


RESEARCH ARTICLE

Not only manganese, but fruit component effects dictate the efficiency of fruit juice as an oral magnetic resonance imaging contrast agent

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Several fruit juices are used as oral contrast agents to improve the quality of images in magnetic resonance cholangiopancreatography. They are often preferred to conventional synthetic contrast agents because of their very low cost, natural origin, intrinsic safety, and comparable image qualities. Pineapple and blueberry juices are the most employed in clinical practice due to their higher content of manganese(II) ions. The interest of pharmaceutical companies in these products is testified by the appearance in the market of fruit juice derivatives with improved contrast efficacy. Here, we investigate the origin of the contrast of blueberry juice, analyze the parameters that can effect it, and elucidate the differences with pineapple juice and manganese(II) solutions. It appears that, although manganese(II) is the paramagnetic ion responsible for the contrast, it is the interaction of manganese(II) with other juice components that modulates the efficiency of the juice as a magnetic resonance contrast agent. On these grounds, we conclude that blueberry juice concentrated to the same manganese concentration of pineapple juice would prove a more efficient contrast agent than pineapple juice.

KEYWORDS

manganese in fruit juice, nuclear magnetic relaxation dispersion, paramagnetic molecules, relaxometry

1 | INTRODUCTION

Oral contrast agents are used in magnetic resonance cholangiopancreatography because they can greatly improve the visualization of biliary tree and pancreatic ducts, the images of which are frequently degraded by the high signal due to the fluid collecting in stomach and duodenum.¹ Ideal oral contrast agents must increase the contrast homogeneously through the gastrointestinal tract, must be nontoxic and easily digestible, palatable, not stimulate peristalsis, with no side effects, and with a low cost.² Fruit juices that are rich in manganese ions fulfill most of the above requirements, and therefore they are conveniently used in magnetic resonance cholangiopancreatography.³⁻⁷ Similar to gadolinium(III), whose complexes with multidentate ligands are used as intravenous MRI contrast agents, manganese(II) is a paramagnetic ion that can increase the longitudinal relaxation rate (R_1) of the neighboring water protons, thus increasing their signal intensity in T1-weighted MRI images.^{3,8-10} This causes a

Abbreviations used: ICP-AES, inductively coupled plasma-atomic emission spectroscopy; NMRD, nuclear magnetic relaxation dispersion.

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higher contrast between tissues where the paramagnetic ions are absorbed and those where they are not present. Manganese (II) is also a T2-agent because, similar to iron oxides, it can increase the transverse relaxation rate (R_2) of the neighboring water protons, thus decreasing their signal intensity in T2-weighted MRI scans. Intravenous administration of contrast agents is a routine method in neurologic and musculoskeletal T1-weighted MRI images; oral contrast agents are mostly used for gastrointestinal and hepatobiliary T2-weighted MRI images.⁷ Because manganese(II) ions can largely increase both R_1 and R_2 , manganese oral contrast agents can be used either as a T2-agent to suppress the signal from bowel fluid, or as a T1-agent to better delineate the gut.¹¹

The most promising and clinically employed juices are pineapple and blueberry juices, due to their relatively high content of manganese (II) ions.¹² These fruit juices have been shown to be effective as oral contrast agents in magnetic resonance images. More recently, concentrated juices added with hydrogels,¹³ and semiliquid preparations of concentrates from pineapple, organic agave syrup, blackcurrant, guar gum (thickening agent), and defoamers,^{14,15} have been proposed to further enhance the contrast.

A field-cycling relaxometric analysis of pineapple juice was recently performed to characterize its relaxation properties in detail, with and without the addition of hydrogels.¹⁶ The field-cycling relaxometric characterization is based on the analysis of the magnetic field dependence of water proton relaxation rates, called the nuclear magnetic relaxation dispersion (NMRD) profile.^{17,18} Water ^1H longitudinal relaxation rates are measured with a fast-field cycling relaxometer, ranging from ~ 0.0002 to 1 T.¹⁹ Longitudinal and transverse relaxation rates can then be measured at higher magnetic fields using high-resolution NMR spectrometers. The decrease in the relaxation rates with increasing magnetic fields, called dispersion, informs on the timescales of the dynamic processes occurring in the system and causing nuclear relaxation,^{18,20–22} whereas the magnitude of the rates can provide information on structural parameters, such as the number and distance of water molecules coordinated to the paramagnetic metal ions, and on the unpaired electron spin density delocalized onto the water protons.¹⁷ The analysis of the NMRD profiles of pineapple juice permitted evaluating the contributions to relaxation arising from the modulation of different types of metal-proton interactions, and to analyze the effects of the addition of alginate, a natural food able to slow down the dynamics of the paramagnetic ions present in the juice and thus to increase the relaxation rates.

In this paper, we analyze the NMRD profiles of blueberry juice, the second most employed fruit juice in oral MRI, and compare its relaxation properties with those of pineapple juice and of a solution containing $[\text{Mn}(\text{H}_2\text{O})_6]^{2+}$. A commercially available blueberry nectar was used to investigate the relaxation properties of a readily obtainable product, which can be both repeatable and immediately available for clinical administration.

2 | MATERIALS AND METHODS

2.1 | Sample preparation

The analyzed juice was Viviverde Coop organic blueberry nectar (fruit, 40% minimum), with ingredients of water, blueberry puree (40%), brown sugar, and citric acid. The centrifuged blueberry juice was prepared by collecting the supernatant after centrifugation of the blueberry nectar at 20,000 rpm at 4°C for 15 min.

2.2 | ^1H NMRD measurements

Water ^1H NMRD profiles were acquired with a Stelar Spinmaster FFC2000-1 T relaxometer by measuring the water proton relaxation rates as a function of the applied magnetic field (0.01–40 MHz proton Larmor frequency). The relaxation measurements, obtained from the fit of the magnetization decay/recovery curves against a monoexponential function, were affected by an error of about $\pm 1\%$.

2.3 | High field NMR measurements

R_1 and R_2 at high field were measured on a Bruker Avance III spectrometer operating at 400 MHz ^1H Larmor frequency (9.4 T), using a 5-mm, BBO probehead. To mitigate the effect of radiation damping, the samples were placed into a capillary tube, coaxial to the 5-mm NMR tube filled with D_2O .

3 | RESULTS AND DISCUSSION

The ^1H NMRD profiles of the blueberry juice were collected at 25 and 37°C. The profiles, reported in Figure 1 as red symbols, show two dispersions, as is typical of solutions containing manganese(II) aqua ions.²³ Figure 1 also shows the relaxation rates measured for pineapple juice (black

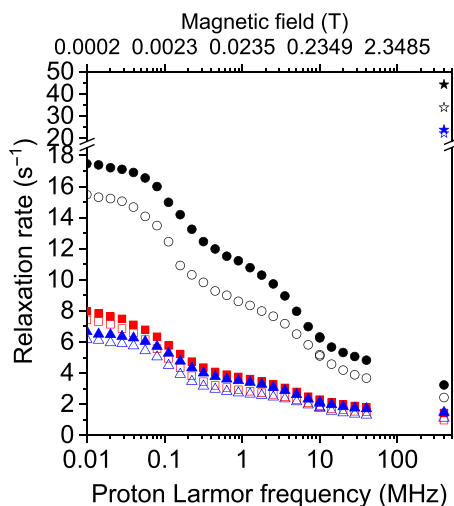


FIGURE 1 Experimental ^1H R_1 profiles of intact blueberry juice (red squares) and of centrifuged blueberry juice (blue triangles) at 25°C (solid symbols) and 37°C (empty symbols). The profiles previously collected for pineapple juice are also reported.¹⁶ ^1H R_2 profiles at 400 MHz in the centrifuged blueberry juice (blue stars) and pineapple juice (black stars) are also shown

symbols), which was determined to contain 0.45 mmol/dm^3 of manganese.¹⁶ The shape of the profiles for the two fruit juices are similar, as a result of the leading contribution from this paramagnetic ion. The lower relaxation rates measured for blueberry juice are in agreement with the lower manganese concentration expected in this juice,¹¹ where water was added to the blueberry puree, with respect to that of the pineapple juice.

The amounts of paramagnetic metals present in the juice were evaluated through ICP-AES. The concentration of manganese in the blueberry juice was measured as equal to 0.116 mmol/dm^3 . The relaxation efficiency of a paramagnetic metal is expressed by its longitudinal and transverse relaxivities, r_1 and r_2 , defined as the longitudinal and transverse relaxation enhancements, respectively, due to the presence of 1 mmol/dm^3 of paramagnetic metal ions in the system under investigation. Therefore, because the manganese concentration in blueberry juice is four times smaller than that in pineapple juice, whereas the relaxation rates at low fields are only about two-thirds smaller, the relaxivities of manganese in blueberry juice are expected to be significantly larger than in pineapple juice.

To evaluate the contribution to the relaxation rates from the manganese (II) ions, the diamagnetic relaxation rates, as well as the contributions from other paramagnetic ions present in the blueberry juice, should be estimated. The appearance of the juice was not that of a clear solution, but rather a fine suspension, so that the presence of some aggregated material is expected. This may largely affect the diamagnetic contribution to the observed relaxation rates, especially at low fields. The juice was thus centrifuged and the NMRD profiles of the centrifuged juice were acquired (shown in Figure 1 as blue symbols). Water ^1H longitudinal and transverse relaxation rates were also measured at 400 MHz. The concentration of manganese in the centrifuged blueberry juice was measured as equal to 0.109 mmol/dm^3 (very close to that of the intact juice, 0.116 mmol/dm^3). Consistently, the rates measured for the centrifuged juice are only slightly smaller than those measured for the intact juice at all frequencies larger than 0.1 MHz. However, at lower frequencies the disagreement becomes relevant. This expected disagreement increases with decreasing magnetic field, and is thus ascribable to the increasing diamagnetic relaxation rates, because of the presence of aggregated material, which yields a typical power-law dependence.

The concentration of iron in both intact and centrifuged blueberry juice was 0.040 mmol/dm^3 . The concentrations of copper, nickel, and cobalt were below 0.002 mmol/dm^3 . The concentration of manganese is thus substantially higher than that of the other paramagnetic metals, so that this metal ion is largely responsible for determining the relaxation profile of the juice. The concentration of iron is, however, not negligible with respect to that of manganese, and therefore this metal ion may also contribute significantly to the relaxation rates observed. The contribution from iron ions largely depends on the oxidation state of this metal and on the pH. In fact, the relaxivity of high spin iron(III) is expected to be large at very low pH (close to 0), and to decrease markedly above pH 3 as a result of the formation and precipitation of a variety of hydroxides.²⁴ On the other hand, the relaxivity of iron(II) is very low, even at very low pH.¹⁷ The pH of the investigated blueberry juice was measured as 3.2. Thus, it is not easy to predict the contributions to relaxation from iron ions at this pH, and experimental information is needed.

To separate the contribution of manganese(II) species to the paramagnetic relaxivity from those of iron species, the contribution from iron ions was estimated using two different approaches. In the first approach, $\text{Fe}(\text{NO}_3)_3$ was dissolved at a concentration of 0.040 mmol/dm^3 in a citrate buffer solution (pH 3.2) containing 0.1 mmol/dm^3 oxalate. Citrate buffer was used because the investigated juice contains citric acid (see the Materials and Methods section), and oxalate was added because the juice was estimated to contain it in the concentration used.²⁵ Basically,

identical profiles were also obtained in the absence of oxalate (Figure S1). The relaxation rates have very little dependence on the magnetic field, ranging from 0.50 to 0.43 s⁻¹ on passing from low fields to 1 T, at 25°C. The water proton relaxivity due to manganese(II) ions in the centrifuged blueberry juice was then calculated from the differences between the relaxation rates of the juice and those of the Fe(NO₃)₃ solution, normalized to a manganese concentration of 1 mmol/dm³ (Figure 2). In the second approach, Fe(NO₃)₃ was added in known concentrations (0.020, 0.040, and 0.120 mmol/dm³, corresponding to 50%, 100%, and 300% of the amount of iron concentration originally present in the juice, respectively) to the centrifuged blueberry juice, so that the relaxation rates in the absence of iron could be extrapolated (Figure S2B). Both approaches provided basically the same relaxivity profiles (Figure S2B) for manganese in the centrifuged blueberry juice.

Figure 2 shows the longitudinal and transverse relaxivity data for manganese in the centrifuged blueberry juice and in the pineapple juice, as well as the relaxivity data of the manganese(II) aqua ion at pH 3.6. As expected, the relaxivity of the blueberry juice is much higher than that of the pineapple juice. Interestingly, at intermediate fields (around 1 MHz), the relaxivity is smallest for the manganese aqua ion, and increases on passing to the pineapple juice, and then to the blueberry juice. This suggests that the reorientation correlation times should increase on passing from the aqua ion to the juices, and thus that the manganese ions partially interact with other molecules in the pineapple juice, and possibly even more in the blueberry juice; a larger relaxivity in blueberry than in pineapple juice may also be due to a higher number of water molecules coordinated to the manganese(II) ion and/or to a slightly higher fraction of manganese(II) bound to macromolecules.

The low field relaxivity is largely determined by the Fermi-contact relaxation. The low field relaxivity in the blueberry juice, similar to that of the manganese aqua ion, indicates a greater fraction of manganese aqua ions, or a larger Fermi-contact coupling constant, than that in pineapple juice (the difference in relaxivity before and after the first dispersion being, however, significantly smaller in the blueberry juice than in the manganese aqua ions). Together with a higher (low field) Fermi-contact longitudinal relaxivity, the transverse relaxivity at high field is also consistently higher in the blueberry than in the pineapple juice.

The relaxivity profiles were fitted using the Solomon–Bloembergen–Morgan model^{26–29} (see the supporting information) and the best fit parameters are reported in Table 1 together with those previously obtained for the pineapple juice and the manganese aqua ion.¹⁶ The best fit profiles are shown in Figure 2, and the different contributions to the relaxivity (inner-sphere dipole–dipole relaxation modulated by slow mobility and by fast mobility, Fermi-contact relaxation, and outer-sphere relaxation) in Figure 3. Clearly, Fermi-contact relaxation provides a very large contribution to the longitudinal relaxivity at low fields, whereas at high fields the longitudinal relaxivity is determined by dipole–dipole interactions. However, the Fermi-contact interaction represents by far the largest source for transverse relaxation at 400 MHz.

The best fit parameters indicate that, as expected from inspection of the profiles, the reorientation time increases on passing from the aqua ion to the juices (from 28 to ~50 ps, at 25°C), with a minor component present only in the juices (with weight 1.4% in the blueberry juice) experiencing reorientation times of a few nanoseconds. This points to the presence of some large manganese complexes in the juices, with a molecular weight of at least 5000 Da.³⁰ The best fit value of hydration water molecules can result from the averaging between those in aqua ions and in other complexes. This value in blueberry juice is higher than that of in pineapple juice, possibly due to a lower concentration of polydentate ligands, which occur naturally in the juice.³¹

The higher r_1 relaxivity and, most importantly, the higher r_2 relaxivity, of blueberry than of pineapple juice suggests a higher efficiency of the former, if concentrated in such a way that the manganese ions have the same concentration than as in the pineapple juice. This assumes that by

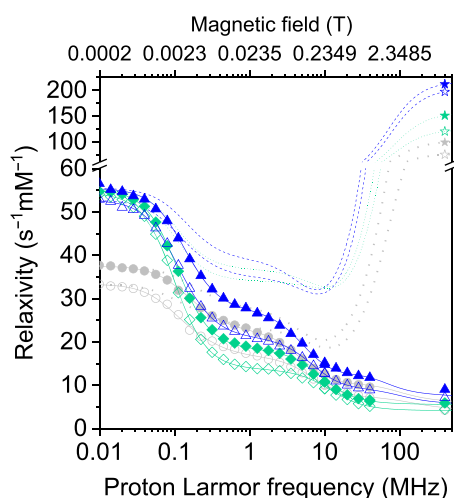


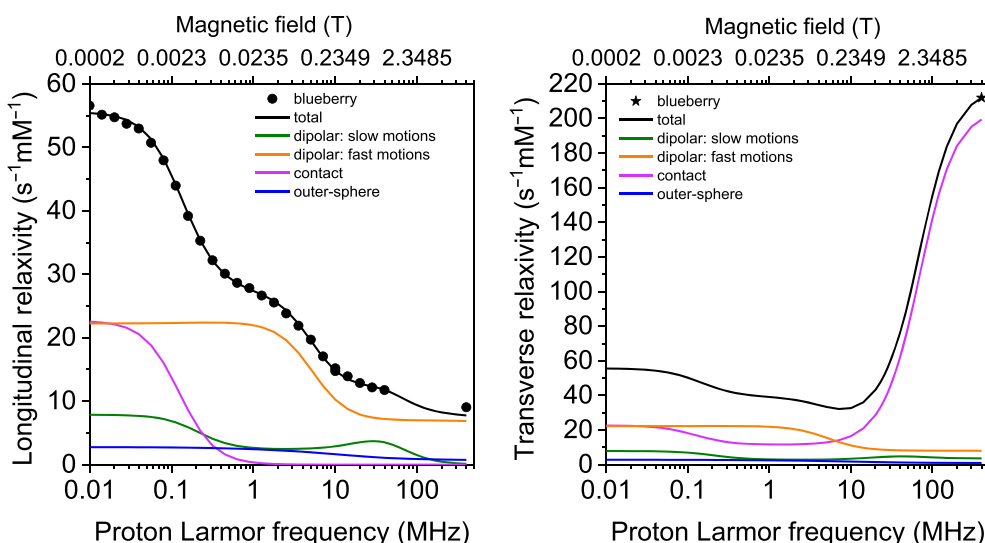
FIGURE 2 ¹H longitudinal relaxivity profiles (blue triangles) and transverse relaxivity at 400 MHz (blue stars) of Mn²⁺ ions in centrifuged blueberry juice at 25°C (solid symbols) and 37°C (empty symbols). The same data for pineapple juice (gray symbols) and Mn²⁺ aqua ions (green symbols) are also shown. The solid and dotted lines represent the best fit profiles of the longitudinal and transverse relaxivities, respectively

TABLE 1 Best fit parameters for the centrifuged blueberry juice, pineapple juice and the Mn^{2+} solution. The corresponding best fit profiles are shown in Figures 2 and 3

	Blueberry juice		Pineapple juice		Mn^{2+} aqua ion		
	25°C	37°C	25°C	37°C	25°C	37°C	
r (^(*))	2.85						Å
q	5.2 ± 0.2		4.0 ± 0.1		6 (^(*))		
Δr (^(*))	0.015				0.018		cm^{-1}
w	0.014 ± 0.003		0.021 ± 0.003		1		
τ_r	2800 ± 900	1600 ± 600	1700 ± 300	1000 ± 200	28 ± 1	20 ± 1	ps
τ_v	9 ± 1	8 ± 1	9 ± 1	7 ± 1	5.3 ± 0.1	4.5 ± 0.1	ps
τ_M	38 ± 2	36 ± 2	39 ± 3	29 ± 2	18 ± 1	14 ± 1	ns
τ_l	48 ± 2	36 ± 1	51 ± 2	36 ± 2	-	-	ps
A^{FC}/h	0.74 ± 0.02		0.55 ± 0.02		0.82 ± 0.01		MHz

Outer-sphere relaxation was also included with $d = 3.6$ Å and $D = 3.0$ and $3.9 \times 10^{-5} \text{ cm}^2/\text{s}$ at 25°C and 37°C, respectively.

(^(*))fixed.

**FIGURE 3** ^1H longitudinal relaxivity (left) and transverse relaxivity (right) of Mn^{2+} ions at 25°C and their dipolar, Fermi-contact, and outer-sphere contributions in the centrifuged blueberry juice

concentrating the blueberry juice there are no significant changes in the parameters upon which its relaxation properties depend (aggregation, lifetimes of water molecules coordinated to manganese(II), tumbling times, and metal ion coordination environment). To verify this higher efficiency of the concentrated blueberry juice, 10.0 mL of the juice was freeze-dried then redissolved in 2.50 mL of H_2O to achieve a manganese(II) concentration of 0.45 mmol/dm^3 (i.e. the same concentration of the pineapple juice). The acquired NMRD profiles are shown in Figure 4 as pink triangles, whereas the profiles calculated from the original blueberry juice (rescaled to account for the increased metal ions concentrations) are shown as red squares. Interestingly, there is very good agreement at the intermediate magnetic fields, whereas the longitudinal relaxation rates are smaller than expected at low magnetic fields and higher at high magnetic fields. These effects were also observed for pineapple juice upon the addition of alginate, and are ascribed to the larger viscosity of the solution resulting from juice concentration and to transient interactions of manganese(II) ions, with possible confinement in a restricted environment, in such a way as to reduce their mobility.¹⁶ This is confirmed by the appearance of a small relaxivity peak at about 25 MHz. The increase in the tumbling time is paralleled by a reduction of Fermi-contact relaxation (due to a smaller fraction of manganese aqua ions, a smaller electron relaxation time at low fields and/or a smaller contact coupling constant), which is also causing a decrease in the observed transverse relaxation rate at 400 MHz with respect to the prediction from the intact blueberry juice data. Nevertheless, both the longitudinal and transverse relaxation rates of the concentrated blueberry juice are substantially larger than those of the pineapple juice, despite having the same Mn^{2+} concentration.

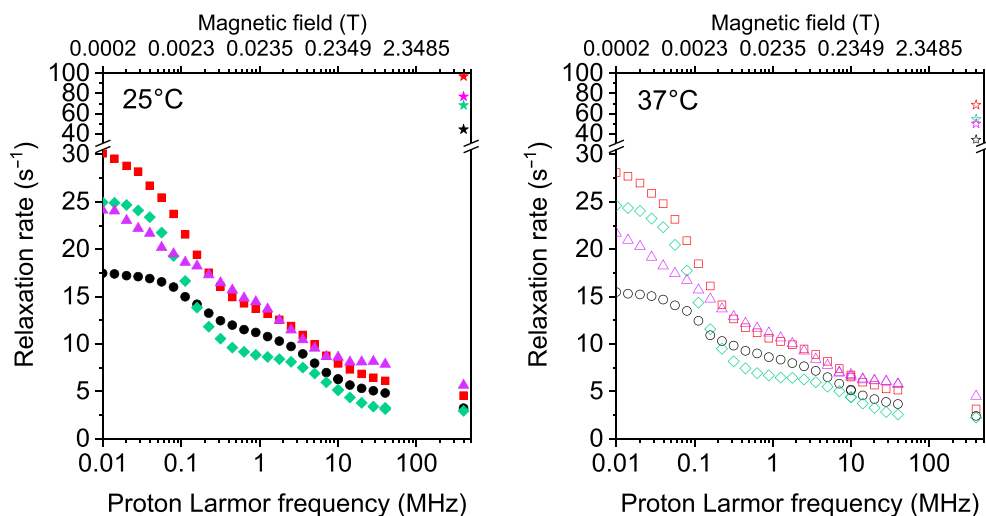


FIGURE 4 Longitudinal relaxation rates (triangles and circles) and transverse relaxation rates at 400 MHz (stars) of the blueberry juice concentrated 4.1 times (pink symbols) and of the pineapple juice (black symbols). The relaxation rates of these samples, containing Mn²⁺ with concentration 0.45 mmol/dm³, are also compared with those of Mn²⁺ aqua ions (green symbols) and those obtained by rescaling the data collected for intact blueberry juice (red symbols) at the same Mn²⁺ concentration. Solid symbols indicate data at 25°C (left), while empty symbols indicate data at 37°C (right)

4 | CONCLUSIONS

The relaxometric analysis performed for blueberry juice indicates that the manganese ions in this juice have a higher relaxivity than those in pineapple juice. Therefore, the water proton relaxation rates in the blueberry juice are increased to a larger extent than in pineapple juice when manganese(II) ions are contained in the same concentration (Figure 4). On the other hand, this implies that a lower quantity of manganese(II) contained in blueberry juice is sufficient to achieve the same relaxation enhancement, and thus the same contrast in the MRI images, obtainable with a larger quantity of manganese(II) contained in pineapple juice.

Very importantly, the transverse relaxation rate at high fields is substantially larger (almost double) in blueberry juice than in pineapple juice when both juices contain the same concentration of manganese(II). This points to a higher efficiency as T₂-agent of the concentrated blueberry juice, similar to that of Mn²⁺ aqua ions, than of pineapple juice. Analysis of the relaxivity profiles shows that this higher efficacy is determined by a larger Fermi-contact contribution to relaxation. This larger transverse relaxation rate is, however, somewhat smaller than expected without considering in the concentrated solution the presence of a larger fraction of metal ions interacting with other molecules/macromolecules contained in the juice. In conclusion, although manganese(II) is the paramagnetic ion responsible for the relaxation enhancements caused by the juices, its interaction with other molecules present in the juices can substantially affect its efficiency as an MRI contrast agent.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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SUPPORTING INFORMATION

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