



# Oolong Tea-Derived Manganese Nanoparticles as an Alternative Oral Negative Contrast Agent for MRCP Imaging

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## Abstract

**Background/Aim:** Conventional natural manganese contrast agent for magnetic resonance cholangiopancreatography (MRCP) have produced suboptimal visualisation of the gastric, duodenum and biliary system. While various studies have explored manganese-based media, limited research has focused on manganese nanoparticles (Mn-NPs). This study investigated oolong tea-derived Mn-NPs as a potential alternative oral contrast agent for MRCP imaging, aiming to enhance image clarity while minimising neurotoxic effects in healthy volunteers.

**Methods:** A true experimental approach with a pre-test and post-test control group setup was employed, involving thirty healthy volunteers divided into three groups: (K1) Mn-NPs derived from oolong tea, (K2) manganese extracted from oolong tea and (K3) standard manganese chloride. Signal-to-noise ratio (SNR), contrast-to-noise ratio (CNR) and blood levels of IL-1 $\beta$  and TNF- $\alpha$  were assessed pre- and post-contrast administration for efficacy and neurotoxicity.

**Results:** The extracted Mn-NPs of oolong tea decreased signal strength in the stomach (3.40 %) and the duodenum (1.60 %), while increasing signal blockage in the gallbladder (0.80 %), cystic duct (4.40 %), common hepatic duct (13.80 %), intrahepatic duct (4.10 %), common bile duct (4.10 %) and pancreatic duct (3.10 %). These results outperformed those of standard contrast agent and manganese sourced from oolong tea. Interleukin 1 beta (IL-1 $\beta$ ) (3.24 pg/mL) and tumour necrosis factor alpha (TNF- $\alpha$ ) (6.9 pg/mL) levels showed no neurotoxic effects. Mn-NPs from oolong tea showed superior imaging performance. This is due to their long residence time and stronger magnetic properties. The anti-inflammatory compounds in oolong tea likely contributed to the stable cytokine levels observed, indicating a good safety profile. In addition, integration with the FIESTA MRI suite further enhances image contrast.

**Conclusion:** Mn-NPs prepared from oolong tea can be used instead of traditional contrast agent in MRCP examinations. They provide better image quality and do not harm the brain.

**Key words:** Oolong tea; Nanoparticles; Manganese; Cholangiopancreatography, magnetic resonance.

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## Introduction

Magnetic resonance cholangiopancreatography (MRCP) may produce a false impression of stric-

ture due to overlap of the gastric, duodenum and pancreaticobiliary system, resulting in changes

to signal strength. A heightened signal can cause misinterpretation in about 5–7 % of cases, where normal findings are mistakenly viewed as abnormal.<sup>1, 2</sup> In MRCP examinations, the presence of fluid in the gastric or duodenum often leads to diagnostic errors. Additionally, fluid and air in the first part of the small intestine (duodenal bulb) may indicate the presence of gallstones.<sup>2–4</sup> Special oral contrast medium can be used to avoid misunderstandings about certain bile duct or pancreas health conditions. These help reduce fluid signals in the gastric and first part of the small intestine. This makes it easier to observe the pancreatic and bile duct systems clearly without interference from the gastric, intestine or other organs.<sup>5, 6</sup>

MRCP studies employ oolong tea as an alternative contrast agent to improve differentiation between the biliary tract and adjacent tissues. However, standard oolong tea is that it does not sufficiently reduce gastric and intestinal signals, so some health issues may not be observed.<sup>7</sup> To overcome this limitation, additional studies are required to standardise and enhance oolong tea as a natural oral negative contrast agent by enhancing its manganese content through nanoparticle technology.

Nanoparticles especially magnetic nanoparticles have been extensively utilised in magnetic resonance imaging (MRI) to formulate new contrast agent.<sup>8</sup> Nanoparticles are a technology that purposes to improve the size of dosage forms in the range of 10–1000 nm. Nanoparticle-sized contrast agent is superior to regular contrast agent because of its stronger magnetic effects. This was due to the higher T1 and T2 relaxometric values, which increased the signal strength. The small size of nanoparticles helps control how drugs move in the body, increasing the time they stay in the blood and allowing them to build up in targeted tissues. Nanoparticles are readily eliminated by the reticuloendothelial system, primarily through the liver and spleen.<sup>9</sup>

## Methods

A true experimental pre-test and post-test in control group design was implemented, with healthy volunteers divided into three groups: K1 received manganese nanoparticles (Mn-NPs) from oolong

tea, K2 received oolong tea-extracted manganese and K3 received standard manganese chloride contrast. Volunteers fasted for 5 hours prior to MRCP and initial blood sampling (3 mL) for interleukin 1 beta (IL-1 $\beta$ ) and tumour necrosis factor alpha (TNF- $\alpha$ ) levels. Furthermore, for all volunteers, MRCP examinations were carried out before the administration of contrast agent with parameters, namely, imaging included a three-plane FIESTA localiser and T2-weighted FIESTA fat-saturated sequences (transverse breath-hold and coronal thick-slab radial), performed with 3D MRCP Respiratory, showed in Table 1. Before patients were administered oral negative contrast agent, signal-to-noise ratio (SNR) and contrast-to-noise ratio (CNR) values in the gastric, duodenum and pancreatobiliary system were assessed using MRCP imaging.

Treatment groups: group (K1) was administered 200 mL of oral negative received contrast formulated with oolong tea derived Mn-NPs and group (K2) received oral negative contrast with manganese extracted from oolong tea. The control group (K3) received 200 mL of standard oral negative contrast agent, manganese chloride (MnCl<sub>2</sub>). MRCP was repeated 5 minutes post contrast using identical settings. MRCP was repeated 5 minutes post contrast using identical settings. MRCP images taken after using oral negative contrast agent were checked to measure the CNR, which measures the difference in signal strength between nearby organs.<sup>10</sup> Following the MRCP procedure, all three groups of healthy volunteers (control and treatment groups) proceeded fast for an additional 5 hours after ingesting the oral negative contrast agent. Subsequently, a second 3 mL blood sample was collected to measure IL-1 $\beta$  and TNF- $\alpha$  levels.

The study compared oolong tea-derived manganese (with and without nanoparticles) and MnCl<sub>2</sub> in reducing gastrointestinal signals and enhancing pancreaticobiliary visibility. Investigation involved boiling 100 grams of dried oolong tea leaves in one litre of water, followed by extraction with a rotary evaporator, yielding a manganese content of 0.94 mg/dL. The volume used to produce the optimal MRCP image was 200 mL, consisting of 15 mL of oolong tea extract dissolved with 185 mL of distilled water. The oolong tea extracted manganese nanoparticles used were processed using the sonication method using 200 W/min<sup>2</sup> energy and given a frequency of 20 kHz for 20 minutes, which resulted in an Mn particle

**Table 1:** Magnetic resonance cholangiopancreatography (MRCP) sequence parameters and imaging protocol on the magnetic resonance imaging (MRI) GE SIGNA Voyager 1.5 Tesla

Parameter	3 plane loc BH	Coronal T2 SSFSE BH	Axial T2 SSFSE BH	2D thick slab	3D MRCP respiratory triggered
Plane	Multiplanar	Transversal	Axial	Coronal	Coronal oblique
TE (ms)	80	90	90	700	700
TR (s)	1200	1200	1200	4500	2500
ETL	-	150	150	300	128
Average	1	1	1	1	1.4
Flip angle	150	160	160	180	160
Phase FOV	100 %	100 %	100 %	100 %	100 %
Read FOV	400 mm	380 mm	380 mm	250 mm	380 mm
Bandwidth	700	470	470	150	500
Parallel Imaging	2	2	2	2	2
Saturation	None	Fat-weak	Fat-weak	Fat-strong	Fat-strong
Freq encode	256	320	320	320	-
Phase encode	180	256	256	256	-
Freq DIR	A >> P	A >> P	A >> P	L >> R	R >> L
Concat	1	3	3	6	1
Slice thickness	6 mm	6 mm	6 mm	50 mm	1 mm
Distance factor	9 mm	1.2 mm	1.2 mm	25 mm	-
Slices	5	30	30	1	72 (per slab)
Scan time	00:18	02:30	02:30	00:50	05:36
Respiratory	-	Breath hold	Breath hold	Multi B-hold	Triggered

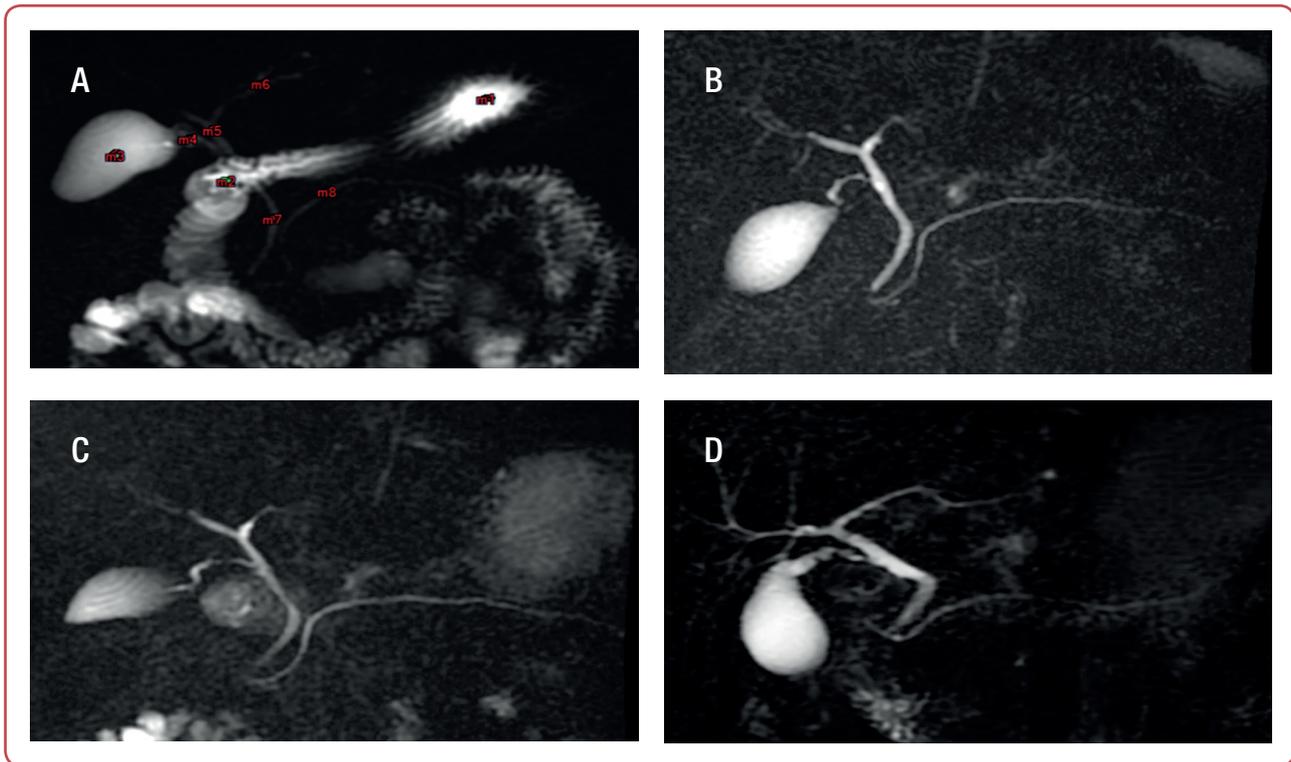
TE: echo time; TR: repetition time; ETL: echo train length; FOV: field of view;

diameter size of 196.456 nm. The World Health Organisation (WHO) recommends a daily Mn consumption for adults of between 0.7 and 10.9 mg, although the use of Mn dietary supplements containing more than 20 mg Mn has been reported in cases of osteoarthritis and osteoporosis.<sup>11</sup> Based on these recommendations, the use of manganese levels in oolong tea in this study was within safe limits.

The researchers assessed the differences in signal strength between the main regions referred to in Ghanati, namely assessing the gastric and pancreatic duct, gastric and common bile duct, duodenum and gallbladder and duodenum and common bile duct, realising that most of the pathological changes occur in the pancreatobiliary system.<sup>5</sup> The neurotoxic impacts of administering oral negative contrast agent to healthy volunteers across three groups control and treatment were evaluated by analysing IL-1 $\beta$  and TNF- $\alpha$  concentrations in blood samples.<sup>12</sup>

## Results

Visual changes in MRCP images were observed in all three treatments used in this study. Figure 1 shows the variation in image quality of the gastric, duodenum and pancreatobiliary system. Before contrast agent was applied (Figure 1 A), the gastric (m1) and duodenum (m2) appeared bright or hyperintense, while the pancreatobiliary structures-including the gallbladder (m3), cystic duct (m4), common hepatic duct (m5), intrahepatic duct (m6), common biliary duct (m7) and pancreatic duct (m8) appeared dark or hypointense. Following the application of standard contrast (Figure 1 B), oolong tea extract manganese (Figure 1 C) and its nanoparticle form (Figure 1 D), signal suppression or darkening was evident, particularly in the gastric and duodenum. Gastric and duodenal signal suppression was comparable between nanoparticle and control groups, unlike the improved pancreaticobiliary clarity observed with nanoparticles in MRCP.



**Figure 1:** Magnetic resonance cholangiopancreatography (MRCP) examination image results: A. In the absence of oral contrast agent; B. Standardised oral contrast agent; C. Using an oral contrast agent to extract manganese nanoparticles (Mn-NPs) from oolong tea; D. Mn-NP extraction from oolong tea using oral contrast agent

### Suppression of gastric and duodenal signal strength in contrast agent administration of Mn-NPs extracted from oolong tea

MRCP images following the administration of an alternative negative oral contrast agent oolong tea extract Mn-NPs demonstrated alterations in signal strength and signal-to-noise ratio (SNR) in the gastric and duodenum, as well as in the pancreaticobiliary system, including the gallbladder, cystic duct, common hepatic duct, intrahepatic ducts and pancreatic duct. Figure 2 compares the signals from gastric and duodenum before and after using a contrast agent. The signals were weaker when Mn-NPs from oolong tea extracts were used. This shows that both the gastric and duodenum become darker after contrast, even though the change in gastric suppression wasn't statistically significant ( $p = 0.349$ ) or duodenum ( $p = 0.524$ ) during the post-contrast phase.

### Mn-NPs contrast agent increasing the signal strength of the pancreaticobiliary system with oolong tea extracted Mn-NPs contrast agent

The pancreaticobiliary system showed improvement on MRI before and after contrast administration. Table 2 illustrates that Mn-NPs derived from oolong tea were more effective in obstructing gallbladder, cystic duct, common hepatic duct, intrahepatic duct, bile duct and pancreatic duct, in comparison to control group, which utilised manganese-extracted oolong tea.

Meanwhile, compared with pre-contrast stitches, the gallbladder, common hepatic duct and pancreatic duct showed better stitches. Obstructions in common bile duct, intrahepatic ducts and cystic duct were accentuated following administration of oolong tea-derived Mn-NPs compared to pre-contrast. Interestingly, the blockage in the gallbladder and various ducts was usually less severe than that in the control group after using oolong tea-extracted manganese.

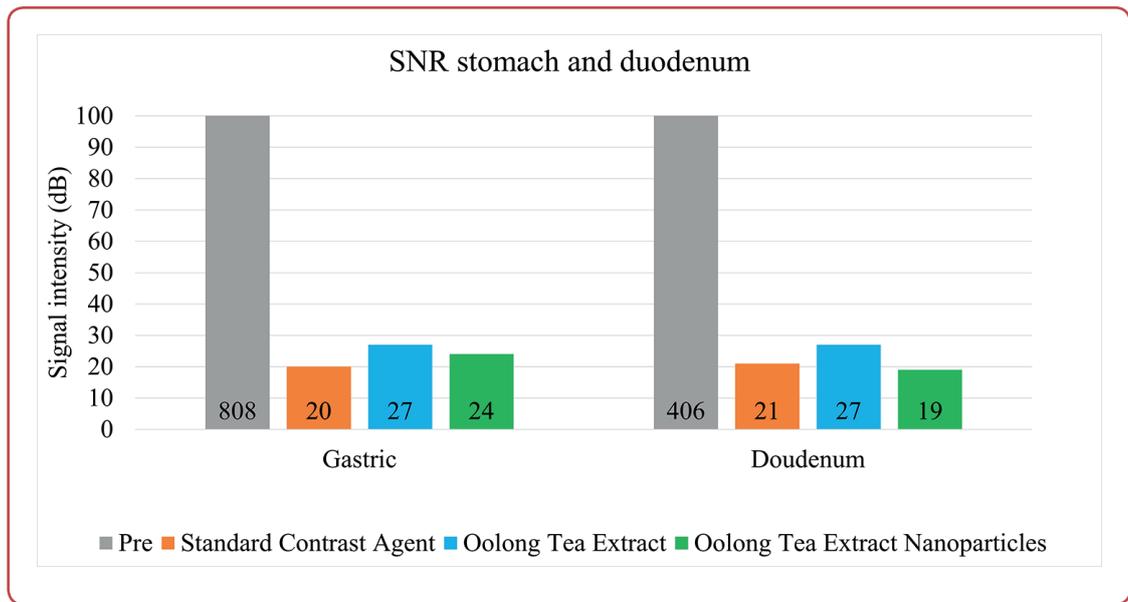


Figure 2: The signal-to-noise ratio (SNR) plot comparison of gastric and duodenal values pre- and post-administration of standard contrast agent, oolong tea-extracted manganese and its nanoparticle form

Table 2: The signal-to-noise ratio (SNR) of pancreaticobiliary tree system at the pre and post administration of standard contrast agent, oolong tea extracted manganese and oolong tea-extracted manganese nanoparticles (Mn-NPs)

Organ	Pre (dB)	Standard contrast agent (dB)	Oolong tea extract (dB)	Oolong tea extract nanoparticles (dB)
Gall bladder	233.0	235.0	198.0	255.0
Cystic duct	84.0	56.0	73.0	79.0
Common hepatic duct	98.0	99.0	111.0	130.0
Intrahepatic duct	99.1	75.5	74.8	99.0
Common bile duct	106.0	93.0	99.0	105.0
Pancreatic duct	62.0	58.0	46.0	76.0

Differences in signal strength between the gastric and duodenum when using a manganese nanoparticle contrast agent from oolong tea in the pancreatic and biliary systems

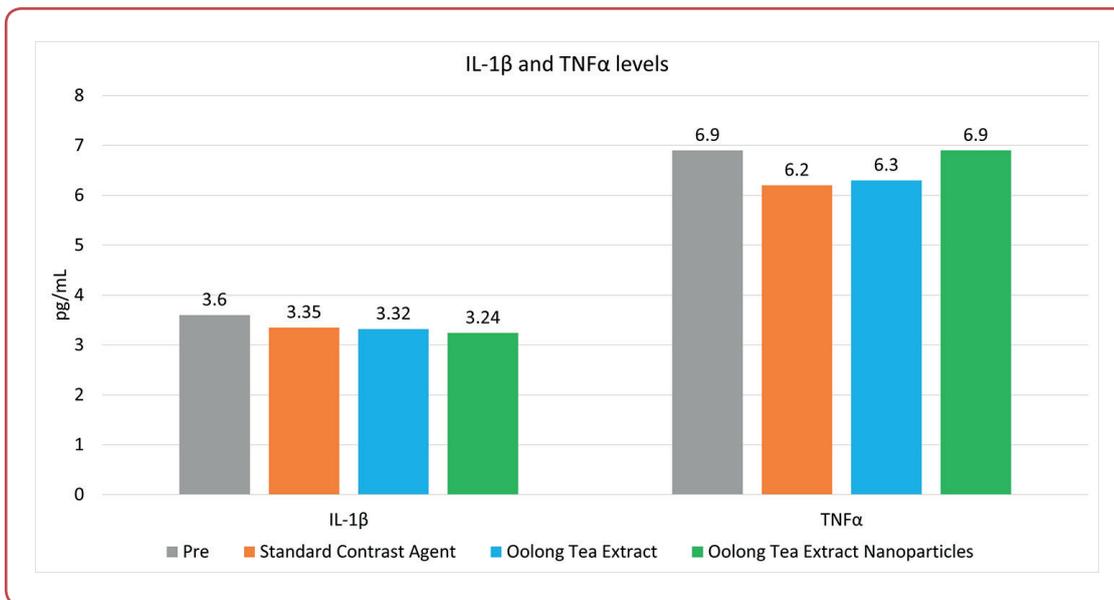
The outcomes of MRCP after using an oolong tea-derived manganese nanoparticle contrast agent were observed. Table 3 shows the difference in CNR, indicating that Mn-NPs extracted from oolong tea produce better CNR than standard contrast agent and non-Mn-NPs extracted oolong tea. Images obtained without contrast showed more pronounced signal obstruction compared to those enhanced with Mn-NPs derived from oolong tea.

IL-1 $\beta$  and TNF- $\alpha$  levels as indicators of neurotoxic impact in the administration of manganese nanoparticle contrast agent derived from oolong tea extraction results

Figure 3 shows lower IL-1 $\beta$  measured (3.32 pg/mL) after oolong tea manganese and 3.24 pg/mL with its nanoparticle form, compared to 3.35 pg/mL with the standard agent. The levels of TNF- $\alpha$  of 6.2 pg/mL with standard contrast agent, 6.3 pg/mL with manganese extracted from oolong tea and 6.9 pg/mL with Mn-NPs extracted from oolong tea were identical to the TNF- $\alpha$  levels before contrast (6.9 pg/mL).

**Table 3:** A contrast-to-noise ratio (CNR) for the gastric-pancreatic duct, gastric-common bile duct, duodenum-gall bladder and duodenum-common bile duct

Organ	Standard contrast agent (dB)	Oolong tea extract (dB)	Oolong tea extract nanoparticles (dB)
Gastric-pancreatic duct	35.70	29.43	48.61
Gastric-common bile duct	74.19	49.94	85.05
Duodenum-gall bladder	175.39	177.77	264.42
Duodenum-common bile duct	73.38	51.66	87.47



**Figure 3:** The levels of interleukin 1 beta (IL-1β) and tumour necrosis factor alpha (TNF-α) before and after standard contrast agent, manganese oolong tea extraction and nanoparticle administration

At the same time, microglia took up oolong tea-derived Mn-NPs faster, which led to higher levels of TNF-α. The increase in TNF-α after using oolong tea-derived Mn-NPs is closely related to how the body keeps balance in the central nervous system and how certain disease processes work, particularly those involving microglia, which are very responsive to small changes in the CNS. Results show that Mn-NPs derived from oolong tea function well as a negative oral contrast agent for MRCP in healthy subjects. This approach reduces the signal strength in the gastric and duodenum while improving the visibility of the pancreatobiliary system.

## Discussion

Mn-NPs derived from oolong tea offered better post-contrast suppression in the gastric than tra-

ditional contrast agent. In the duodenum, signal suppression using oolong tea-extracted Mn-NPs was notably more effective than both the oolong tea-extracted manganese alone and the standard contrast agent used as controls. This is because Mn-NPs have a unique property known as blood circulation time, where nanoparticles last longer in the duodenum, resulting in better suppression.<sup>9</sup> Suppression of the signal strength in the gastric and duodenum occurs because Mn-NPs have five unpaired electrons and are the second most powerful base material for contrast agent after gadolinium.<sup>13, 14</sup>

Physiologically, the introduction of manganese into the bloodstream in modest quantities is sufficient for essential plasma functions. However, excess manganese is excreted by liver cells, conjugated in bile, passed on to the small intestine and excreted in faeces.<sup>15</sup> Manganese is absorbed mainly through the gastrointestinal tract, with a low oral absorption efficiency of less than 5 %

of total intake. This absorption arises through active transport mechanisms that are saturable, have a high affinity and a low capacity. Iron (Fe) status, the composition of the food matrix, bio-availability and the presence of promoter compounds like vitamin D3 and some amino acids may all contribute to absorption significantly more effectively. Vitamin D3, for example, has been reported to increase the accumulation of Mn on the intestinal wall and accelerate its uptake by hepatocytes, which further increases bile excretion.<sup>14, 16</sup>

Upon entry into the portal circulation, Mn is mostly bound to macroglobulin and quickly captured by the liver for excretion via bile. Renal excretion plays a very minimal role. Therefore, although Mn can reach the systemic circulation, its presence in the blood is transient with a half-life of less than two hours, reflecting the highly efficient hepatic clearance process. In this context, blood levels of Mn reflect short-term exposure and gastrointestinal-liver transport dynamics rather than steady systemic accumulation.<sup>14, 17-19</sup>

Notably in previous studies, there was no specific mention of the difference in the SNR of the pancreatobiliary tree between pre- and post-contrast images.<sup>1, 2</sup> Studies have shown that pre-contrast enhancement is strongly affected by the technical parameters of the pulse sequence employed. MRCP examinations utilise fast imaging technique known as steady-state acquisition (FIESTA) pulse sequence. This pulse sequence is a gradient echo sequence based on the basic principle of a fully refocused steady-state sequence and produces a gradient echo T2 image.<sup>20</sup> At a very fast scanning time (patient breath-hold), organs that contain fluid in the pancreaticobiliary tree system will appear bright and suppress signals that do not contain fluid around them.<sup>3</sup> The integration of oolong tea-extracted Mn-NPs with the FIESTA produced superior strobing effects compare to the separate application. This suggests that the nanoparticles not only provide an independent contribution to image contrast but also enhance the contrast generated by the sequence.

An improved contrast effect on the studied organs was achieved by administering a manganese nanoparticle contrast agent derived from oolong tea. Tissues exhibiting a prolonged T2 relaxation time appear bright on the image, demonstrating a significantly high T2/T1 ratio, whereas tissues with a brief relaxation time undergo saturation. This aligns with the earlier research conducted by Mandarano and Chavhan.<sup>3, 21</sup>

Assessing IL-1 $\beta$  and TNF- $\alpha$  concentrations was intended to detect neurotoxicity, using healthy reference ranges of  $4.6 \pm 0.2$  pg/mL and  $15.94 \pm 0.89$  pg/mL, respectively.<sup>11</sup> Manganese tends to accumulate in the liver and pancreas during excretion; if manganese transporters malfunction, it may accumulate in the CNS and liver, leading to toxicity. This happens because manganese levels in the blood show the overall amount in the body and manganese leaves the blood quickly, usually in less than 2 hours, because the liver filters it out quickly.<sup>22</sup>

The main source of IL-1 $\beta$  is microglia, but cytokines are also a source of IL-1 $\beta$  produced by astrocytes, excretion in oligodendrocytes and neurons. Neurotoxicity occurs when IL-1 $\beta$  levels are at very high concentrations and when prolonged exposure occurs.<sup>23, 24</sup> Increased IL-1 production occurs in response to infection.<sup>25</sup> The low IL-1 $\beta$  levels in this study could be caused by the anti-inflammatory process of polyphenol content in oolong tea. Novilla reported that oolong tea and tea polyphenols have antioxidant, antimutagenic, anticancer and anti-inflammatory effects.<sup>26</sup> The anti-inflammatory properties of OTEE and EGCG in this study were able to inhibit the production of TNF- $\alpha$ , IL-6, IL-1 $\beta$ , COX-2 and NO in LPS-induced mouse macrophage-like cells (RAW 264.7).<sup>27</sup> Despite a minimal rise in TNF- $\alpha$  levels, this has resulted in slight activation that inhibits microglial apoptosis and mitigates progressive inflammatory processes, leading to protective outcomes in neurodegenerative conditions.<sup>28</sup>

The use of Mn-NPs derived from oolong tea as an alternative oral negative contrast agent for MRCP examinations has several benefits: accessible raw materials, cost efficiency, a familiar and pleasant taste and enhanced magnetic properties. These enhancements are evident as elevated T1 and T2 relaxation values, leading to heightened signal intensity and superior image quality. In comparison, natural oral negative contrast agents used in previous studies still present limitations: blueberry juice is difficult to obtain in Indonesia, pineapple juice has a sour taste, black tea is very bitter and ferumoxsil has an unpleasant metallic flavour.<sup>5, 6, 29</sup> Based on monitoring data on the administration of alternative contrast media of oolong tea extracted manganese nanoparticles to healthy volunteers, no one expressed discomfort, nausea or bitterness after treatment.

## Conclusion

Oolong tea extraction provides Mn-NPs which were proven to replace oral negative contrast media in MRCP imaging. These Mn-NPs significantly enhance signal suppression in the gastrointestinal tract and improve CNR for clearer delineation of biliary structures. Furthermore, administration of these materials did not cause any neurotoxic effects as evidenced by stable IL-1 $\beta$  and TNF- $\alpha$  levels. Future research should concentrate on assessing the shelf life of these nanoparticles and creating appropriate stabilising agents in order to avoid aggregation or sedimentation during room temperature storage.

## Ethics

This study was approved by the Health Research Ethics Committee of RSUP Dr Kariadi Semarang, under approval number 817/EC/KEPK-RS-DK/2021, dated 4 May 2021. Written informed consent was obtained from all healthy volunteers prior to participation.

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## Conflicts of interest

The authors declare that there is no conflict of interest.

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## Data access

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

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