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ORIGINAL PAPER

Food-mediated exposure of Hofmeister ions in *Oryza sativa* (Rice) from selected CKDu endemic regions in Sri Lanka

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Abstract The objectives of this study were to determine selected Hofmeister anions and cations that are important for kidney health, in raw rice samples from selected Chronic Kidney Disease of unknown etiology (CKDu) endemic and non-endemic areas in Sri Lanka and their intake. The anions and cations were analyzed by Ion Chromatography and Microwave Plasma Atomic Emission Spectrometry (MP-AES), respectively, after alkaline and acid digestion in thirty raw rice samples each from CKDu endemic and non-endemic areas, and the dietary intake was estimated. The mean concentrations of fluoride (F^-), chloride (Cl^-), phosphate (PO_4^{3-}), sulfate (SO_4^{2-}), sodium (Na^+), magnesium (Mg^{2+}), potassium (K^+), and calcium (Ca^{2+}) in raw rice in CKDu endemic areas were 53.317, 1515.3, 2799.6, 2704.9, 30.603, 300.76, 1001.3, and 90.075 mg/kg, respectively. The mean concentration of the anions and cations in raw rice from CKDu non-endemic areas were 22.850, 947.52, 4418.7, 6080.2, 23.862, 364.45, 955.78, and 96.780 mg/kg, respectively. Significantly higher differences ($p < 0.05$) were reported in the mean concentration of F^-, Cl^-, and Na^+ in raw rice from CKDu endemic areas in comparison with the samples from non-endemic areas. The aggregated estimated daily intake (EDI) and cumulative EDI of F^- via consumption of cooked non-traditional samba rice from CKDu endemic areas for adults were the highest (0.155 and 0.172 mg/kg bw/d, respectively), which were higher than the recommended tolerable upper intake value (0.15–0.2 mg/kg bw/d). In contrast, the traditional rice from CKDu non-endemic areas for adolescents, reported the lowest values (0.0210 and 0.0470 mg/kg bw/d, respectively). Adults who consume non-traditional samba rice from CKDu endemic areas were at health risk, while children were the most vulnerable group due to their low body weight. These results indicate that the consumption of rice rich in Hofmeister ions may contribute to the total intake and act as risk factors to negatively affect weak kidneys in CKDu endemic areas. Further research to analyze Hofmeister ions in cooked rice and rice from different countries is recommended.

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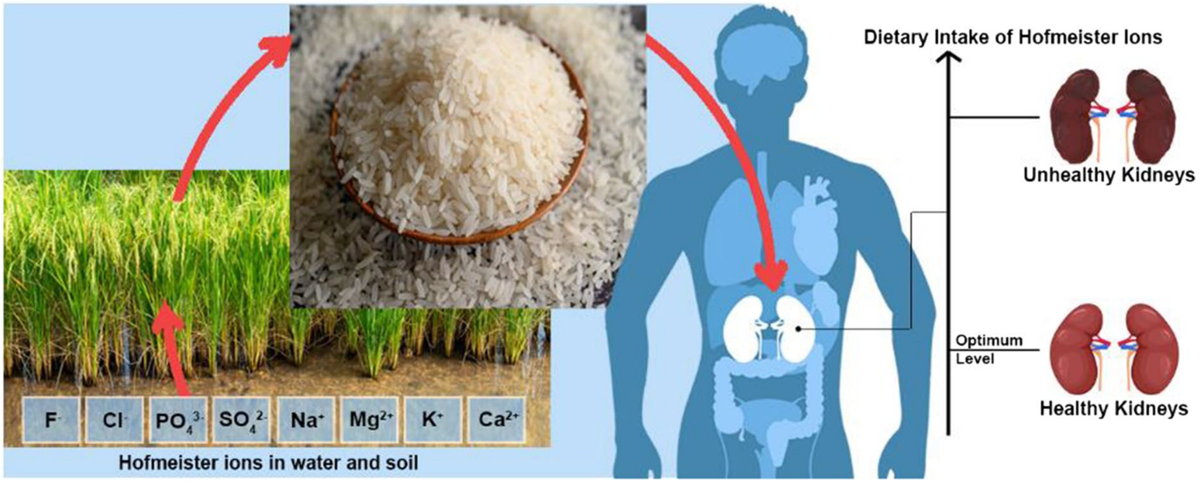
Graphical abstract



Keywords CKDu · Dietary intake · Estimated daily intake · Fluoride · Hofmeister ions · Rice

Introduction

Rice (*Oryza sativa*) is the main staple food in the Asian diet which contains essential nutrients including vitamins and minerals and provides a significant amount of calories. Globally, more than a thousand million people obtain their basic multiple nutrition requirements from rice and rice-associated foods (Mohidem et al., 2022; Zhao et al., 2020). The elements in water and soil can accumulate in rice grains and possess both beneficial and detrimental effects on human health. However, considering food security, high or low levels of specific ions in the food are a significant concern. Rice is particularly prone to accumulate different contaminants when grown in contaminated agricultural soils (Oliveira et al., 2012; TatahMentan et al., 2020). Accumulation of arsenic in rice grains poses a significant adverse effect on human health (TatahMentan et al., 2020; Watson & Gustave, 2022). In addition, 77.4% of the chronic cadmium intake for the residents in a mining area in China is a result of rice consumption (Song et al., 2017; Zhu et al., 2016). Therefore, unfortunately, communities with a bowl of rice as a staple food are more vulnerable to those toxic element exposures via their diet (Bielecka et al., 2020; Chandrasiri et al., 2022).

Throughout the last three decades, chronic kidney disease of unknown etiology (CKDu) emerged as an important attributer for chronic kidney diseases in many tropical and subtropical countries (Rajapakse et al., 2016). CKDu is predominant in Sri Lanka, Japan, India, Peninsula, Saudi Arabia, Egypt, and Central America (Hettithanthri et al., 2021; Pearce et al., 2019; Pett et al., 2022). Previous studies suggested etiologies for CKDu; however, the definitive reason is not identified yet. CKDu is identified among young men and occasionally women in the marginalized agricultural communities in Sri Lanka (Rajapakse et al., 2016). In 1994, the first case of CKDu was reported in Sri Lanka (Abeysekera et al., 1996). Since then CKDu has been a burden to the agricultural community in the island's dry zone, mainly in Anuradhapura and Polonnaruwa in the North Central province of Sri Lanka. Histopathological analysis of renal biopsies from CKDu patients in Sri Lanka, reveals a condition of interstitial nephritis, which occurs as a consequence of chronic or acute exposure to potential nephrotoxins (Pett et al., 2022). The CKDu prevalent areas show unique chemistry geographically as well as in water sources (Imbulana & Oguma, 2021). Therefore, CKDu in Sri Lanka appears to be caused by environmental factors (Imbulana & Oguma, 2021; Udeshani et al., 2022). Among many risk factors such as dehydration, long-term toxic exposure to heavy metals and agrochemicals, genetic predisposition, cyanotoxins, high F^- and hardness in drinking water, prolonged exposure to high ionicity via drinking water is considered one of the predominant risk factors for CKDu by Hofmeister-type protein denaturing mechanism in the kidney (Dharma-Wardana et al., 2015; Nanayakkara et al., 2020).

The Hofmeister series defines as the ions which have the ability to "salting in" and "salting out" of proteins which ultimately involves in protein stabilization in aqueous solutions (Kang et al., 2020). Therefore, these ions could potentially affect the function of the kidneys (Dharma-Wardana, 2018). A recent study by Liyanage et al. (2022) reveals that the F^-, Na^+, Mg^{2+} and hardness in groundwater in CKDu endemic areas were significantly higher than in the control areas. Furthermore, the high F^- levels and hardness of water with relation to CKDu has been comprehensively studied in previous literature (Cooray et al., 2019; Dharma-Wardana, 2018; Gobalarajah et al., 2020; Imbulana & Oguma, 2021). Consumption of tea brewed with fluoride-enriched groundwater is considered a factor that can enhance the human dietary intake of F^- and other Hofmeister ions (Chandrajith et al., 2022; Edussuriya et al., 2023). Apart from beverages, Hofmeister ions can enter the body via the edible plants that uptake Hofmeister ions from soil and water, plus cooking them using groundwater enriched with Hofmeister ions. Many studies have investigated the CKDu risk factors in groundwater in CKDu prevalent areas in Sri Lanka (Imbulana & Oguma, 2021; Shi et al., 2022; Zeng et al., 2022). Moreover, the recent study Sandanayake et al. (2023) studied the hydro-geochemistry of driking water in CKDu endemic Girandurukotte, Dehiattakandiya and CKDu non-endemic Sewanagala, Sri Lanka which are the same sampling areas studied in the current study. It unveiled the Hofmeister ion concentrations in groundwater and poor water quality in drinking water in the sampling areas. No studies have attempted to investigate the possible exposure to Hofmeister ions by rice consumption, which is the staple food in the country. A few studies have shown the F^- uptake in rice in fluoride-rich areas (Havale et al., 2022; Sawangjang & Takizawa, 2020, 2023), however; a lack of attention is diverted towards the Hofmeister ion concentrations and their enrichments by cooking with groundwater (Havale et al., 2022). It is essential to understand the overall health risk of consuming rice cultivated in the CKDu endemic areas from elevated dissolved ion exposure for weak kidneys in particular areas. Therefore, this study aims to evaluate the total selected Hofmeister ions; F^-, Cl^-, PO_4^{3-}, SO_4^{2-}, Na^+, Mg^{2+}, K^+, and Ca^{2+} concentrations of rice cultivated in both CKDu endemic and non-endemic areas in Sri Lanka and estimate the dietary intake and possible health risks to CKDu by rice consumption.

Materials and methodology

Samples collection

Thirty locally cultivated rice (*Oryza sativa*) samples were collected from CKDu endemic Dehiattakandiya and Girandurukotte areas in Sri Lanka. A total of thirty samples including 15 locally cultivated rice samples from CKDu non-endemic Sewanagala area in Sri Lanka, and locally cultivated 15 traditional rice varieties from other CKDu non-endemic areas in Sri Lanka, were acquired as control samples (Traditional rice varieties are native to Sri Lanka which are rich in nutrients and are recommended for the patients with non-communicable diseases). Sampling in Dehiattakandiya was held during the wet season (April) in 2021 while the sampling in Girandurukotte was held during both wet (February) and dry (August) seasons in 2020. The sampling of the control samples was held during the wet season (March) in 2021. By the time of sampling, the rice paddy fields had been treated with chemical fertilizers and pesticides which are commonly used in rice cultivation in the country. Further, flooded rice cultivation systems had been practised in both CKDu endemic and non-endemic areas. The collected rice samples were washed with ultrapure water, air-dried, and ground into fine powder to make them homogenized for analysis using a ceramic mortar and pestle. The mortar and pestle were cleaned with Ethanol (75%) after grinding of each sample. The details of the collected rice samples are summarized in Table 1.

Table 1 The details of the collected raw rice samples

	Sampling areas	Rice variety with sample number (*n*)
CKDu endemic areas	Dehiattakandiya (7° 33.1′ N to 7° 40.1′ N and 80° 59.8′ E to 81° 04.8′ E) Girandurukotte (7° 25.3′ N to 7° 33.1′ N and 80° 58.5′ E to 81° 03.5′ E)	Non-traditional Nadu rice ($n=18$) Non-traditional Samba rice ($n=07$) Non-traditional Red rice ($n=05$)
CKDu non-endemic areas	Sewanagala (6° 17.5′ N to 6° 24.1′ N and 80° 54.7′ E to 80° 59.9′ E)	Non-traditional Red rice ($n=15$)
	Other areas	Traditional rice ($n=15$)-Kuruluthuda, Duru wee, Maa wee, Batapolal, Kalu Heenati, Sudu Heenati, Rathu Heenati, Weda Heenati, Madathawalu, Pachchaperumal, Gonabaru, Suwandel, Keerinaran, Kahamaala, Kahawanu

Chemicals and reagents

Potassium hydroxide (KOH; 85%), sodium bicarbonate ($NaHCO_3$; 99.5%), and sodium carbonate ($NaCO_3$; 99%) were of analytical grade, purchased from Sisco Research Laboratories Ltd, India. HNO_3 and NaOH were used for pH adjustments. Deionized water was used to prepare solutions.

Concentrations of Hofmeister ions

Total concentrations of Hofmeister ions including, four anions; F^-, Cl^-, PO_4^{3-}, SO_4^{2-}, and four cations; Na^+, Mg^{2+}, K^+, Ca^{2+} were determined in the collected raw rice samples.

Determination of anions

The homogenized powdered rice samples, (0.50 g of each) were weighed into the nickel crucibles. And then, 2 mL of 50% w/v KOH solution was added. Then samples were heated at 100 ℃ for 30 min using a hot plate and transferred into the muffle furnace (Nabertherm, Germany) set at 300 °C. The temperature was increased by 50 °C every 15 min up to 600 °C and the samples were kept for 30 min at the same temperature (Naik et al., 2017). After the treatment, cooled samples were transferred into a 50 mL volumetric flask and made up to the volume with ultrapure water. The resulting solution was filtered through a 0.45 µm nylon syringe filter. Then, 10 mL of the sample was diluted five times, and the pH was adjusted to around 7. Finally, the samples were subjected to Ion Chromatography (IC) analysis (Metrohm A Supp 5–250/4.0 column). The injected volume was 20 µL with a flow rate of 0.7 mL/min and the eluent was 3.19 m mol/L $NaCO_3$ and 1.0 m mol/L $NaHCO_3$. The results were reported as an average value of triplicates and blank samples were run for the quality of data. The limit of detection (LOD) and limit of quantification (LOQ) values of IC were 0.03 mg/L and 0.1 mg/L, respectively.

Determination of cations

The homogenized powdered rice samples, 0.375 g, were weighed and transferred into digestive vessels. Then, the powdered samples were digested using 3.00 mL of HNO_3 (65%) and 0.75 mL of HCl (35%). Digested solutions were diluted up to 10 mL with ultrapure water and filtered through 0.22 µm nylon syringe filters for the analysis. The contents of total cations in the samples were analyzed by Microwave Plasma Atomic Emission Spectrometry (MP-AES) (Agilent 4210) with microwave digestion (Anton Paar GmbH, Graz, Austria). The experiments were run in triplicates and results were reported as an average. Blank samples were done for the quality of data. The LOD and LOQ values of MP-AES were 3 µg/L and 10 µg/L, respectively.

Statistical analysis

Two sample t-test assuming that the variance was not equal (Welch's t-test) was done to find whether there is a statistical significance ($p<0.05$) between the raw rice samples from CKDu endemic areas and the samples collected from CKDu non-endemic areas. The statistical analysis was performed using Origin 2018 software (The obtained extreme values were replaced by the mean value to carry out the comparison).

Estimated Daily Intake for F^- and dietary intake for other Hofmeister ions

The aggregated dietary intake of other Hofmeister ions via the consumption of cooked rice for an adult was calculated, and the aggregated estimated daily intake (EDI) values for F^- were assessed using Eq. 1 (Mridha et al., 2021). The fact that F^- content in water could be absorbed when raw rice grains are cooked with Hofmeister ions containing groundwater, was assumed. The water amount to get 500 g of cooked non-traditional samba, nadu, red rice, and traditional rice was measured in the laboratory as 0.251, 0.335, 0.293, and 0.480 L. Three age groups including children (3–10 years), adolescents (11–19 years), and adults (20–70 years) were considered for the EDI calculations. The age groups' weight was considered as 19, 52, and 70 kg, respectively. The rice consumption per day for children, adolescents, and adults was considered as 100, 250, and 500 g, respectively. The mean Hofmeister ion contents in groundwater (except PO_4^{3-}) for the calculations were taken from previous literature (Table 2), which evaluated the Hofmeister ion contents in groundwater collected from the same sampling sites in the present study (Total of 142 water samples including samples from CKDu wells (n = 87) and non-CKDu wells (n = 41) from CKDu endemic Girandurukotte and Dehiattakandiya and water samples from CKDu non-endemic Sewanagala (n = 14)). Further, the EDI of F^- only in raw rice was also calculated to get the EDI values for uncooked rice.

$$\mathrm{EDI}\ (\mathrm{mg/kg\ \ bw/d}) = \frac{(C \times \mathrm{IR}\ \times \mathrm{EF}\ \times \mathrm{ED}\ \times \mathrm{AF}\ \times \mathrm{CF})}{(\mathrm{BW}\ \times \mathrm{AT})} \quad (1)$$

where EDI is estimated daily intake (mg/kg bw/d), C is the concentration of an ion in rice (mg/kg), IR is the daily intake of rice (mg/d), EF is exposure frequency (d/year), ED is exposure duration (year), AF is absorption factor (unitless), CF is conversion factor (kg/mg), BW is body weight (kg). The AT is averaging time (d).

The cumulative EDI value for F^- was calculated using Eq. 2, assuming that drinking water consumption per day for children, adolescents and adults is 1, 1.5, and 2 L, respectively.

$$\mathrm{EDI\ (cumulative)} = \mathrm{EDI\ (cooked\ rice)} + \mathrm{EDI\ (drinking\ water)} \quad (2)$$

Results and discussion

Hofmeister anions in rice

F^- concentration in the raw rice samples from CKDu endemic areas considered in the current study ranged from 15.000 to 306.000 mg/kg, 53.317 ± 10.374 mg/

Table 2 Mean concentrations of Hofmeister ions in groundwater from previous literature

Sampling sites	Mean concentrations of Hofmeister ions in groundwater (mg/L) (reference except for PO_4^{3-}: Sandanayake et al. (2023), reference for PO_4^{3-}: Hettithanthri et al. (2021))							
	F^-	Cl^-	SO_4^{2-}	PO_4^{3-}	Na^+	Mg^{2+}	K^+	Ca^{2+}
CKDu endemic								
Girandurukotte wet season (uGKw)	0.56	26.3	16.0	0.87	33.3	15.8	0.80	31.3
Girandurukotte dry season (uGKd)	1.01	19.9	16.7	–	28.8	14.0	0.43	21.7
Dehiattakandiya wet season (uDHw)	0.71	41.6	13.0	–	24.4	15.2	1.06	29.5
Girandurukotte wet season (nGKw)	0.28	25.6	12.0	–	17.8	7.51	0.75	24.9
Girandurukotte dry season (nGKd)	0.51	25.7	16.7	–	20.4	12.3	0.50	20.4
Dehiattakandiya wet season (nDHw)	0.72	68.5	24.3	–	38.7	23.3	1.26	44.9
CKDu non-endemic								
Sewanagala wet season (SWw)	0.91	29.4	31.8	–	46.3	33.4	1.50	39.4

u CKDu, *n* non−CKDu, *GK* Girandurukotte, *DH* Dehiattakandiya, *SW* Sewanagala, *w* wet season, *d* dry season

Table 3 Summary of the analysis of Hofmeister anions and cations in collected raw rice samples

Ion	CKDu endemic areas ($n=30$)				CKDu non-endemic areas ($n=30$)			
	Range (mg/kg)	Mean concentration (mg/kg)	Median (mg/kg)	SE of Mean	Range (mg/kg)	Mean concentration (mg/kg)	Median (mg/kg)	SE of Mean
F^-	15.000–306.00	53.317	39.250	10.374	1.5000–69.500	22.850	17.250	3.1300
Cl^-	329.00–3447.5	1515.3	1475.3	124.61	200.50–4616.5	947.52	679.75	151.78
PO_4^{3-}	1446.0–4961.0	2799.6	2823.3	146.68	402.50–12973	6080.2	5962.0	638.59
SO_4^{2-}	2137.5–3798.5	2704.9	2645.0	69.807	257.50–12131	4418.7	2858.0	608.88
Na^+	16.672–60.341	30.603	26.779	2.1700	8.0810–94.304	23.862	18.231	3.3800
Mg^{2+}	180.52–491.02	300.76	282.23	12.554	56.765–776.07	364.45	228.78	46.407
K^+	645.27–1393.6	1001.3	962.88	39.880	251.01–2106.5	955.78	580.51	118.39
Ca^{2+}	56.422–210.55	90.075	85.003	4.9920	40.570–182.46	96.780	96.320	7.9600

Table 4 Mean concentrations of Hofmeister anions and cations in collected raw rice varieties

Sampling areas	Rice varieties	Mean concentration of Hofmeister ions in raw rice samples (mg/kg)							
		F^-	Cl^-	PO_4^{3-}	SO_4^{2-}	Na^+	Mg^{2+}	K^+	Ca^{2+}
CKDu endemic areas	SR	95.643	1653.3	2323.3	2547.8	33.460	299.88	978.65	110.45
	NR	41.417	1344.9	2662.5	2822.5	32.170	274.15	972.24	81.790
	RR	36.900	1543.9	3960.0	2501.4	20.910	397.70	1143.3	91.350
CKDu non-endemic areas	RR	27.470	742.80	7371.9	6380.2	10.820	148.11	401.92	60.580
	TR	18.230	1152.2	4788.5	2457.1	36.880	580.77	1509.6	132.97

SR non-traditional Samba rice, *NR* non-traditional Nadu rice, *RR* non-traditional Red rice, *TR* Traditional rice

kg of mean concentration. Meantime, the F^- concentration ranged from 1.5000 to 69.500 mg/kg with an mean of 22.850 ± 3.1300 mg/kg in control samples (Table 3). Traditional rice showed the lowest value for F^- (18.230 mg/kg) while non-traditional samba rice showed the highest (95.640 mg/kg) (Table 4). Traditional rice in Sri Lanka is known to possess antioxidant properties (Abeysekera et al., 2011; Gunaratne et al., 2013). These antioxidants may restrict the accumulation of F^- in the plant cells in fluoride stress, which could be the reason for the reported lower value (Singh & Roychoudhury, 2021). However, the F^- content of all the raw rice samples was considerably greater than the earlier studies, such as those reported for Ethiopia (0.1–5.2 mg/kg) and Spain (0.53–3.62 mg/kg) (Jaudenes et al., 2020; Tegegne et al., 2013). Further, the study by Mridha et al. (2021) reported that the F^- concentration in raw rice samples collected from Bankey Bazar and Rajauli areas in India was in the range of 0.23–4.11 mg/kg with a mean of 1.15 ± 0.82 mg/kg and 0.40–4.46 mg/kg with a mean of 1.37 ± 0.67 mg/kg, respectively. The study by Havale et al. (2022) revealed that there's a strong positive correlation between the F^- content in rice and soil of rice in highly fluoridated Wadloor, Karnataka in India, which reported 0.79 mg/kg F^- content in rice. The presence of high F^- content in the raw rice grains in the present study may be due to the irrigation with fluoride-containing groundwater and growing them in fluoride-containing soil. Apart from the natural geological weathering of minerals, an excess amount of F^- can be added to the soil due

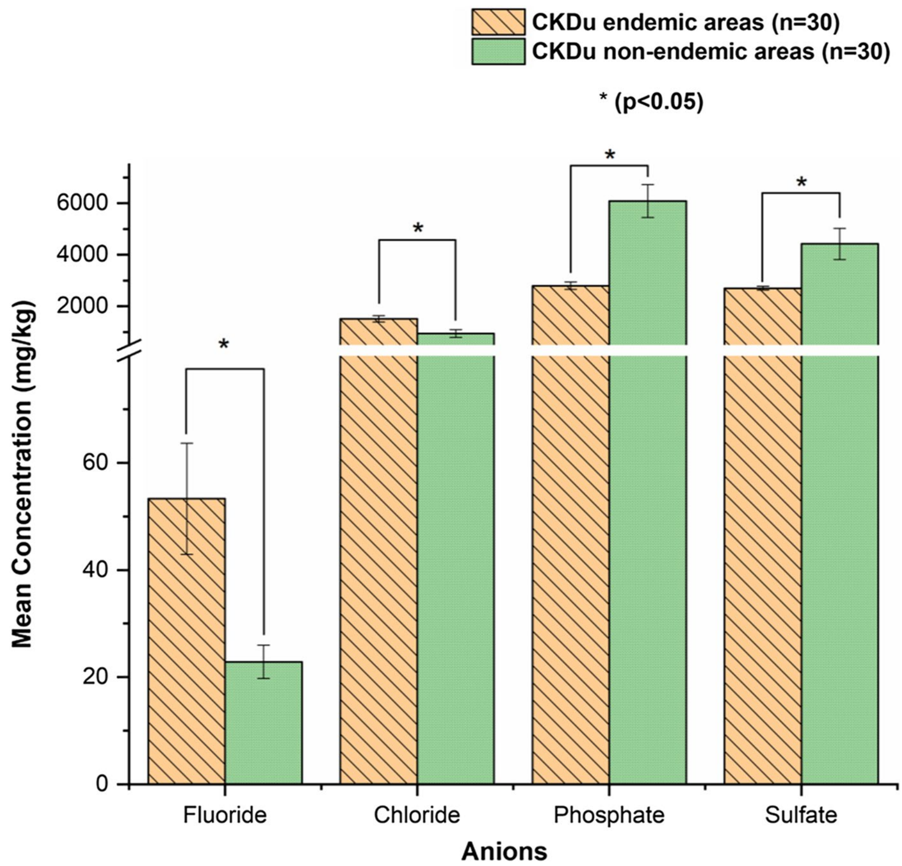


Fig. 1 Mean concentrations of the Hofmeister anions in collected raw rice samples from CKDu endemic and CKDu non-endemic areas

to agricultural fertilizers (Bhattacharya et al., 2017). Groundwater in most of the CKDu endemic areas in the dry zone of Sri Lanka reported high F^- concentrations (Chandrajith et al., 2020). The current study reported the accumulated F^- content only in raw rice. Nevertheless, when the rice is cooked with fluoride-containing water, it could also add some amount of F^- to the diet (Sawangjang & Takizawa, 2020; Tegegne et al., 2013). On the other hand, the accumulation of high F^- could affect grain development and reduce the formation of mature grains, which could finally affect the yield (Banerjee et al., 2021). The statistical comparison of the anion contents in raw rice samples revealed that the concentration of F^- in raw rice samples collected from CKDu endemic areas was significantly higher than in the control raw rice samples ($p < 0.05$) (Fig. 1, Table 3). The significant difference may be due to the excessive F^- content in groundwater and soil in CKDu endemic areas. Chronic exposure to F^- for an extended period can damage several organs, especially the kidneys. The study by Yang et al. (2022) reported that kidney damage could be induced by high F^- and water hardness in groundwater collected from CKDu endemic Vavuniya in the Northern Province of Sri Lanka. Therefore, besides drinking water, rice consumption could contribute to F^- intake in the human body and pose a health risk to the kidneys.

The current study reported that Cl^- content in raw rice samples from CKDu endemic areas was in a range of 329.00–3447.5 mg/kg with an mean concentration of 1515.3 ± 124.61 mg/kg. Cl^- in control raw rice samples was 200.50–4616.5 mg/kg with an mean concentration of 947.52 ± 151.78 mg/kg (Table 3). The lowest Cl^- content (742.80 mg/kg) was reported in non-traditional red rice from CKDu non-endemic areas while the highest was reported in non-traditional samba rice samples from CKDu endemic areas (1653.3 mg/kg) (Table 4). The statistical comparison results in the study revealed that the Cl^- content in raw rice samples from CKDu endemic areas was significantly higher ($p < 0.05$)

than in the control. In a previous study, Balasooriya et al. (2020) revealed that the Cl^- content of well water in CKDu endemic areas was higher than the CKDu non-endemic areas in Sri Lanka. Furthermore, the studies such as Gobalarajah et al. (2020) and Cooray et al. (2019) which focused on water quality in different CKDu endemic areas around Sri Lanka, agree with that. Therefore, the higher Cl^- content in raw rice samples collected from CKDu endemic areas in the study may be due to the high Cl^- content in those areas. However, the Cl^- content in all the raw rice samples was much higher than in a previous study conducted by, Tsukada et al. (2007) which reported that the Cl^- concentration in polished rice grains was 130–220 mg/kg. Even though Cl^- is an essential element to the human body, a high intake of Cl^- continuously for an extended period can induce the risk of devising hypertension and cardiovascular diseases (Strohm et al., 2018).

The PO_4^{3-} and SO_4^{2-} content in the raw rice collected from CKDu endemic areas ranged from 1446.0–4961.0 and 2137.5–3798.5 mg/kg, respectively. The mean concentration of PO_4^{3-} and SO_4^{2-} in rice samples collected from CKDu endemic areas were 2799.6 ± 146.68 and 2704.9 ± 69.807 mg/kg, respectively. The mean concentration of PO_4^{3-} and SO_4^{2-} in the raw rice samples collected from control sampling areas were 402.50–12973 and 257.50–12131 mg/kg, respectively. The mean concentrations were 6080.2 ± 638.59 and 4418.7 ± 608.88 mg/kg, respectively (Table 3). The highest PO_4^{3-} and SO_4^{2-} contents were reported in non-traditional red rice samples from CKDu non-endemic areas (Table 4). The statistical analysis reported that the PO_4^{3-} and SO_4^{2-} content in control samples was significantly higher than in the rice samples from CKDu endemic areas ($p < 0.05$). The levels of PO_4^{3-} and SO_4^{2-} in rice varieties were not discussed in the previous literature. However, discrepancies may result from differences in the rice varieties, fertilizers utilized, types of soil, and water quality used for the plantation (Tegegne et al., 2013). Figure 1 shows the mean concentrations of the

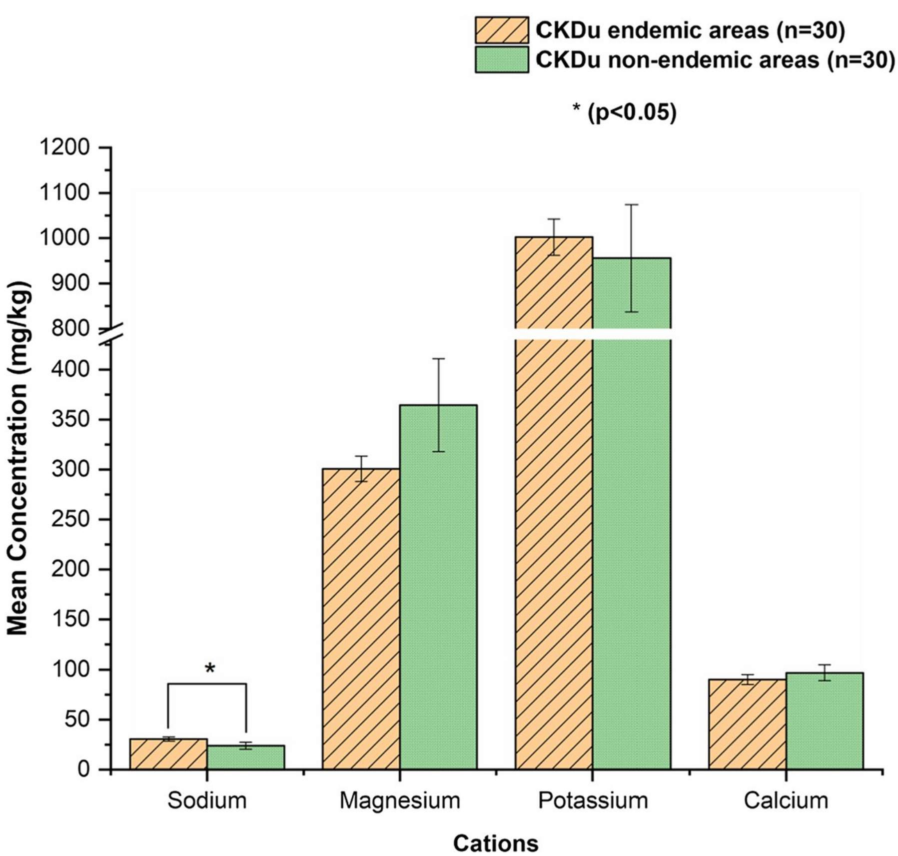


Fig. 2 Mean concentrations of the Hofmeister cations in CKDu endemic and CKDu non-endemic areas

analyzed anions in the raw rice samples collected in the current study.

Hofmeister cations in rice

Figure 2 shows the composition of analyzed cations in all the raw rice samples collected. According to the results, Na^+ and K^+ concentrations in raw rice samples from CKDu endemic areas were higher than in control samples. The amount of Na^+ in CKDu endemic and control raw rice samples were in the range of 16.672–60.341, 8.0810–94.304 mg/kg with the mean concentrations of 30.603 ± 2.1700 and 23.862 ± 3.3800 mg/kg, respectively (Table 3). However, the mean Na^+ contents reported in the present study were lower than the results of Tegegne et al. (2017), which reported Na^+ levels in imported and Ethiopian rice as 70.6–78.6 and 26.7–80.9 mg/kg, respectively. Among the tested rice samples non-traditional red rice from CKDu non-endemic areas reported the lowest Na^+ concentration (10.820 mg/kg) (Table 4). Again that has in agreement with Tegegne et al. (2017), which showed the lowest Na^+ content in Ethiopian red rice (26.7 mg/kg). The Na^+ levels in the study's raw rice samples from CKDu endemic areas were significantly higher than in control samples ($p = 0.01$). As per the previous literature, Gobalarajah et al. (2020) reported a higher Na^+ content in groundwater in CKDu endemic areas (13.52 ± 11.46 mg/L) than in control areas (7.2 ± 5.43 mg/L) in Mullaitivu, Sri Lanka. With an agreement, the previous studies, Piyathilake et al. (2022) and Cooray et al. (2019) reported that Na^+ was the dominant cation in groundwater in CKDu endemic areas in Sri Lanka. Therefore, a significant difference in the present study's Na^+ content in raw rice samples may be due to the high Na^+ level in groundwater in CKDu endemic areas. The K^+ content in raw rice samples collected from CKDu endemic areas ranged from 645.27 to 1393.6 mg/kg. The mean content of K^+ was 1001.3 ± 39.880 mg/kg. The K^+ content in control raw rice samples ranged from 251.01 to 2106.5 mg/kg with a mean concentration of 955.78 ± 118.39 mg/kg (Table 3). Traditional rice contained the highest K^+ content (1509.6 mg/kg) while the lowest was non-traditional red rice (401.92 mg/kg) (Table 4). The K^+ content in rice samples in the study by Tegegne et al. (2017) has some agreement with the values in the present study, yet it showed the highest in Ethiopian red rice (3020 mg/kg). K^+ being an essential element for human body, adequate intake is needed for the health of kidney as well as the heart. High or low intake of potassium would have adverse effects on kidneys (Weaver, 2013). The Mg^{2+} range in CKDu endemic and control raw rice samples were 180.52–491.02 and 56.765–776.07 mg/kg, respectively. The mean concentration values for Mg^{2+} were 300.76 ± 12.554 and 364.45 ± 46.407 mg/kg, respectively (Table 3). Traditional rice showed the highest Mg^{2+} content (580.77 mg/kg) among the tested rice (Table 4). Ca^{2+} content in raw rice samples collected from CKDu endemic areas ranged between 56.422 to 210.55 mg/kg while the mean concentration was 90.075 ± 4.9920 mg/kg. The Ca^{2+} amount in control raw rice samples was 40.570–182.46 mg/kg, with a mean concentration value of 96.780 ± 7.9600 mg/kg (Table 3). The highest Ca^{2+} content (132.97 mg/kg) was reported in traditional rice (Table 4). The differences in the contents of Mg^{2+} and Ca^{2+} among tested rice varieties in the current study may be due to variations in hydro-geochemical parameters in groundwater and soil in the particular areas (Udeshani et al., 2022). When compared with the Mg^{2+} and Ca^{2+} contents in Ethiopian rice (99.5–2250 and 205–427 mg/kg, respectively) in the previous study by Tegegne et al. (2017), the current study reported much lower Mg^{2+} and Ca^{2+} contents. However, Mg^{2+} and Ca^{2+} content in the imported rice, respectively, were in the range between 90.6–150, and 75.8–630 mg/kg, which showed the values closer to the present study. The reason for these discrepancies may be due to the different environmental conditions in rice cultivation and the difference between the rice species (*Oryza sativa* in the present study and *Oryza glaberrima* in Tegegne et al., 2017). Both Mg^{2+} and Ca^{2+} are essential elements which are involved in several important activities of the human body (Antoine et al., 2012). According to the statistical comparison in the present study, there were no significant differences between these elements between CKDu endemic and control raw rice samples.

Table 5 Dietary intake of Hofmeister ions other than F^- from cooked rice (in raw rice + cooking water) obtained from CKDu endemic and non-endemic areas in Sri Lanka

Sampling sites		Rice variety	Aggregated dietary intake of Hofmeister ions via consumption of cooked rice (mg/d) for an adult						
			Cl^-	PO_4^{3-}	SO_4^{2-}	Na^+	Mg^{2+}	K^+	Ca^{2+}
CKDu endemic	uGKw	SR	255.84	350.46	388.10	13.411	49.177	147.73	24.514
		NR	207.04	392.75	421.40	15.897	45.703	143.58	22.541
		RR	230.11	570.69	365.02	12.773	61.920	164.92	22.334
	uGKd	SR	254.23		388.28	12.280	48.724	147.64	22.102
		NR	204.90		421.63	14.390	45.100	143.45	19.325
		RR	228.23		365.22	11.454	61.392	164.81	19.520
	uDHw	SR	259.69		387.35	11.175	49.026	147.80	24.062
		NR	212.17		420.39	12.916	45.502	143.66	21.938
		RR	234.59		364.14	10.164	61.744	165.00	21.806
	nGKw	SR	255.67		387.09	9.5160	47.094	147.72	22.906
		NR	206.84		420.06	10.705	42.926	143.56	20.397
		RR	229.90		363.84	8.2300	59.490	164.91	20.458
	nGKd	SR	255.69		388.28	10.170	48.297	147.66	21.776
		NR	206.84		421.63	11.576	44.530	143.48	18.890
		RR	229.93		365.22	8.9920	60.894	164.83	19.139
	nDHw	SR	266.44		390.18	14.767	51.061	147.85	27.931
		NR	221.18		424.18	17.706	48.215	143.73	27.097
		RR	242.48		367.45	14.356	64.118	165.06	26.320
CKDu non-endemic	SWw	RR	115.62		**928.39**	15.130	31.126	58.336	20.276
		TR	223.82		462.46	28.936	121.73	275.47	43.113
Recommended values			2300 (Strohm et al., 2018)	700 (Antoine et al., 2012)	850	1500 (Strohm et al., 2018)	320–420 (Antoine et al., 2012)	4700	1000–1300

u CKDu, *n* non-CKDu, *GK* Girandurukotte, *DH* Dehiattakandiya, *SW* Sewanagala, *w* wet season, *d* dry season, *NR* non-traditional Nadu rice, *SR* non-traditional Samba rice, *RR* non-traditional Red rice, *TR* Traditional rice

Evaluation of aggregated dietary intake of Hofmeister ions

As groundwater in CKDu endemic areas is rich in Hofmeister ions, an addition of concentrations of these ions could occur when rice is cooked with groundwater. Therefore, the present study calculated the aggregate dietary intake values (Table 5) using the Hofmeister ion contents in raw rice samples observed in the study (Table 4). The results revealed that only cooked non-traditional red rice samples collected from CKDu non-endemic Sewanagala exceeded the recommended dietary intake value for SO_4^{2-} (928.39 mg/d). This high value may be due to using fertilizers containing SO_4^{2-} in the rice paddy fields when cultivated (Chandrajith, 2021). Aggregate dietary intake values for the other Hofmeister ions in rice samples were less than the recommended values, which discloses that a portion of recommended dietary intake of those elements is fulfilled by the consumption of rice. It is important to acknowledge that only the Hofmeister ion contents in the raw rice samples were analyzed in the present study, revealing both bio-labile and non-labile ion content in rice grains. However, analysis of cooked rice would indicate only the presence of bio-labile ion content in the rice grains. The present study did not include an analysis of Hofmeister ions in cooked rice which represents a limitation of the study.

Estimated daily intake (EDI) of F^-

F^- has both beneficial and detrimental effects on the human body. F^- exposure to the human body could occur through drinking water, dermal contact, dental products, and food consumption (Sawangjang & Takizawa, 2020). It is known that F^- may damage renal function when it is consumed at excessive levels for an extended (Dharmaratne, 2015; Perera et al., 2018). As per the Institute of Medicine in the United States, the tolerable upper intake level of F^- is 0.15–0.20 mg/kg body weight per day for an adult, while it is 0.1 mg/kg body weight per day for children (IOM, 1997).

The F^- content in cooking water could make differences in F^- content in cooked rice as per the study by Sawangjang and Takizawa (2020), which reported increased F^- intake of 0.1 ± 0.25 and 6.33 ± 5.14 mg/capita/day when used bottled water and tap water as cooking water, respectively. Sawangjang and Takizawa (2023) reported that the F^- level in rice increased when fluoride-containing cooking water was boiled to 100 °C. Further, it described that F^- in water could be absorbed and adsorb to the rice grain. This agrees with the study by Tegegne et al. (2013), which reported that the F^- level in cooked rice was increased depending on the F^- content in the water used for cooking. Referring to Sandanayake et al.

Table 6 Aggregated EDI (from raw rice + cooking water) and cumulative EDI (aggregate EDI via cooked rice + EDI via drinking water) values of F^- via consumption of cooked rice for three age groups

Sampling sites	Sampling sites	Rice variety	Aggregated EDI of F^- via consumption of cooked rice (mg/kg bw/d)			Cumulative EDI of F^- via cooked rice + drinking water (mg/kg bw/d)		
			Children	Adolescents	Adults	Children	Adolescents	Adults
CKDu endemic	uGKw	SR	0.115	0.103	0.156	0.144	0.120	0.172
		NR	0.050	0.045	0.067	0.079	0.061	0.083
		RR	0.043	0.039	0.059	0.073	0.055	0.075
	uGKd	SR	0.116	0.104	0.157	0.169	0.133	0.186
		NR	0.0510	0.0460	0.069	0.104	0.075	0.098
		RR	0.0440	0.0400	0.0600	0.0970	0.0690	0.0890
	uDHw	SR	0.115	0.104	0.156	0.153	0.124	0.177
		NR	0.0500	0.0450	0.0680	0.0870	0.0660	0.0880
		RR	0.0440	0.0390	0.0590	0.0810	0.0600	0.0790
	nGKw	SR	0.114	0.103	0.155	0.129	0.111	0.163
		NR	0.0490	0.0440	0.0660	0.0640	0.0520	0.0740
		RR	0.0430	0.0380	0.0580	0.0570	0.0460	0.0660
	nGKd	SR	0.115	0.103	0.156	0.142	0.118	0.170
		NR	0.0500	0.0450	0.0670	0.0760	0.0590	0.0820
		RR	0.0430	0.0390	0.0590	0.0700	0.0540	0.0730
	nDHw	SR	0.115	0.104	0.156	0.153	0.124	0.177
		NR	0.0500	0.0450	0.0680	0.0880	0.0660	0.0890
		RR	0.0440	0.0390	0.0590	0.0820	0.0600	0.0800
CKDu non-endemic	SWw	RR	0.0330	0.0300	0.0450	0.0810	0.0560	0.0710
		TR	0.0230	0.0210	0.0400	0.0710	0.0470	0.0660
CKDu endemic GK and DH	Uncooked SR	0.113	0.102	0.154	–	–	–	
	Uncooked NR	0.0650	0.0430	0.0650	–	–	–	
	Uncooked RR	0.0420	0.0370	0.0570	–	–	–	
CKDu non-endemic SW	Uncooked RR	0.0310	0.0280	0.0420	–	–	–	
	Uncooked TR	0.0190	0.0170	0.0350	–	–	–	

u CKDu, *n* non-CKDu, *GK* Girandurukotte, *DH* Dehiattakandiya, *SW* Sewanagala, *w* wet season, *d* dry season, *NR* non-traditional Nadu rice, *SR* non-traditional Samba rice, *RR* non-traditional Red rice, *TR* Traditional rice

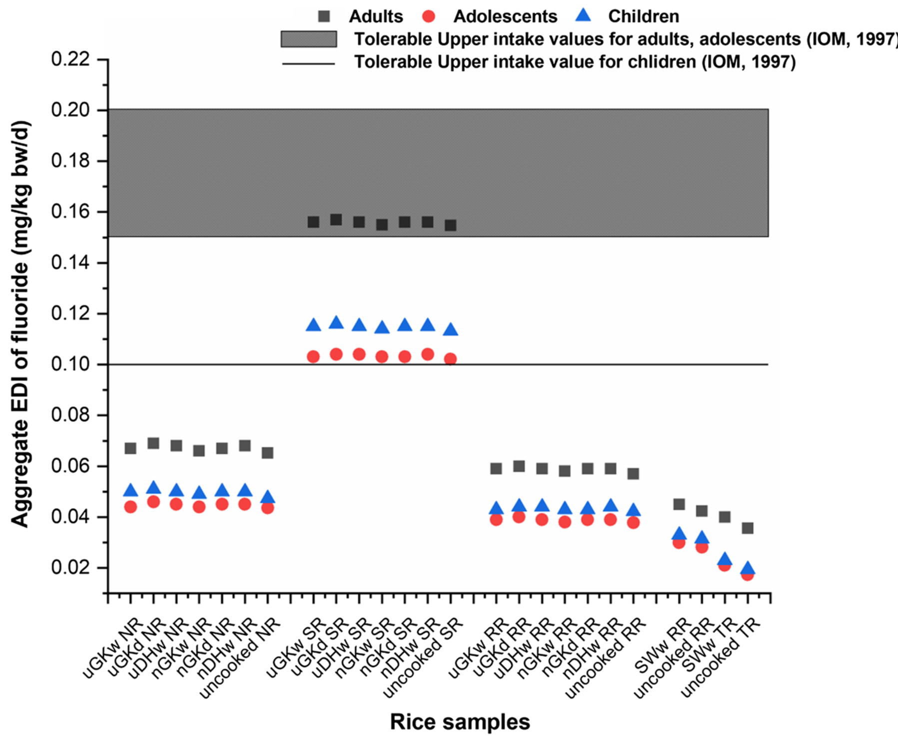


Fig. 3 Comparison of aggregated EDI values of F^- (in raw rice + cooking water) in three age groups via consumption of cooked rice (*u* CKDu, *n* non-CKDu, *GK* Girandurukotte, *DH* Dehiattakandiya, *SW* Sewanagala, *w* wet season, *d* dry season, *NR* non-traditional Nadu rice, *SR* non-traditional Samba rice, *RR* non-traditional Red rice, *TR* Traditional rice)

(2023), F^- content in drinking water surpassed the recommended permissible limit of 0.6 mg/L for the dry zone of Sri Lanka in both CKDu endemic areas and the non-endemic area (Table 2). These F^- content could potentially enter into rice grains during washing and boiling process, and ultimately leading to its consumption by humans. Therefore, the current study calculated the aggregated EDI of F^- via the consumption of cooked rice and the cumulative EDI of F^- via the consumption of cooked rice and drinking water, for three age groups (Table 6). The calculated EDI of raw non-traditional samba rice for children, adolescents and adults were 0.113, 0.102, and 0.154 mg/kg bw/d, respectively, in CKDu endemic areas. The calculated EDI of raw non-traditional nadu rice for children, adolescents and adults in CKDu endemic areas were 0.0474, 0.0436, and 0.0652 mg/kg bw/d, respectively, while for raw non-traditional red rice the values were 0.0422, 0.0377, and 0.0569 mg/kg bw/d, respectively. In CKDu non-endemic area, the calculated EDI values of raw non-traditional red rice for three age groups were 0.0314, 0.0281 and 0.0423 mg/kg bw/d while the values of raw traditional rice were 0.0194, 0.0173 and 0.0355 mg/kg bw/d, respectively. The calculated EDI values for raw rice were slightly lower than the aggregated EDI values for cooked rice (Fig. 3, Table 6). Comparatively, aggregated EDI values for cooked non-traditional samba rice with water from Girandurukotte wet and dry seasons, Dehiattakandiya wet season were much higher than the other aggregated EDI values (Fig. 3). According to the calculations, adults and children were exposed to F^- via consumption of non-traditional samba rice cooked with CKDu endemic areas' groundwater, in which the aggregated EDI values exceeded the recommended tolerable upper intake level. However, the same for adolescents was below the recommended values (Fig. 3). When considering CKDu endemic areas, non-traditional nadu, and non-traditional red rice showed lower levels of aggregated EDI values, than non-traditional samba rice for three age groups. For all three age groups, the non-traditional samba rice samples showed the highest aggregated EDI of F^- values, while the non-traditional red rice samples showed the lowest when considering CKDu endemic areas. The traditional rice samples showed the lowest aggregated EDI of F^- of all the other rice samples for the three age groups, which implies that it shows the lowest risk of consuming F^- for all three groups. Interestingly, the aggregated EDI value of all three

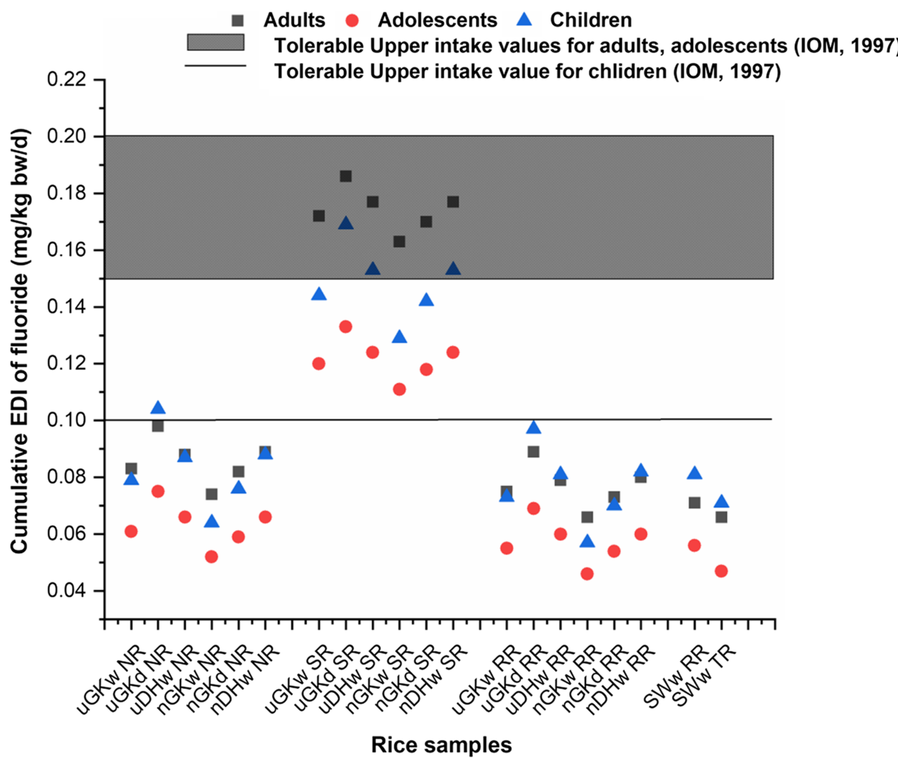


Fig. 4 Comparison of cumulative EDI values of F^{-} (aggregate EDI via cooked rice + EDI via drinking water) for three age groups via consumption of cooked rice and drinking water (*u* CKDu, *n* non-CKDu, *GK* Girandurukotte, *DH* Dehiattakandiya, *SW* Sewanagala, *w* wet season, *d* dry season, *NR* non-traditional Nadu rice, *SR* non-traditional Samba rice, *RR* non-traditional Red rice, *TR* Traditional rice)

age groups for non-traditional red rice from CKDu non-endemic areas was lower than that of non-traditional red rice collected from CKDu endemic areas. However, the calculated aggregated EDI of F^{-} for all rice samples varied as adults > children > adolescents. Adults show higher aggregate EDI values since the amount of cooked rice consumed by adults daily is higher. When considering children, the aggregate EDI values are higher, due to their low body weight.

According to the results of cumulative EDI of F^{-} calculations (Table 6), adults and children are more vulnerable to health risks when consuming non-traditional samba rice and drinking water from Girandurukotte and Dehiattakandiya during wet and dry seasons. Children who consume non-traditional samba rice and drinking water from CKDu endemic areas are at high risk since the cumulative EDI values exceeded the tolerable upper intake level for children (Fig. 4). Furthermore, consumption of non-traditional nadu and non-traditional red rice with drinking water from CKDu endemic areas during the dry season in the Girandurukotte area may also pose a health risk to children (Fig. 4). Relatively, a difference in cumulative EDI of F^{-} for all samples for three age groups between the wet and dry seasons in Girandurukotte could be observed. Surprisingly, cumulative EDI for red rice and drinking water from non-CKDu Girandurukotte areas during the wet season (0.0658 mg/kg bw/d) and cumulative EDI for traditional rice and drinking water from Sewanagala (0.0662 mg/kg bw/d) held almost the same value for the adult group. When comparing the cumulative EDI for F^{-} among three age groups, adolescents showed the lowest health risk, which did not exceed the recommended level.

Sawangjang and Takizawa (2020) and Bhattacharya et al. (2017) conducted field surveys in Thailand and India, respectively, to describe that children could be more vulnerable to F^{-} ingestion than adults and adolescents. Similar observations were also reported from India by Mridha et al. (2021). The results of the present study reveal that estimating F^{-} intake only from drinking water underestimates the total content of F^{-} intake in the area where people mainly consume rice. Therefore, assessing and comparing F− content in cooked rice from CKDu endemic and non-endemic areas is vital by analyzing the daily consumption of rice and water, body weight, gender, and age among the people. As well as rice, the concern should be gained on the F^- content in mainly consumed vegetables in CKDu endemic areas in Sri Lanka as vegetables are more prone to accumulate and absorb a high amount of F^- from water (Sawangjang & Takizawa, 2023). Hence to assess the overall Hofmeister ion intake, it is essential to consider all sources of ions, including drinking water, beverages, cooking rice, and vegetables. The use of treated water for all rice cooking is one option for reducing F^- and other Hofmeister ions exposure; alternatively, consumption of traditional rice.

Conclusion

According to the results of the current study, F^-, Cl^-, and Na^+ content in raw rice samples collected from CKDu endemic areas were significantly higher ($p<0.05$) when compared to the raw rice samples collected from CKDu non-endemic areas. Notably, the amount of SO_4^{2-} and PO_4^{3-} in raw rice samples collected from CKDu non-endemic areas were significantly higher ($p<0.05$) than CKDu endemic areas. Further, aggregated dietary intake of SO_4^{2-} only for red rice samples from CKDu non-endemic areas was higher than the recommended value. The aggregated EDI and cumulative EDI of F^- for non-traditional samba rice, drinking water, and cooking water from CKDu endemic areas for adults and children were higher than the recommended tolerable upper intake values suggested by the Institute of Medicine, US (0.15–0.2, 0.1 mg/kg bw/d, respectively). The highest aggregated EDI and cumulative EDI values for F^- were shown in cooked non-traditional samba rice from CKDu endemic areas. In contrast, the lowest was shown in cooked traditional rice from CKDu non-endemic areas. Rice can considerably increase the amount of Hofmeister ions. Specifically F^- is consumed overall. Hence it is advised to use treated water with the recommended level of F– for cooking in CKDu endemic areas. Furthermore, it is recommended to assess the overall Hofmeister ion intake by taking into account all sources of ions including drinking water, beverages, cooked rice, and vegetables in CKDu endemic areas.

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Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by SB, MV, and OH. Conceptualization, supervision, project administration reviewing, and editing were done by DNM-A, RW, MV, AUR, CJ and AK. The first draft of the manuscript was written by SB and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability The datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

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