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Contrast enhancement potential of food-based imaging agents in cholangiopancreatography and digestive tract investigations using MRI: A systematic literature review and meta-analysis

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ABSTRACT

Objective: To evaluate the contrast enhancement potential of food-based substances (FBS) as clinical imaging agents in MR cholangiopancreatography (MRCP) and digestive tract investigations.

Methods: A systematic literature search was conducted using a pre-defined strategy and inclusion criteria to identify relevant articles. Two review authors independently screened and selected papers for inclusion, conducted risk of bias assessment using ROBINS-I (Risk of Bias In Non-randomised Studies of Interventions) tool and assessed certainty of evidence using the Cochrane's GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. Areas of disagreement were resolved through consensus and the involvement of a third reviewer. The data obtained were *meta*-analysed using both random and fixed effects models with inverse variance methods, depending on the included studies' methodological heterogeneity, to estimate the pooled mean difference and odds ratio.

Results: 16 studies (1360 participants) were included in this review. Eight studies each examined the effectiveness of FBS for contrast enhancement in MRCP and MRE, respectively. The pooled mean differences between MRCP with pineapple juice and non-contrast MRCP were 1.04 (95 % CI: 0.23, 1.84; $I^2 = 96$ %, $p < 0.01$) for bile duct visibility and 0.95 (95 % CI: 0.04, 1.85; $I^2 = 95$ %, $p < 0.01$) for pancreatic duct visibility. Compared to non-contrast MRCP, MRCP with pineapple juice showed improved pancreaticobiliary duct visibility (Combined odds ratio, 5.01; 95 % CI: 2.34, 10.64; $p < 0.0001$). However, when compared with synthetic contrast agents, there is a lower likelihood of obtaining excellent quality MRE images with food-based contrast agents (FBCAs) (odds ratio, 0.36; 95 % CI: 0.18, 0.73, 0.73; $p = 0.004$). A generally high safety and acceptance profile was reported across the included studies for FBCAs. The certainty of the evidence obtained was considered moderate across all outcomes.

Conclusion: Oral administration of pineapple juice improves the diagnostic quality of MRCP investigations, while the contrast enhancement potential of FBS is limited in MRE studies. The high heterogeneity of results and moderate certainty of the evidence, however, require a cautious admission of results. Therefore, further research is necessary to gain a comprehensive understanding of the reliability of FBS in these MRI investigations, as well as in other imaging modalities that are yet to be explored.

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1. Introduction

Contrast agents have diverse functions depending on the imaging technique and clinical examination. In clinical radiology, the importance of contrast media is widely acknowledged for greatly increasing diagnostic confidence across different tissues to precisely identify pathologies [1,2,3,4]. Their mechanism of action relates to their active base components; for instance, those containing gadolinium are mainly used in MRI, while iodine and barium-based agents are employed in fluoroscopy and CT scans. Of note, most of the imaging agents that are currently in use are of a synthetic base, and their increasing production and utilisation [5] have been associated with adverse physiological reactions [1,6,7] and environmental sustainability concerns [8–11], presenting limitations in sustainable contrast media administration.

Besides the biosafety, gadolinium-based substances used in MRI are relatively regarded as safe [12,13] because only minimal doses are required for effective tissue enhancement [14]. Although gadolinium deposits have been detected in the brain following its intravenous administration [15], there is currently no evidence linking its retention to clinical symptoms or harm [16]. Additionally, while both iodine and gadolinium-based contrast agents are contraindicated for patients with impaired kidney function, ferumoxytol MRI agent provides a reliable alternative, as it does not rely on the kidneys for clearance [17,18,19]. However, ferumoxytol usage is not cost-effective, making it unaffordable to a wide range of populations.

Some food-based contrast agents (FBCAs) have shown promise in providing environmentally friendly alternatives in some radiological investigations. These agents have been mainly employed in MR cholangiopancreatography (MRCP) and digestive tract investigations through the oral administration route [20,21,22,23]. However, the diverse and fragmented reports of their contrast enhancement capabilities and safety profiles have not yet been *meta*-synthesised to inform their adoption in clinical practice.

MRCP mainly consists of T2-weighted sequences, where inherent tissue properties, such as fluid composition of structures, provide natural contrast. This means MRCP generally does not require exogenous contrast agents; however, negative oral contrast agents, such as pineapple juice, are sometimes used to suppress high signal from adjacent fluid-filled structures by exploiting their paramagnetic qualities [20,22]. Conversely, MR enterography (MRE) often requires oral contrast agents to achieve luminal distension, thereby providing additional contrast to bowel structures. These oral MRE agents mainly serve for mechanical distension rather than signal manipulation, and although water is suitable, it is rapidly absorbed and less effective without additives [24].

With this background, several independent studies [20–24] have explored the inherent qualities of various natural food-based substances (FBS) as biodegradable oral contrast agents; however, their potential for image enhancement, safety, and patient acceptance remains underresearched. Nonetheless, the diversity in existing literature underscores the need for *meta*-analyses to evaluate the effectiveness of these substances in contrast enhancement, specifically for MRCP and MRE. This study, therefore, employs a systematic literature review methodology with *meta*-analysis to evaluate the effectiveness of natural food-based contrast agents (FBCAs) in improving image quality in MRCP and MRE compared to non-contrast scans and those using synthetic commercial agents.

2. Methods

A systematic literature review methodology was employed to synthesise evidence from published primary studies while adhering to the Preferred Reporting Items for Systematic Reviews and Meta-analysis of Diagnostic Test Accuracy (PRISMA-DTA) guidelines [25]. Due to time constraints, the search strategy and protocols were not registered a priori. Nevertheless, while prospective registration is strongly encouraged to enhance methodological transparency, it has been considered a non-mandatory requirement [26].

2.1. Search strategy and eligibility criteria

An advanced literature search was performed across EBSCOhost (hosting MEDLINE, CINAHL, Scopus, EMBASE and Academic Search Ultimate databases) and the PubMed database during May and June 2024, with an updated search conducted on 28th June 2024. The employed search terms were ((radiography) OR (radiology) OR (medical imaging) OR (diagnostic imaging) AND ("contrast medi*") OR ("contrast agent*") AND (food*) OR (product*) OR (juice*) OR (syrup*) AND (natural)). A focused search was also conducted in leading Radiology speciality journals, including Radiology, the American Journal of Roentgenology, Clinical Radiology, European Radiology, European Journal of Radiology, and Abdominal Imaging to identify additional relevant publications. Additional articles were identified from a hand search in Google Scholar and citation searching from bibliographies of relevant primary studies.

The search period was for 20 years (2004–2024) and included peer-reviewed primary studies published in English that investigated the contrast-enhancing potential of naturally occurring food products and their efficacy in MRCP and digestive tract MR imaging. This timeframe allows for the inclusion of evidence from the last twenty years, during which research on this subject has become more common. Additionally, this range includes the latest studies published up to 2024, ensuring that the review captures the most recent evidence on the efficacy of these substances in clinical practice.

This study excludes reviews, opinion reports, commentaries, grey literature, non-peer-reviewed articles, and studies that solely explore the current commercial contrast agents. Furthermore, as recommended in Cochrane guidelines [27], the exclusion criteria encompassed studies failing to assess the outcomes of interest of this review. Study designs eligible for inclusion included randomised controlled trials (RCTs), Non-Randomised studies of interventions (NRSIs), cross-sectional, and cohort studies. However, only the RCT's and NRSIs were deemed appropriate for inclusion in *meta*-analysis as these measured the outcomes that addressed the primary objective of the review.

2.2. Data extraction and quality assessment

All retrieved studies were imported into EndNote Library™ (a reference management tool), and using its inbuilt "Find duplicates" feature, SD and TNA identified and removed duplicates. Thereafter, Covidence™ (a web-based collaboration software platform for systematic and other reviews) was used to independently screen the titles and abstracts of the remaining studies to assess their eligibility. Full-text screening was subsequently conducted for studies deemed potentially relevant. Using the data extraction tool in Covidence™, data related to the chemistry, contrast enhancement capacity, safety profiles, and patients' acceptance of FBS were extracted.

The relevant quantitative extracted data were imported into Meta-analysisonline™ for *meta*-analysis. Most of the included studies were of pre-post intervention observational designs; therefore, the Risk of Bias in Non-randomised Studies of Intervention (ROBINS-I) [28], was employed as a quality appraisal tool to evaluate the risk of bias of included studies in estimating intervention effectiveness [29]. The tool has seven domains for bias assessment, namely, bias due to confounding, selection of participants, classification of interventions, deviation from the intended interventions, missing data, measurement of outcomes, and selection of the reported results. Each domain was assessed as having either "low risk", "moderate risk", "serious risk", or "critical risk" of bias.

2.3. Statistical analysis

As highlighted by Haidich [30], a *meta*-analysis was performed on studies that were sufficiently homogeneous in terms of study designs,

the interventions applied, and the outcomes assessed. Using the random effect and fixed effect models, depending on the methodological heterogeneity of studies included in the *meta*-analysis, the mean difference (MD) and odds ratio (OR) were employed to evaluate the contrast-enhancing effectiveness of commonly used natural food substances as contrast agents, compared to non-contrasted procedures or those using synthetic commercial agents. The pooled odds ratio (OR) of obtaining excellent image quality among the natural FBCA interventions was also calculated to compare the study arms. Further, the I^2 statistics were used to assess the heterogeneity of results in the analysed studies. In accordance with Cochrane guidelines [30], heterogeneity was classified as follows: low (0–40 %), moderate (30–60 %), substantial (50–90 %), and considerable (75–100 %). The *meta*-analyses of quantitative data were conducted in Metaanalysisonline™ using a 95 % confidence interval. Lastly, the certainty of evidence was assessed using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) criteria against five factors, including the risk of bias, inconsistency, indirectness, imprecision, and publication bias [27,29].

Screening, data extraction, risk of bias assessment and *meta*-analysis were conducted by two reviewers (SD and TNA), both with respective 3 and 13 years of clinical and academic experience in MRI, while disagreements were resolved through a consensus meeting. A third reviewer (EI) with certified Cochrane training and experience in systematic reviews also provided arbitration in areas of disagreement for the certainty of evidence assessment.

3. Results

3.1. Search results

The initial search identified 228 articles, 62 % (n = 141) from PubMed and 38 % (n = 87) from EBSCOhost, specifically, from Medline Complete (n = 39), Academic Search Ultimate (n = 46) and CINAHL (n = 2) databases. Other search methods identified an additional 12 articles, with 50 % (n = 6) sourced through web searches and 50 % (n = 6) obtained via citation searching of previously identified articles. As summarised in Fig. 1, out of 19 articles deemed relevant, 16 met the predefined inclusion criteria [20–24,31–41]. 2 out of 19 retrieved articles were of a report type [42] and a literature review type [43] and therefore excluded. Additionally, one retracted article [44] was excluded.

3.2. Characteristics of the included studies

50 %(n = 8) of the included studies assessed the contrast-enhancing effectiveness of natural food substances as negative MRI contrast agents in MRCP, and the other half (n = 8) assessed these substances as positive contrast agents for digestive tract examinations in vivo. Some of the included studies also incorporated the prior in vitro assessments of these agents. The characteristics of the included studies and their in vivo results offering insights into image quality outcomes, acceptability, and safety are summarised (Table 1). The in-vitro results of these studies report the chemistry and contrast enhancement characteristics of FBCAs, and these data are also recorded (Supplementary Table 1).

Of the 16 studies included, 87.5 % (n = 14) compared intervention and control groups in vivo. The ROBINS-I risk of bias assessment for these studies varied between low (74 %) and serious (26 %), indicating an overall low risk of bias. The included studies reported no conflicts of interest or external funding sources. The assessment results of each study's quality against domains of the ROBINS-I tool were reported using the risk of bias visualisation model (45) (Fig. 2a, Fig. 2b).

3.3. Meta-analysis findings

The details of the included studies and their key findings are summarised (Tables 1 and supplementary Table 1), and the findings from the

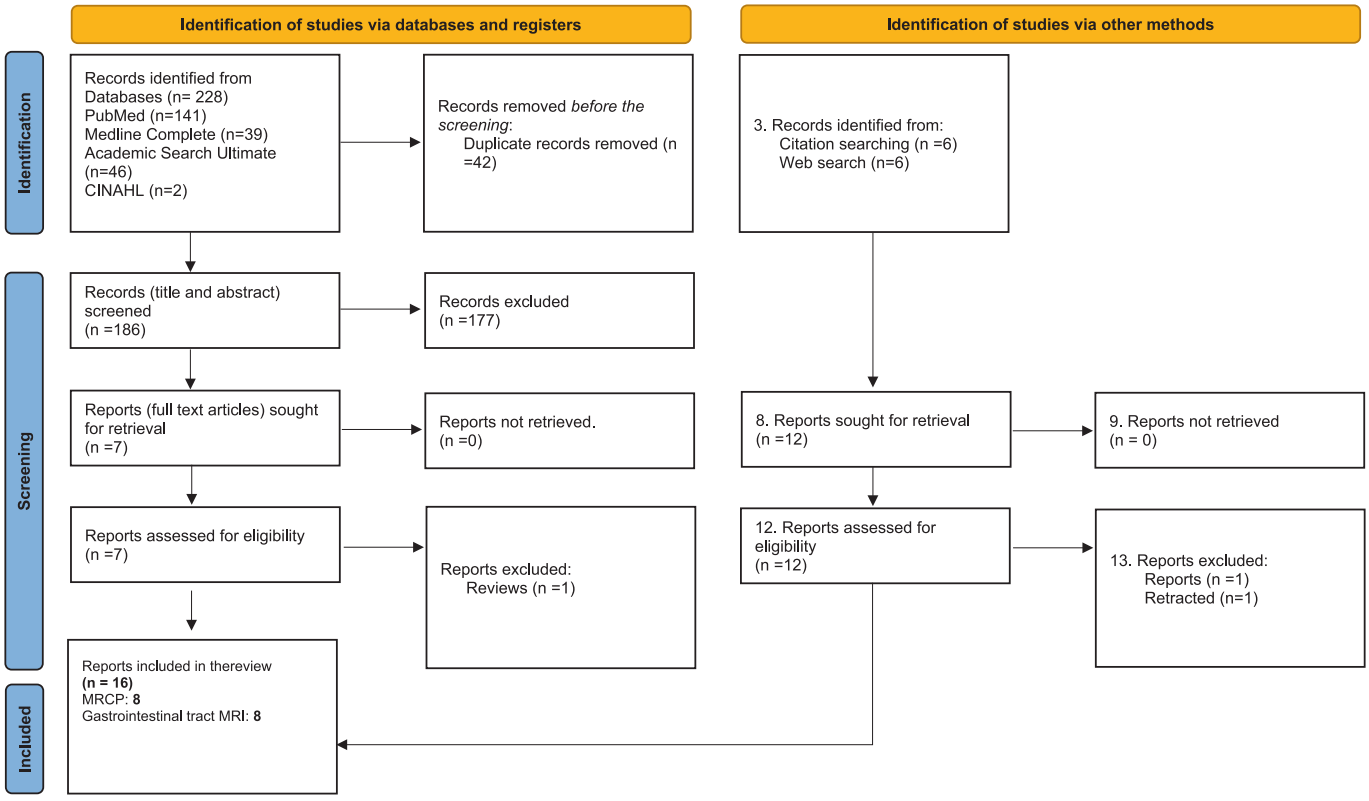

Fig. 1. PRISMA flow diagram. Legend: CINAHL: The cumulative Index to Nursing and Health Literature, MRCP: Magnetic Resonance Cholangiopancreatography, MRI: Magnetic Resonance Imaging..

Table 1
Summary characteristics and findings of the included studies.

Study Number	References and Journal	Type of Radiological examination	Study design and analysis	Sample characteristics	The type of natural food explored	Study aims	Study findings			Key Conclusion
							Image Enhancement	Acceptability Profile	Safety Profile	
1.	Arthurs et al. (2014) BMC Medical Imaging	MRE	Cross-sectional study with qualitative analysis	Healthy adult volunteers (n = 3) and neonate (n = 1)	Pineapple, Apple/ beetroot, blueberry, Raspberry, blackberry, prune, blackcurrant, orange juices,	To evaluate the use of fruit juice with interactive inversion recovery MRI pulse sequence to visualise Gastrointestinal tract (GIT)	The conventional Single-Shot Fast Spin Echo (SSFSE) did not differentiate signals from administered P. J., and pre-existing gastro-intestinal fluids. However, with Inversion Recovery SSFSE (IR-SSFSE), bowel fluid signals were nullified while P.J. demonstrated high signals	No data reported	No data reported	Pineapple juice is the most promising natural, commercially available short T1 contrast medium suitable for imaging the neonatal GIT using IR-SSFSE sequence.
2.	Coppens et al. (2005) European Radiology	MRCP	Pre-post interventional study. Quantitative and qualitative data analysis	Patients with suspected biliopancreatic duct disease (n = 35)	Pineapple juice (PJ) with minimal gadolinium	To prepare in vitro PJ-minimal gadolinium mixture and to assess in vivo its negative oral contrast potential during MRCP	The ingestion of 180 mL PJ., labelled with 1 mL Gd-DOTA, significantly improved Pancreatobiliary duct visualisation ($p < 0.01$) and overall MRCP image quality score ($p < 0.05$).	All the participants easily ingested the contrast agent (180 ml with 2.76 mmol gadolinium-DOTA concentration), and found it palatable	No adverse reaction reported post-ingestion	Labelling minimal gadolinium amounts served as an efficient and convenient negative oral contrast agent for MRCP.
3.	Duarte et al. (2012) Journal of Abdominal Imaging	MRCP	Pre-post interventional multicentric study. Quantitative analysis	Adult patients (n = 71) in three centres ($n_1 = 33$, $n_2 = 19$, $n_3 = 19$)	Pineapple juice (PJ) with gadopentetate dimeglumine	To evaluate the efficacy of PJ-gadopentetate dimeglumine mixture (180:1) as oral negative contrast for MRCP	Pre-contrast and post-contrast MRCP images were obtained for all participants. Post-contrast, Radiologist 1 and Radiologist 2 showed higher scores than Radiologist 3 ($p = 0.013$). Moreover, the correlation between mean scores given by three radiologists was statistically significant ($p < 0.01$ or $p < 0.05$). The mean image quality score by 3 radiologists before was close to 2 while the mean score post-contrast administration was	The agent was well tolerated as small amount of added gadolinium did not change the pineapple juice's taste.	No adverse reactions post-ingestion.	Irrespective of the scanner's magnetic field, the mixed agents improve MRCP image quality. It is cost-effective and is broadly accepted by patients.

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Table 1 (*continued*)

Study Number	References and Journal	Type of Radiological examination	Study design and analysis	Sample characteristics	The type of natural food explored	Study aims	Study findings			Key Conclusion
							Image Enhancement	Acceptability Profile	Safety Profile	
							close to 3, and the difference was statistically significant ($p < 0.001$)			
4.	Elsayed et al. (2015) The Egyptian Journal of Radiology and Nuclear Medicine	MRE	A comparative longitudinal study. quantitative data analysis	Healthy volunteers (n = 14) each having 3 scans with different agents	P.J., water, milk (1.5 L each)	To identify the most natural and cost-effective oral contrast agent for small bowel MRI with the best artefacts-free image quality, maximum bowel extension, and no or minimal side effects.	Both agents significantly distended the bowel ($p < 0.05$). overall good image quality with P.J., bad quality with water, and severe artefacts in milk subjects.	Pineapple juice was tolerable by all participants and has very little abdominal discomfort	No side effects were reported after ingestion of water and P. J. however, the latter was associated with discomfort due to large volume. Milk had the most side effects ($p = 0.05$), where 50 % of patients showed symptoms	P.J is an ideal contrast for MRE as it is natural without a need to reduce its absorption as for water, with good bowel distention, artefacts-free good image quality, good taste with very minimal discomfort
5.	Faletti et al. (2018) European Radiology Experimental	Oesophageal MRI	Cross-sectional study. Qualitative analysis	Patients undergoing MRA (n = 38)	Pineapple juice	To assess the feasibility of oesophageal visualisation post ingestion of concentrated pineapple juice solution during MRA.	97.4 % (37/38) of patients showed complete oesophageal enhancement and the peristaltic waves were the cause of incomplete enhancement in one patient	No data reported	No immediate or late complications	Post-appropriate concentration processes and modified starch addiction, pineapple juice is as hyperintense as the MRI diluted contrast media and allows oesophagus visualisation with no side effects during MR Angiography
6.	Govindarajan et al. (2014) American Journal of roentgenology	MRCP	Pre-post study. Quantitative analysis	Patients undergoing MRCP (n = 60) before and after oral contrast ingestion.	Date syrup	To compare the in-vitro effects of date syrup and other MRCP oral negative contrasts and evaluation of its in-vivo use to improve MRCP image quality	The Images acquired post-ingestion of 100 ml date syrup showed a signal-to-noise ratio comparable to those acquired using ferumoxsil in T2-weighted and MRCP sequences. There was also a significant improvement in GIT signal suppression ($p < 0.001$) with enhanced visibility of pancreaticobiliary ducts ($p < 0.001$).	All 60 participants ingested 100 ml of date syrup, and found it palatable.	No adverse reactions in any of the participants.	Date syrup can serve as a negative oral contrast agent to suppress gastrointestinal tract signals during MRCP
7.	Hosseini et al. (2021)IEEE Open	MRI of stomach	Cross-sectional study.	Healthy volunteers (n = 4)	Pineapple Juice	To quantify the contractions of the	The mean speed of all contractions was 2.4	No data reported	No data reported	The study shows the feasibility of PJ as

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Table 1 (*continued*)

Study Number	References and Journal	Type of Radiological examination	Study design and analysis	Sample characteristics	The type of natural food explored	Study aims	Study findings			Key Conclusion
							Image Enhancement	Acceptability Profile	Safety Profile	
	Journal of Engineering in Medicine & Biology (OJEMB)		Quantitative data analysis			stomach using pineapple juice as an MRI oral contrast agent	± 0.9 mm/s which agreed with the previous gadolinium-enhanced gastric motility studies.The gastric contraction speed was higher in the greater curvature (2.9 ± 0.8 mm/s) than in the lesser curvature (1.9 ± 0.5 mm/s)			an oral contrast agent for MRI measurement of gastric motility.
8.	Karpagam et al. (2024) The Cureus Journal of Medical Science	MRCP	RCT. Quantitative analysis	Healthy adults (n = 90). Each group ingested different agents: 100 ml date syrup (n = 30), 200 ml P.J (n = 30), and 30 ml hematinic syrup diluted with 200 ml water (n = 30)	Date syrup, pineapple juice, and hematinic syrup	To evaluate the effects of hematinic syrup, date syrup, and pineapple juice on MRCP image quality	In vivo, P.J. has the highest mean SNR, with less variability indicated by the lowest standard deviation ($p < 0.001$). P.J. has also the highest gastric and duodenal SNR ($p < 0.001$) and the highest CBD CNR ($p < 0.001$).	No data reported	The study reported absence of side effects.	The use of date syrup, hematinic syrup, and pineapple juice inhibit GIT signals due to their T2 shortening paramagnetic ion components. Date and hematinic syrups are rich sources of iron, making them suitable agents. However, they result in images of low SNR and CNR, which degrades the overall image quality.
9.	Kulinna-Cosentini et al. (2021) Journal of European Radiology	MRI swallow	A Comparative Retrospective study. Quantitative analysis	Patients (n = 129) who underwent MR swallowing studies (146 examinations). One group received a gadolinium-butter milk mixture (GBM 1:40 dilution, n = 53), 1:1 diluted LumiVision (LWM, n = 44) for the other, and the undiluted LumiVision (L, n = 49)	LumiVision®, a semi-liquid made from pineapple, organic agave syrup, blackcurrant, guar gum, and defoamers	To evaluate the image quality when LumiVision®, a biological mixture is used vs a gadolinium buttermilk mixture during dynamic MR swallow	Both image quality evaluators showed significantly better results in contrast to LWM ($p = 0.03$, $p = 0.002$). Significant better results were also overall reported for L than LWM in both readers ($p = 0.004, 0.042$). No significant difference in overall evaluation between L and GBM ($p = 0.914$, $p = 0.376$). The interobserver agreement was substantial (Cohen's kappa = 0.738)	No data reported	No data reported	Undiluted LumiVision® demonstrated equivalent image quality to the gadolinium-buttermilk mixture. However, the use of diluted LumiVision degraded the image quality.

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Table 1 (*continued*)

Study Number	References and Journal	Type of Radiological examination	Study design and analysis	Sample characteristics	The type of natural food explored	Study aims	Study findings			Key Conclusion
							Image Enhancement	Acceptability Profile	Safety Profile	
							between both readers.			
10.	Mohabir et al. (2020) South African Journal of Radiology	MRCP	Pre-post interventional study. Quantitative data analysis	Adult patients undergoing Magnetic resonance cholangiopancreatography (MRCP) examination (n = 50)	Local off-shelf pineapple juice (PJ)	To evaluate the efficacy of the local pre-packaged pineapple juice (250 ml) as a negative oral contrast agent for MRCP.	Comparing pre and post-contrast images, the measured (1661.51 vs 1409.94, $p < 0.01$) and perceived (2.16 vs 2.72, $p < 0.01$) duodenal signal reduction were statistically significant. However, no significant change in measured (1081.17 vs 1044.38, $p = 0.34$) or perceived 2.73 vs 2.84, $p = 0.14$) gastric signal intensity. The CBD visibility was significantly improved (3.67 vs 3.86, $p < 0.01$), however, there was no significant improvement in the main pancreatic duct (2.92 vs 2.86, $p = 0.44$)	The juice was conveniently consumed in supine position	There were no serious adverse events in this study,	Pineapple juice ingestion improves MRCP image quality by reducing signals from the duodenum, which improves CBD visualisation.
11.	Renzulli et al. (2019) Clinical Radiology Journal	MRCP	Pre-post intervention study. quantitative data analysis	Healthy volunteers (n = 15)	4 brands of pineapple juice & 1 Blueberry juice	To identify, in vitro, the best fruit juice to use as a natural MRCP contrast agent and to test it, in vivo, with the in vitro identified sequence parameters	The image quality was significantly high in patients with 2.38 mg/dl PJ and poor non-diagnostic in those without oral contrast administration ($p < 0.001$).	No data reported	No data reported	All juices have the minimum required manganese concentration and their oral ingestion before MRCP suppresses gastrointestinal fluids signals irrespective of inevitable dilution as the juice passes into the stomach and duodenum
12.	Renzulli et al. (2022) Scientific Reports	MRCP	RCT Quantitative analysis	MRCP Fasted patients (613) who ingested 150 ml P.J (n = 308) compared to those who consumed 300 ml P.J (n = 305).	Pineapple juice (PJ)	To evaluate the potential variability of Mn^{2+} content in one brand's pineapple juices produced in different years and to identify the	The previously identified PJ to have the highest manganese concentration (Renzulli et al. 2019) was re-evaluated to investigate the	No data reported	No serious adverse events	The manganese concentration in the same brand's juices produced in different years did not change (2.37 mg/dl). Moreover,

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Table 1 (*continued*)

Study Number	References and Journal	Type of Radiological examination	Study design and analysis	Sample characteristics	The type of natural food explored	Study aims	Study findings			Key Conclusion
							Image Enhancement	Acceptability Profile	Safety Profile	
						optimal concentration and correct amount to suppress signals from the gastroduodenal liquid during MRCP	concentration consistency among juices produced in different years. No significant difference was found in manganese concentrations (2.37 vs 2.38 mg/dl). Furthermore, using pure manganese solutions and P.J., it was found that it required a manganese concentration of 0.5–1.0 mg/dl to best suppress gastroduodenal signals. Clinically, considering a gastroduodenal fasting content of 200 ml, a 150 ml P.J having 2.37 mg/dl manganese concentration if diluted in that content produces a concentration of approximately 1 mg/dl, which is enough to suppress unwanted signals.In vivo, in group 1 which received 150 ml, 95.4 % showed complete or good GD suppression which is not statistically different from 91.8 % found in group 2 which received 300 ml ($p = 0.07$).			regardless of the amount of gastroduodenal liquid, administration of 150 ml of P.J is adequate for suppressing the signal from duodenum and stomach, which improves MRCP image quality
13.	Renzulli et al. (2023) Gastroenterology insights	MRE	Comparative longitudinal (polyethylene glycol (PEG) solution vs natural beverage)	Patients for MRE (n = 35)	Aqueous-based mixture of mucilages, polysaccharides, carbohydrates/ saccharides, salts, and antioxidants which mimics	To test a new oral contrast medium for MRE, composed of natural components.	No statistical difference in image quality and bowel distention (97.1 % and 94.3 % for PEG and beverage respectively) was noted. No statistical	Patients highly appreciated the natural beverage (97.1 %), compared to the PEG solution (8.6 %), while	No adverse reactions with natural beverage.	This novel beverage has demonstrated superior palatability and alternative to the synthetic counterpart PEG, addressing its

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Table 1 (*continued*)

Study Number	References and Journal	Type of Radiological examination	Study design and analysis	Sample characteristics	The type of natural food explored	Study aims	Study findings			Key Conclusion
							Image Enhancement	Acceptability Profile	Safety Profile	
					PEG's osmotic characteristics.		difference in image quality scores ($p = 0.785$)			multiple contraindications.
14.	Riordan et al. 2004 The British journal of radiology	MRCP	Longitudinal pre-post study	Healthy volunteers (n = 10)	12 agents: orange juice, grapefruit juice, apple juice, pineapple juice, milk, prune juice, cranberry juice, blueberry and apple juice, barium 2 %, dilute barium (50:50 with water), concentrated gastrografin, ferumoxsil, and water.	To evaluate pineapple juice (PJ) as an oral negative contrast agent in MRCP	Pineapple Juice had the lowest relative signal intensity on the T2WI TSE sequence compared with other fruit juices, milk, barium, and gastrografin. However, it had a relatively higher signal intensity than ferumoxsil. With single shot MRCP radial sequence, PJ had the lowest signal intensity, apart from ferumoxsil and gastrografin. The manganese concentration in PJ was 2.76 $mgdl^{-1}$ Between the pre and 15-minute post-PJ images, the visualization of the Ampulla, CBD, CHD, and IHD was significantly improved, but IHD was only at the best poor. However, no significant difference seen between the pre and 30-minute PJ images for these segments.	All study participants found the PJ palatable and consumed the entire 400 ml dose	No adverse effects.	The results demonstrate that PJ, may be used as an alternative to commercially available negative oral contrast agent in MRCP.
15.	Saini et al. 2014	MRE	Retrospective comparative study	MRE Patients (n = 45) who either received 1.5 L of 3 % sorbitol (n = 20) or 2 L of 1.6 g kg^{-1} psyllium (n = 25)	1.6 g kg^{-1} psyllium (2 L) Comparator: 3 % sorbitol (1.5 L)	To compare the degree of small bowel distension achieved by 3 % sorbitol and a psyllium-based bulk fibre as oral	Small bowel distension was not significantly different in any of the five small bowel segments between the use of sorbitol	No data reported	No data reported	Sorbitol and psyllium are not significantly different at distending the small bowel and both may be used as oral

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Table 1 (*continued*)

Study Number	References and Journal	Type of Radiological examination	Study design and analysis	Sample characteristics	The type of natural food explored	Study aims	Study findings			Key Conclusion
							Image Enhancement	Acceptability Profile	Safety Profile	
						contrast agents in MRE	and psyllium. Visualisation of the ileum was good or excellent in 65 % of the examinations in both groups.			contrast agents for MRE studies.
16.	Zulkifle et al. (2023) Medical Journal of Malaysia	MRE	Comparative cross-sectional study	Patients (n = 75) undergoing MRE with P.J (n = 25), 3.3 % mannitol (n = 25), and 3.7 % mannitol (n = 25)	Pineapple juice	To compare the degree of bowel distention and image quality between P.J. and different mannitol concentrations oral contrast agents during MR enterography, patients' acceptance, and their side effects. performance of pineapple juice and that of 6.7 % and 3.3 % mannitol concentrations in bowel distention and image quality during MRI enterography, as well as patient tolerance and side effects	Each patient ingested 1.5 L of one specific agent. The mean diameter of bowel distention was 2.1 cm, 2.0 cm, and 1.6 cm for patients who ingested 6.7 % mannitol, 3.7 % mannitol, and P.J respectively. There were good-quality images in two-thirds of patients who received mannitol solutions but 68 % of the PJ group revealed poor MRE image quality.	96 % of patients receiving PJ rated it (slightly) acceptable while only 48 % in the 6.7 % mannitol group rated it (slightly) acceptable.	88 % and 44 % of patients reported at least one side effect in mannitol 6.7 % and 3.3 mannitol group respectively, while 18 % was recorded in the PJ group	3.3 % mannitol provides optimum bowel distention and good image quality. No significant improvement in using higher mannitol concentration (6.7 %) but poorer patient acceptance and increased side effects. Despite its increased tolerability, P.J is conflicted with artefacts

Legend: **MRE**: Magnetic Resonance Enterography, **MRI:** Magnetic Resonance Imaging, **GIT:** Gastrointestinal Tract, **MRA**: Magnetic Resonance Angiography **T1**: Longitudinal Relaxation Time, **T2:** Longitudinal relaxation time**, T1WI**: T1 Weighted Imaging, **T2WI**: T2 Weighted Imaging, **P.J**.: Pineapple Juice, **MRCP**: Magnetic Resonance Cholangiopancreatography, **Gd-DOTA**: Gadoterate meglumine, **RCT**: Randomised Controlled Trial, **CBD**: Common Bile Duct, **CHD**: Common Hepatic Duct, **IHD**: Intrahepatic Duct, **CNR:** Contrast to Noise Ratio, **SNR**: Signal to Noise Ratio, **MD**: Mean Difference, **OR**: Odds Ratio, **FIESTA**: Fast Imaging Employing Steady-State Acquisition

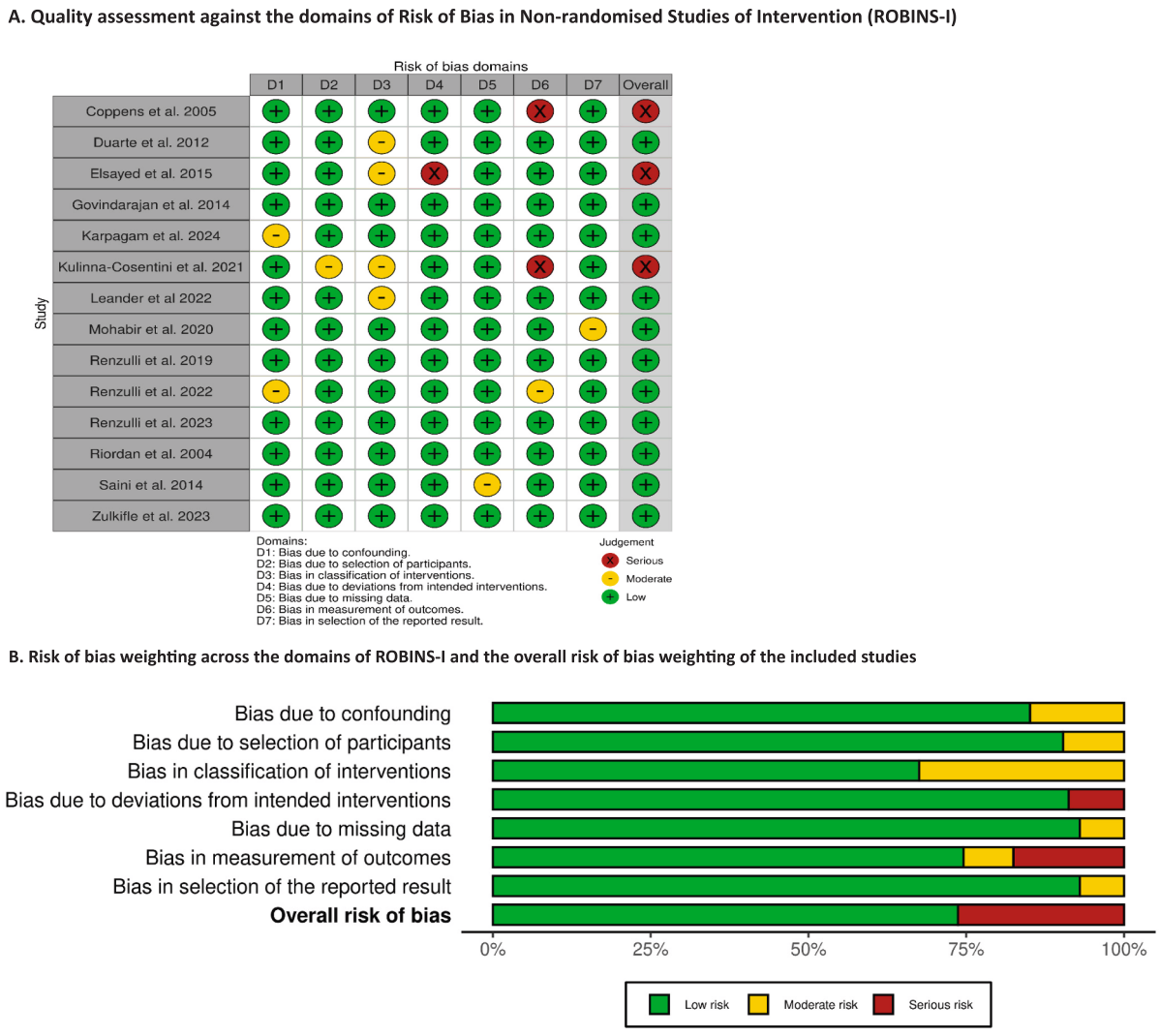


Fig. 2. Risk of bias assessment for quality of the included studies. A. **Quality assessment against the domains of Risk of bias in Non-randomised Studies-Of Intervention (ROBINS-I). B. Risk of bias weighting across the domains of ROBINS-I and the overall risk of bias weighting of the included studies.**

meta-analysis of quantitative data are captured in Figs. 3 and 4. The scales of image quality assessment employed across the included studies were comparable using similar units (1 = poor, 2 = fair, 3 = good, 4 = excellent image quality).

The pooled mean difference between MRCP with pineapple juice and non-contrast MRCP is 1.04 (95 % CI: 0.23, 1.84; $I^2 = 96$ %, $p < 0.01$) for bile duct visibility and across all three included studies [23,31,38], with one being multicentric, involving 156 participants showing positive visibility mean scores (Fig. 3a). Also, the pooled mean difference between MRCP with pineapple juice and non-contrast MRCP is 0.95 (95 % CI: 0.04, 1.85; $I^2 = 95$ %, $p < 0.01$) for pancreatic duct visibility (Fig. 3b) and only one [31] out of the five experiments/protocols across the three included studies [23,31,38] showed slight negative visibility mean scores (mean difference= − 0.05, CI = 0.35).

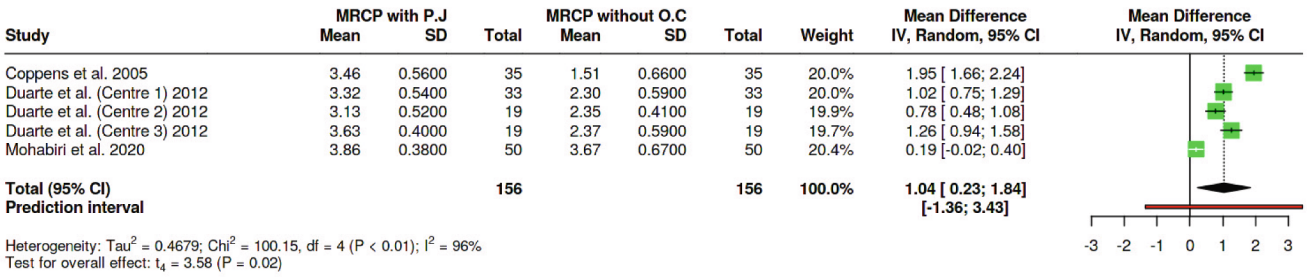
Three studies [23,31,36] compared pancreaticobiliary duct visibility outcomes in the same cohort of study participants before and after ingestion of pineapple juice(PJ) solutions for MRCP examinations. There was an overall likelihood of excellent pancreaticobiliary duct visibility outcomes with PJ solutions (Combined odds ratio, 5.01; 95 % CI, 2.36–10.64, $p < 0.0001$) than without. In addition, we found a lower likelihood of achieving excellent quality MRE images with FBCAs than with synthetic contrast agents [Odds ratio = 0.36, (95 % CI: 0.18 to 0.73), p = 0.004] [Fig. 4].

The assessment of the certainty of the evidence showed a moderate degree of certainty that PJ administration improved the visibility of the common bile duct and pancreatobiliary ducts in MRCP examinations. The certainty had been downgraded due to variations that exist in the concentration and dosage of PJ solutions administered to participants in the included studies. However, the evidence on excellent-quality MRE images with FBCAs, compared with synthetic contrast agents, achieved a high certainty of evidence (Table 2).

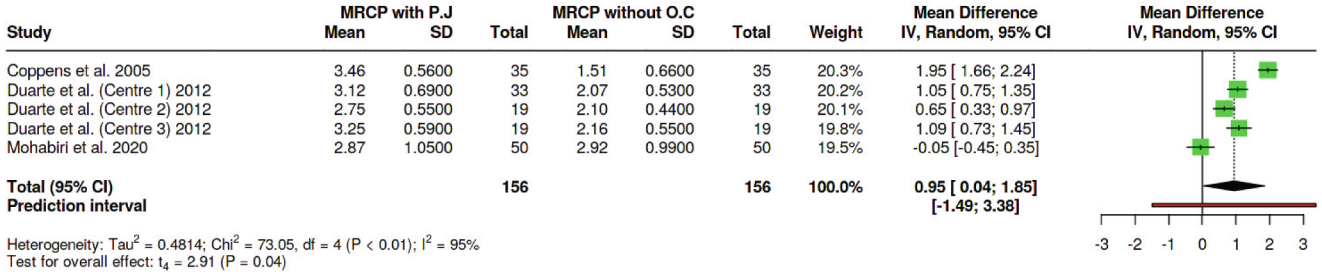
4. Discussion

To the best of our knowledge, this is the first systematic literature review integrating a *meta*-analysis to evaluate the efficacy of natural FBS as contrast agents in clinical imaging. The studies explored the potential of FBCAs for use in MRI, focusing on natural substances that contain paramagnetic manganese and/or iron ions. Our findings show that the efficacy of natural FBCAs in MRI is predominantly determined by the concentration of paramagnetic ions, particularly manganese and iron (supplementary Table 1). These agents were tested through the oral administration route in MRCP [20,22,23,31,33,36,38,41], gastric MRI [39], oesophageal MRI [21,32], and MRE [24,34,35,37,40].

A. Forest plot of Common Bile Duct (CBD) visibility mean scores between intervention (MRCP with pineapple juice) and control (non-contrasted MRCP)



B. Forest plot of pancreatic duct visibility mean score between MRCP with and without Pineapple juice



C. Forest plot showing an overall excellent pancreaticobiliary duct visibility records (events) in MRCP images before and after oral pineapple juice administration

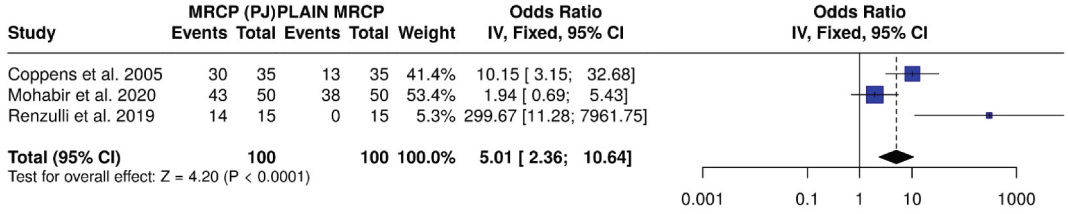


Fig. 3. Meta-analysis of MRCP studies. **A.** Forest plot of Common Bile Duct (CBD) visibility mean scores between intervention (MRCP with pineapple juice) and control (non-contrasted MRCP). **A Legend:** The right side favours MRCP with pineapple juice as an oral contrast agent, and the left favours MRCP without oral contrast. MRCP: Magnetic Resonance Cholangiopancreatography, P.J: Pineapple Juice, SD: Standard Deviation, O.C: Oral Contrast, CI: Confidence Interval, IV: Inverse Variance Method. **B.** Forest plot of pancreatic duct visibility mean score between MRCP with and without Pineapple juice. **B Legend:** The right side favours MRCP with pineapple juice as an oral contrast agent, and the left favours MRCP without oral contrast. **C.** Forest plot showing an overall excellent pancreaticobiliary duct visibility records (events) in MRCP images before and after oral pineapple juice administration. **C Legend** PLAIN MRCP: MRCP without oral contrast, MRCP (PJ): MRCP with Pineapple Juice.

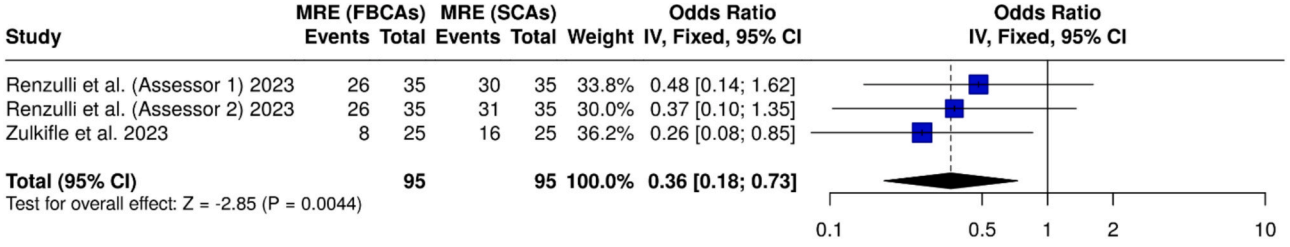


Fig. 4. Forest plot showing an overall excellent MRE image quality record (events) in the synthetic contrast agent group relative to the food-based contrast group. Legend: MRE: Magnetic Resonance Enterography, FBCAs: Oral Food-Based Contrast Agents, SCAs: Oral Synthetic Contrast Agents, IV: Inverse Variance method, CI: Confidence Interval.

4.1. Contrast enhancement potential of natural food-based substances in MRCP and MRE

Findings from the *meta*-analysis indicate that compared to non-contrasted MRCP, performing MRCP with oral pineapple juice administration increases the mean score of the common bile duct and pancreatic duct visibility by 1.04 and 0.95, respectively. However, these results should be interpreted cautiously due to the high heterogeneity ($I^2 = 96\ \%$; $p < 0.01$ and $I^2 = 95\ \%$; $p < 0.01$), respectively, and the wide limits of confidence observed. This could be due to the very low sample sizes of most of the studies included and variations in the pineapple juice dosage, concentrations, and ingredients. The reflection of this is seen in

Table 2
Certainty of evidence assessment findings.

Outcomes	Anticipated absolute effects* (95 % CI)		Relative effect size	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk without intervention	The risk with food-based contrast agent intervention[λ]				
1.Contrast enhancement & anatomical visibility						
a. Visibility of common bile duct post pineapple juice (PJ) administration	The mean common bile duct visibility score was 2.44	MD: 1.04 higher (0.23,1.84)	–	156 participants (3 studies [23,31,38][23,31,38,]), one reporting results from three centres[38]	⊕⊕⊕⊖ Moderate [a]	The certainty is downgraded by the variation in dosage and concentration of PJ administered among the studies included in this analysis. Mixing the juice with on-market gadolinium-based agents as in Coppens's 2005 [23] and Duarte's [38] teams and identified risk of bias may have further contributed to the pooled mean difference. This inconsistency is evidenced by the high heterogeneity (I^2: 96 %). Despite the comparability of the scales employed across the included studies for the image quality assessment, the units of assessment and application of the scales are considered to be subjective with potential inter and intra-reliability grading concerns.
b. Visibility of pancreatic duct post pineapple juice (PJ) administration	The mean pancreatic duct visibility score was 2.15	MD: 0.95 higher (0.04,1.85)	–	156 participants (3 studies [23,31,44]), one reporting results from three centres[44]	⊕⊕⊕⊖ Moderate [a]	The certainty is downgraded by the variation in dosage and concentration of PJ administered among the studies included in this analysis. Mixing the juice with on-market gadolinium-based agents as in Coppens's 2005 [23] and Duarte's [38] teams and identified risk of bias may have further contributed to the pooled mean difference. This inconsistency is evidenced by the high heterogeneity (I^2: 95 %). Despite the comparability of the scales employed across the included studies for the image quality assessment, the units of assessment and application of the scales are considered to be subjective with potential inter and intra-reliability grading concerns.
c. Excellent overall pancreaticobiliary duct visibility	86 per 100	52 per 100	OR: 5.01 [2.36,10.64]	100 participants (3 studies [23,31,36]	⊕⊕⊕⊖ Moderate [a]	Using the FIESTA sequence and 90^0 flip angle may have contributed to the image quality results in the intervention arm of the study by Renzulli et al. 2019 [36] included in this *meta*-analysis. The wide confidence interval of the pooled odds ratio highlights an imprecision study that cautions the certainty of evidence. Despite the comparability of the scales employed across the included studies for the

(*continued on next page*)

Table 2 (*continued*)

Outcomes	Anticipated absolute effects* (95 % CI)		Relative effect size	Number of participants (studies)	Certainty of evidence (GRADE)	Comments
	Risk without intervention	The risk with food-based contrast agent intervention[λ]				
						image quality assessment, the units of assessment and application of the scales are considered to be subjective with potential inter and intra-reliability grading concerns.
d. Excellent MRE image quality records	60 per 98	77 per 98	OR: 0.36 (0.18, 0.73)	98 participants (2 studies[35,37], one having two assessors results [37])	⊕⊕⊕⊕ High	There is little to no difference in excellent image quality records (events) in the intervention and control arms of the studies included in this *meta*-analysis. This implies that the true effect lies close to that of the estimate of effect, as evidenced by the narrower confidence interval limits and homogeneity test (I^2:0%).
2. Safety & Acceptance profile						
a. Adverse reactions post-ingestion of food-based contrast agents (pineapple juice and date syrup) during MRCP	–	0 per 929	A *meta*-analysis was not conducted because all studies reported zero events in the intervention arm, and the control group also lacked sufficient event reporting.	944 participants, 6 studies administering pineapple juice [22,23,31,36,38,41], and 2 administering date syrup [20,33]	⊕⊕⊕⊖ Moderate [a]	We are moderately confident in the certainty of evidence as we were not able to *meta*-analyse the results to measure the effect size. Further, one study [38], which involved 15 participants, did not report data on adverse reactions.
b. Acceptance and palatability of food-based contrast agents (pineapple juice and date syrup) during MRCP	–	In MRCP, 206 per 206 found the agents palatable and were able to consume the entire dose.	A *meta*-analysis was not conducted due to the nature of the data reported in the intervention arm, and the control group also lacked sufficient event reporting.	944 participants, 6 studies administering pineapple juice [22,23,31,36,38,41], and 2 for date syrup [20,33]	⊕⊕⊕⊖ Moderate [a]	We have moderate confidence in the certainty of evidence as we were not able to *meta*-analyse the results, mostly due to a lack of data in the comparator arms of included studies. Further, 3 studies [23,35,38]did not report data on acceptance and/or palatability.

Legend: *The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

[λ] The scales of image quality assessment employed across the included studies are comparable using similar units (1 = poor, 2 = fair, 3 = good, 4 = excellent image quality).

GRADE Working Group grades of evidence.

High certainty: we are very confident that the true effect lies close to that of the estimated effect.

Moderate certainty: we are moderately confident in the estimated effect: the true effect is likely to be close to the estimated effect, but there is a possibility that it is substantially different.

Low certainty: There is limited confidence in the estimated effect: the true effect might be substantially different from the estimated effect.

Very low certainty: we have very little confidence in the estimated effect: the true effect is likely to be substantially different from the estimated effect.

Downgraded by one level for:

[a] Heterogeneity in study designs and relatively low sample sizes.

the moderate certainty of evidence from GRADE assessment, indicating the potential that actual performance of FBCA's could be substantially different from what is being reported. There is therefore a need for further studies of higher quality. Further analysis shows that the odds of obtaining MRCP images with excellent pancreaticobiliary duct visibility are higher with pineapple juice as an oral contrast agent than in MRCP without contrast (odds ratio: 5.23). The intervention by Renzulli et al. [36] shows a remarkably high individual odds ratio. This effect may be attributed to the prior optimisation of manganese concentration in pineapple juice, accounting for the potential dilution by gastroduodenal fluids, and utilisation of optimal FIESTA sequence and 90° flip angle, which resulted in high image quality outcomes. These results further highlight the critical role of concentrating paramagnetic ions in MRI-based FBCAs, as demonstrated in previous studies [21,32] and the possible efficacy of oral administration of pineapple juice in improving MRCP image quality, which is consistent with previous research findings [22,31,36].

Labelling the pineapple juice with a minimal amount of gadolinium was found to enhance image quality and may serve as an effective compromise. For example, Coppens and colleagues [23] administered 180 mL of pineapple juice labelled with 1 mL of gadolinium to the intervention group and observed a significantly greater mean difference in common bile duct and pancreatic duct visibility between MRCP images acquired with and without the intervention. Therefore, future research should aim to further compare the effectiveness of a gadolinium-spiked pineapple juice to that of concentrated pineapple juice.

Studies investigating alternative contrast agents for MRE have

revealed mixed results regarding their efficacy. For instance, the separate investigations by Zulkifle et al. [35] and Elsayed et al. [24] reported poor image quality in over 50 % of participants using pineapple juice in magnetic resonance enterography (MRE). This is consistent with our *meta*-analysis findings of a pooled odds ratio of 0.36 for excellent MRE image quality outcomes with natural versus synthetic contrast agents. Zulkifle et al. [35] showed that the inadequacy of pineapple juice in distending the small bowel leads to artefacts. This artefactual phenomenon was also reported by Elsayed's team using milk as an intervention, although they found adequacy with bowel distension. Despite the cautious interpretation of the results due to the small sample size, it is suggested that administering pineapple juice in conjunction with a single-shot fast spin-echo sequence and inversion times of 900–1100 ms addresses these challenges [20]. Conversely, Hosseini et al. [39] reported excellent gastric MRI image quality with pineapple juice, possibly due to the lesser potential for contrast dilution in the stomach than would be expected in small bowel imaging.

4.2. Safety and acceptance profiles of key food-based contrast agents

Studies involving natural FBCAs in MRCP [20,22,31,33,36], oesophageal MRI [21], and MRE [37] have reported the absence of post-contrast side effects (Table 1). This implicates a high level of patient acceptance and biocompatibility of food-based contrast agents. Studies also reveal that in instances where minimal doses of gadolinium-based contrast agents were diluted in pineapple juice [23,38], the juice maintained its taste and palatability, enabling the ingestion of the optimum amount required for imaging. This is, therefore, more advantageous than the conventional gadolinium-water dilution [45]. While these findings may suggest the readiness of these substances as imaging contrast agents, the observed inconsistent administered volume and diverse concentration of active elements in these agents present barriers to the standard applicability in clinical practice. More specifically, food-based contrast agents are variably *absorbed* (absorption kinetics), variably *diluted*, and the effect on luminal *change motility* is widely variable [24]. All three factors make the intraluminal concentration, distribution, and timing of the "contrast" unpredictable, giving poor, non-standardised, and often non-reproducible radiological images compared with purpose-designed oral contrast agents. Additionally, as these agents may not be reimbursed by insurance as standard care, their application may pose a financial burden to the patient or the clinical services in some settings.

However, the findings by Elsayed et al. [24] show that few of the patients who were administered pineapple juice during MRE experienced discomfort and flatulence and that half of the patients who were administered milk experienced various side effects, including discomfort, diarrhoea, constipation, colic, and flatulence. Although our findings show a possible significant improvement in pancreatic and common bile duct visibility with pineapple juice as an oral contrast agent compared to non-contrast MRCP, the use of oral contrast agents in MRCP remains an elective practice rather than a universally accepted standard [46].

4.3. Food substances and their chemical basis for contrast-enhancement in MRI and CT

The evidence indicates that oral administration of manganese- and/or iron-rich substances such as pineapple, blueberry, rosehip, and blackcurrant juices during MRCP procedures effectively suppresses gastroduodenal signals due to their T2-shortening effects [23,34,47,48]. In undiluted states, pineapple juice, rosehip, and blackcurrant show significantly high T1 and T2-shortening effects [21,32,34,48]. An interesting finding is that some of these undiluted juices exhibited shorter T1 and T2 times than a 1 mM gadolinium diethylenetriamine pentaacetic acid (Gd-DTPA) solution [48]. The role of concentrated pineapple juice as a contrast agent is also evident in the MRI studies of the alimentary canal. For instance, Faletti and colleagues [21] reported that 97.4 % of participants orally administered with concentrated pineapple juice achieved complete oesophageal enhancement. This is consistent with Kulinna-Cosentini et al. [32] who recently found that the undiluted mixture of pineapple, organic agave syrup, blackcurrant, guar gum, and defoamers produces MRE image quality outcomes comparable to a gadolinium-butter milk agent. This finding highlights that concentration is likely a major factor in the effectiveness of natural food-based contrast agents, as is seen with gadolinium-based contrast agents.

4.4. Limitations, recommendations, and conclusion

The scope of this review was limited to the primary studies published in English, which may have omitted useful insights from relevant literature in other languages. The methodological heterogeneity within the included studies, particularly in interventions and assessed outcomes, complicated the analysis and synthesis. However, the use of GRADE criteria to assess the certainty of evidence added rigour to the review design.

Based on the findings of the present study, some recommendations are made. Firstly, research should expand beyond the MRI modality to address the biosafety concerns and environmental impacts of synthetic contrast agents used in other imaging modalities. For example, in CT that uses iodine-based oral agents like gastrografin, the ability to use food substances with sufficient X-ray attenuation would provide a sustainable solution. Alternatively, foam-based materials for use in CT that do not require heavy elements should be further explored. Research should also focus on standardising the paramagnetic ion concentration in the potentially identified food items by controlling variations across brands and geographical regions. This will ensure the consistency of image quality outcomes and, therefore, the reliability in clinical practice, with improved contrast-enhancing effectiveness. Furthermore, as the designs of the studies included in this review resulted in moderate certainty of evidence, there is a need to undertake a randomised controlled trial with a sufficient sample size and thus statistical power to evaluate the effectiveness of FBCAs in cholangiopancreatography imaging examinations.

In conclusion, various natural food items exhibit intrinsic contrast potential primarily determined by the concentration of specific contrast-enhancing molecules. However, research has focused mainly on natural contrast agents in MRI, particularly in MRCP and MRE, leaving their potential applications in other imaging modalities largely unexplored. In MRCP, the oral administration of pineapple juice enhances pancreaticobiliary duct visibility, thereby improving the overall image quality. These outcomes are further enhanced by increasing the manganese concentration in the juice or by labelling the juice with minimal doses of gadolinium. The moderate certainty of evidence, however, indicates that the actual effect may be considerably different from the reported effect, and therefore, there is a need for further investigation. Furthermore, the likelihood of obtaining improved contrast in MRE with food-based substances is diminished compared to synthetic contrast agents. The natural abundance and availability of food-based agents reflect their potential to provide eco-friendly solutions in radiology. This systematic review with *meta*-analysis has demonstrated the exciting potential of food substances as contrast agents in clinical imaging and recommends further research into the enhancement of these agents and their application across further modalities and procedures.

CRediT authorship contribution statement

Samuel Dushimirimana: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Edozie Iweka:** Writing – review & editing, Validation. **Hannah Rickman:** Writing – review & editing, Validation, Investigation. **Benard Ohene-Botwe:** Writing – review & editing, Validation. **Theophilus N. Akudjedu:** Writing – review & editing,

Supervision, Project administration, Methodology, Investigation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejrad.2025.112633.

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