induced epilepsy, confirming its neurotoxic effect.

but to a toxin found in it, called caramboxin, ruling out the hypothesis that the neurotoxicity is caused exclusively by the oxalate present in the fruit.[4] Moreover, a large oxalate content can also be found in spinach (180-730 mg/100 g) and in some types of cereals, including wheat bran (457 4 mg/100 g).[17] However, to date, there are no reports that these foods are toxic to patients with CKD.

The carambola toxin has an excitatory, seizure-causing and neurodegenerative action.[4] This toxin seems to specifically inhibit the GABAergic signaling system.[3] Of the two major classes of neuroactive amino acids, GABA is the major inhibitory amino acid of the CNS, while glutamate It is the main excitatory amino acid.[5]

Caramboxin slightly inhibits glutamate uptake by the high affinity transporters present in astrocytes adjacent to the synapse, and alters the binding of GABA to its receptors.[18] Furthermore, caramboxin acts on the main glutamate receptors involved in the mechanism of neuronal excitotoxicity, the amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) and N-methyl-D-aspartate (NMDA), are capable of activating it.[4] The AMPA receptor activation determines the influx of sodium ions in the postsynaptic neuron, facilitating neuronal depolarization. This facilitates the entry of calcium ions into the postsynaptic neuron, through specific channels, and also by glutamate acting on the NMDA receptor. Excessive concentrations of glutamate in the synaptic cleft result in overstimulation of receptors and excessive influx of calcium ions into the postsynaptic terminal, activating the intracellular mechanisms of excitotoxicity, culminating in neuronal death.[5,19,20]

High amounts of this ion in the intracellular space, result in the activation of a variety of intracellular enzymes, such as phospholipases, endonucleases, proteases and nitric-oxide synthetase, which during prolonged seizure activity cause the uncoupling of oxidative phosphorylation, a direct lesion to the cell skeleton, besides the formation of free radicals that accelerate this process. The injured neuron releases more glutamate into the extracellular space, facilitating the injury of neighboring neurons.[21] These effects may explain the ability of caramboxin to induce seizures and may be considered a relevant neurotoxin in the onset and evolution of intoxication.

When CKD patients ingest the fruit or its juice, caramboxin can induce bouts of hiccups, vomiting, mental confusion, agitation, prolonged seizures and even death. The chemical structure of caramboxin was elucidated: a non proteinogenic amino acid whose molecular formula is C11H13NO6 + H, with a molecular weight of 256.08 u.[4]

Although the incidence of a person without CKD history feel sick after eating star fruit is small, it does not mean that they are not under risk. Two studies in this review showed that the high oxalic acid content present in carambola may, eventually, produce acute renal failure, kidney stones and neurotoxicity in sensitive individuals. Therefore, the fruit should be avoided.[11,12]

In this paper we noticed a quantitative shortage of studies investigating the relationship between starfruit consumption and intoxication in CKD patients. However, using current data (71.42% posted in the last 10 years), this review helps educate healthcare professionals about the risks that their patients are under upon eating carambola. Therefore, healthcare professionals should be attentive to warn patients with CKD that carambola should be excluded from their diets.

Conclusion

Studies have found an association between consumption of carambola and intoxication. The fruit has a toxic substance called caramboxin, which is the main factor responsible for the effects hereby described. So it is important to warn patients with CKD not to eat carambola. This warning role should be taken over mainly

by nutritionists, but also by all those involved in patient care. In addition, it is recommended that persons with normal renal function should also avoid ingesting the fruit, both in the form of juice or fresh.

References

1. Prati P, Nogueira JN, Dias CTS. Avaliação de carambola (Averrhoa carambola L.) dos tipos doce e ácido para o processamento de fruta em calda. Bol Centro Pesqui Process Aliment 2002;20:221-46.
2. Cuppari L, Avesani CM, Kamimura MA. Terapia nutricional da doença renal crônica. In: Cuppari L, Avesanni CM, Kamimura MA. Nutrição na doença renal crônica. Barueri: Manole; 2013.
3. Martin LC, Caramori JST, Barretti P, Soares VA. Soluço intratável desencadeado por ingestão de carambola ("Averrhoa carambola") em portadores de insuficiência renal crônica. J Bras Nefrol 1993;15:92-4.
4. Garcia-Cairasco N, Moyses-Neto M, Del Vecchio F, Oliveira JA, dos Santos FL, Castro OW, et al. Elucidating the neurotoxicity of the star fruit. Angew Chem Int Ed Engl 2013;52:13067-70. DOI: http://dx.doi.org/10.1002/anie.201305382
5. Forman SA, Chou J, Strichartz GR, Lo EH. Farmacologia da Neurotransmissão GABAérgica e Glutamatérgica. In: Golan DE, Tashjian AH, Armstrong EJ, Armstrong AW. Princípios da farmacologia: a base fisiopatológica da farmacoterapia. 2a ed. Rio de Janeiro: Guanabara Koogan; 2009. p.148-65.
6. Tse KC, Yip PS, Lam MF, Choy BY, Li FK, Lui SL, et al. Star fruit intoxication in uraemic patients: case series and review of the literature. Intern Med J 2003;33:314-6. DOI: http://dx.doi.org/10.1046/j.1445-5994.2003.00402.x
7. Wu CC, Denq JC, Tsai WS, Lin SH. Star fruit-induced neurotoxicity in two patients with chronic renal failure. J Med Sci 2002;22:75-8.
8. Hung SW, Lin ACM, Chong CF, Wang TL, Ma HP. Fatal outcome after star fruit (averrhoa carambola) ingestion in patient with chronic renal insufficiency. Ann Disaster Med 2004; 3:56-9.
9. Auxiliadora-Martins M, Alkmin Teixeira GC, da Silva GS, Viana JM, Nicolini EA, Martins-Filho OA, et al. Severe encephalopathy after ingestion of star fruit juice in a patient with chronic renal failure admitted to the intensive care unit. Heart Lung 2010;39:448-52. DOI:http://dx.doi.org/10.1016/j.hrtlng.2009.09.003
10. Tsai MH, Chang WN, Lui CC, Chung KJ, Hsu KT, Huang CR, et al. Status epilepticus induced by star fruit intoxication in patients with chronic renal disease. Seizure 2005;14:521-25. DOI: http://dx.doi.org/10.1016/j.seizure.2005.08.004
11. Neto MM, Silva GEB, Costa RS, Neto OMV, Cairasco NG, Lopes NP, et al. Star fruit: simultaneous neurotoxic and nephrotoxic effects in people with previously normal renal function. Nephrol Dial Transplant 2009;2:485-8. DOI: http://dx.doi.org/10.1093/ndtplus/sfp108
12. Yamamoto R, Morita S, Aoki H, Nakagawa Y, Yamamoto I, Inokuchi S. Acute renal failure and metabolic acidosis due to oxalic acid intoxication: a case report. Tokai J Exp Clin Med 2011;36:116-9. PMID: 22167493
13. Scaranello KL, Alvares VR, Carneiro DM, Barros FH, Gentil TM, Thomaz MJ, et al. Star fruit as a cause of acute kidney injury. J Bras Nefrol 2014;36:246-9. DOI: http://dx.doi.org/10.5935/0101-2800.20140036
14. Chang CT, Chen YC, Fang JT, Huang CC. Star fruit (Averrhoa carambola) intoxication: an important cause of consciousness disturbance in patients with renal failure. Ren Fail 2002;24:379-82. DOI: http://dx.doi.org/10.1081/JDI-120005373
15. Fang HC, Chen CL, Wang JS, Chou KJ, Chiou YS, Lee PT, et al. Acute oxalate nephropathy induced by star fruit in rats. Am J Kidney Dis 2001;38:876-80. PMID: 11576894 DOI: http://dx.doi.org/10.1053/ajkd.2001.27710
16. Fang HC, Lee PT, Lu PJ, Chen CL, Chang TY, Hsu CY, et al. Mechanisms of star fruit-induced acute renal failure. Food Chem Toxicol 2008;46:1744-52. DOI: http://dx.doi.org/10.1016/j.fct.2008.01.016
17. Moysés Neto M. Star fruit as a cause of acute kidney injury: a case report. J Bras Nefrol 2014;36:118-20. DOI: http://dx.doi.org/10.5935/0101-2800.20140019
18. Resumos de Dissertações de Mestrado e Teses de Doutorado apresentadas na FMRP-USP [editorial]. Medicina (Ribeirão Preto). 2006;39:604-58.
19. Casella EB, Mângia CMF. Abordagem da crise convulsiva aguda e estado de mal epiléptico em crianças. J Pediatr (Rio J) 1999;75:197-206. DOI:http://dx.doi.org/10.2223/JPED.389
20. Ruggiero RN, Bueno-Júnior LS, Ross JB, Fachim HA, Padovan-Neto FE, Merlo S, et al. Neurotransmissão glutamatérgica e plasticidade sináptica: aspectos moleculares, clínicos e filogenéticos. Medicina (Ribeirão Preto) 2011;44:143-56. DOI: http://dx.doi.org/10.11606/issn.2176-7262.v44i2p143-156
21. Benevides CMJ, Souza MV, Souza RDB, Lopes MV. Fatores antinutricionais de alimentos: revisão. Segur Aliment Nutr. 2011;118:67-79.