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Analysis of Folic Acid in Commercial Pharmaceuticals and the Effect of Food Beverages on Its Stability

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تحليل حمض الفوليك في المستحضرات الصيدلانية التجارية وتأثير المشروبات الغذائية على ثباته

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Abstract:
Folic acid is essential to one-carbon metabolism and prevention of folate-responsive neural tube defects, but its quantitative determination in pharmaceutical and beverage matrices is vulnerable to matrix interference. This laboratory study measured folic acid in four commercial tablet products (coded A–D) using an indirect ferric chloride–2,2′-bipyridyl spectrophotometric assay (0.5–18 µg/mL; 520 nm) and explored five media: distilled water, diluted coffee (1:20), diluted orange juice (1:10), diluted green tea (1:10), and undiluted Seven-Up. A descriptive questionnaire was also administered to an academic convenience sample (n = 66). Apparent folic acid concentrations differed markedly between products and media. In distilled water, values ranged from 1.174 to 21.170 µg/mL. Across beverage media, measured values ranged from 3.697 to 12.109 µg/mL, but changes were non-monotonic and matrix dependent; therefore, they cannot be interpreted as degradation or bioavailability without beverage-matched calibration, recovery testing, and a stability-indicating chromatographic comparator. In the questionnaire, 78.78% had heard of folic acid, 60.60% understood its importance, 51.51% reported supplement use, and 29.16% of married respondents reported pregnancy planning. The assay is suitable for

exploratory screening, but the present data do not establish pharmacopeial compliance, beverage-induced loss, or in-vivo interaction. Confirmatory analysis should use validated HPLC/UPLC with labeled-strength normalization, replicate preparations, forced-degradation specificity, and formal statistical testing.

Keywords: folic acid; pharmaceutical analysis; spectrophotometry; beverage matrix; stability

الملخص

حمض الفوليك ضروري لاستقلاب الكربون الواحد وللوقاية من عيوب الأنبوب العصبي المستجيبة للفولات، إلا أن تقديره الكمي في المصفوفات الدوائية ومصفوفات المشروبات يكون عرضة لتداخلات المصفوفة. قامت هذه الدراسة المخبرية بقياس حمض الفوليك في أربعة منتجات تجارية من الأقراص، رُمّز لها بـA–D ، باستخدام اختبار طيفي غير مباشر يعتمد على كلوريد الحديديك و2,2′-ثنائي البيريديل، ضمن مدى تركيز 0.5–18 ميكروغرام/مل وعند طول موجي قدره 520 نانومتر، كما استكشفت خمسة أوساط هي: الماء المقطر، والقهوة المخففة بنسبة 1:20، وعصير البرتقال المخفف بنسبة 1:10، والشاي الأخضر المخفف بنسبة 1:10، ومشروب سفن أب غير المخفف. كما تم تطبيق استبيان وصفي على عينة ملائمة من الوسط الأكاديمي بلغ حجمها 66 مشاركًا.اختلفت تراكيز حمض الفوليك الظاهرية بصورة ملحوظة بين المنتجات والأوساط المختلفة. ففي الماء المقطر، تراوحت القيم بين 1.174 و21.170 ميكروغرام/مل. وعبر أوساط المشروبات، تراوحت القيم المقاسة بين 3.697 و12.109 ميكروغرام/مل، إلا أن التغيرات كانت غير أحادية الاتجاه ومعتمدة على طبيعة المصفوفة؛ ولذلك لا يمكن تفسيرها على أنها تحلل أو توافر حيوي من دون استخدام معايرة مطابقة للمشروبات، واختبارات الاسترجاع، ومقارنة بوسيلة كروماتوغرافية دالة على الثبات. في الاستبيان، أفاد 78.78% بأنهم سمعوا بحمض الفوليك، و60.60% بأنهم يفهمون أهميته، و51.51% باستخدامهم للمكملات، فيما أفاد 29.16% من المتزوجين بالتخطيط للحمل. وتُعد هذه الطريقة مناسبة للفحص الاستكشافي، إلا أن البيانات الحالية لا تثبت المطابقة الدستورية الدوائية، أو الفقد الناتج عن المشروبات، أو وجود تفاعل داخل الجسم الحي. وينبغي أن يستخدم التحليل التأكيدي تقنية HPLC/UPLC متحققًا من صلاحيتها، مع توحيد النتائج وفق التركيز المعلن على العبوة، وتحضير مكررات للعينات، والتحقق من خصوصية الطريقة باستخدام التحلل القسري، وإجراء اختبارات إحصائية رسمية.

الكلمات المفتاحية: حمض الفوليك؛ التحليل الصيدلاني؛ القياس الطيفي؛ مصفوفة المشروبات؛ الثبات.

Introduction

Folate is an essential water-soluble B vitamin required for nucleotide synthesis, methylation, cellular division, and erythropoiesis. An umbrella review published in 2026 found strong evidence that adequate folate status protects against megaloblastic anaemia and neural tube defects (NTDs), while a 2023 systematic review of more than 1.2 million participants supported periconceptional folic acid supplementation for NTD prevention (Yoo et al., 2026; Viswanathan et al., 2023). A separate umbrella review estimated a 57% reduction in NTDs with prenatal folic acid or multivitamin supplementation, although substantial heterogeneity remained (Abate et al., 2025).

At the population level, fortification policy is associated with higher plasma folate and lower NTD prevalence, but implementation is uneven. A global systematic review reported lower mean NTD prevalence in settings with mandatory fortification than in settings with voluntary or no fortification (Huo et al., 2024). In sub-Saharan Africa, a 2025 meta-analysis estimated that only 14.10% of women used folic acid during the preconception period; certainty was low because heterogeneity and publication bias were substantial (Aweke et al., 2025). These findings support local surveillance of product quality and awareness but do not replace direct, setting-specific evidence.

Folic acid quantification is analytically challenging because pH, light, heat, oxidation, and matrix constituents may alter chemical stability or spectroscopic response. Recent primary studies have validated UV-visible, ferric-bipyridine, RP-HPLC-PDA, and UPLC/PDA approaches for folic acid-containing matrices (Modupe et al., 2020; Naji et al., 2020; Alshehri et al., 2023; Lusi et al., 2025). Food-matrix evidence also shows that liberation, stability, and apparent bioaccessibility depend on matrix composition, whereas mechanistic information about specific interactions remains incomplete (Liu et al., 2024).

This study aimed to: (1) quantify folic acid in four commercial tablet products using an indirect ferric chloride–2,2′-bipyridyl assay; (2) compare the assay response in water, coffee, orange juice, green tea, and a carbonated soft drink; and (3) describe folic acid awareness and reported supplementation in an academic convenience sample. Because the experiment lacked matrix-matched validation and a stability-indicating comparator, beverage results are reported as apparent concentration rather than confirmed degradation or bioavailability.

Material and methods

Study design

A laboratory-based comparative study was combined with a small descriptive questionnaire survey. Four commercially available folic acid tablet products obtained from local pharmacies were anonymized as A–D. The laboratory component compared assay responses across five media. The questionnaire component included 66 persons from an academic setting; only aggregate percentages were available in the source record.

Reagents and apparatus

All reagents were analytical grade, and bidistilled water was used. The assay used folic acid reference standard, sodium hydroxide, ferric chloride hexahydrate, 2,2′-bipyridyl, hydrochloric acid, and acetic acid. Absorbance was measured with a UV-visible spectrophotometer at 520 nm. Recent ferric-bipyridine evidence confirms the underlying reduction of Fe(III) to Fe(II) followed by formation of a colored Fe(II)-bipyridine complex, but selectivity must be demonstrated for each matrix (Naji et al., 2020).



Figure 1. Commercial folic acid tablet products coded A–D.

Standard solutions

A 1000 µg/mL folic acid stock was prepared by dissolving 0.1000 g of reference material in 10 mL of 0.1 M NaOH and diluting to 100 mL with the same solvent. The stock was protected from light and stored at 5 °C. Ferric chloride solution (0.02 M) was prepared by dissolving 0.5406 g $FeCl_3 \cdot 6H_2O$ in 5 mL of 1 M HCl and diluting to 100 mL in an amber flask. A 0.01 M 2,2′-bipyridyl solution and 0.1 M NaOH were freshly prepared.

Tablet preparation

Tablets were weighed, finely powdered, and a quantity stated to be equivalent to 0.1 g folic acid was dissolved in 0.1 M NaOH, shaken, filtered, washed, and diluted to 100 mL. A nominal 100 µg/mL working solution was prepared by tenfold dilution, followed by serial dilution. Product label strengths, batch numbers, manufacturers, tablet weights, number of tablets pooled, and replicate preparations were not preserved in the source document; consequently, results cannot be expressed as percentage label claim or assessed against pharmacopeial acceptance criteria.



Figure 2. Powdering of commercial tablet samples before extraction.



Figure 3. Addition of ferric reagent during color development.



Figure 4. Preparation of sample and reagent-blank solutions.



Figure 5. Incubation of assay mixtures in a thermostatic water bath.



Figure 6. UV-visible spectrophotometer used for absorbance measurement.

Calibration and assay

Aliquots of the 100 µg/mL standard were transferred into 10 mL calibrated flasks to produce 0.5–18 µg/mL. Ferric chloride (0.5 mL; 0.02 M) and 2,2′-bipyridyl (2.5 mL; 0.01 M) were added. Mixtures were incubated at 60 °C for 35 min, cooled, treated with 1.0 mL of 0.02 M acetic acid, diluted to volume, rested for 5 min, and read at 520 nm against a reagent blank. The original calibration equation was $A = 0.0642C + 0.0386$ with $R^2 = 0.9985$, where A is absorbance and C is folic acid concentration in µg/mL.

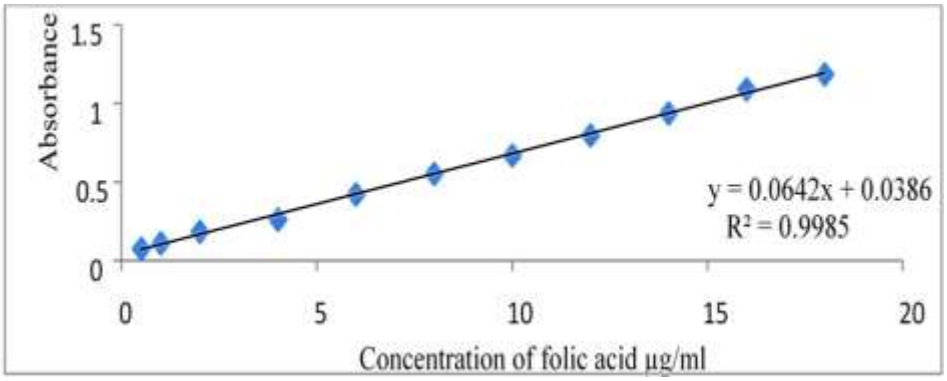


Figure 7. Calibration curve for the indirect spectrophotometric determination of folic acid (0.5–18 µg/mL).

Beverage conditions

Each coded sample was evaluated in distilled water, coffee diluted 1:20, orange juice diluted 1:10, green tea diluted 1:10, and undiluted Seven-Up. These media were selected as commonly consumed beverages. The source record did not preserve beverage brands, preparation procedures, initial pH, incubation time, exact mixing ratio

with tablet extract, light exposure, temperature history, or replicate measurements. Because coffee, tea, and juice contain reducing and light-absorbing constituents, beverage-specific blanks, standard-addition recovery, and orthogonal chromatography are required to separate true folic acid loss from analytical interference (Liu et al., 2024).

Questionnaire

A convenience questionnaire was completed by 66 persons in an academic setting. Four aggregate outcomes were retained: awareness of folic acid, understanding of its importance, previous supplement use, and pregnancy planning among married respondents. The questionnaire wording, denominator for the pregnancy-planning item, demographic characteristics, validity, response rate, consent procedure, and ethics approval identifier were unavailable; therefore, the survey is reported only as exploratory descriptive evidence.

Data analysis

The calibration equation was used to calculate apparent concentration. Laboratory values and questionnaire outcomes were summarized descriptively. No replicate-level dataset, standard deviations, confidence intervals, hypothesis tests, limits of detection or quantification, recovery studies, or uncertainty estimates were available. Inferential claims were therefore avoided.

Results and discussion

Calibration performance

The assay was linear over 0.5–18 µg/mL, with A = 0.0642C + 0.0386 and R^2 = 0.9985 (Fig. 7). High linearity alone does not demonstrate accuracy, precision, selectivity, robustness, or stability-indicating capability; recent validated methods report these parameters explicitly (Alshehri et al., 2023; Lusi et al., 2025).

Ferric reagent consumption

The recorded ferric reagent volume was constant in distilled water (0.3 mL) but varied across beverage media from 0.6 to 2.3 mL (Table 1; Fig. 8). This pattern indicates matrix-dependent reducing demand and supports concern about interference in the indirect redox-colorimetric assay.

Table 1. Ferric reagent volume recorded for commercial samples in each medium.

Sample	Water	Coffee 1:20	Orange 1:10	Green tea 1:10	Seven-Up
A	0.3	1.2	1.8	2.0	0.6
B	0.3	1.9	1.9	1.9	0.9
C	0.3	2.0	1.7	2.2	1.0
D	0.3	2.0	2.1	2.3	1.2

Values are reported as mL from the original laboratory record; replicate-level variability was unavailable.

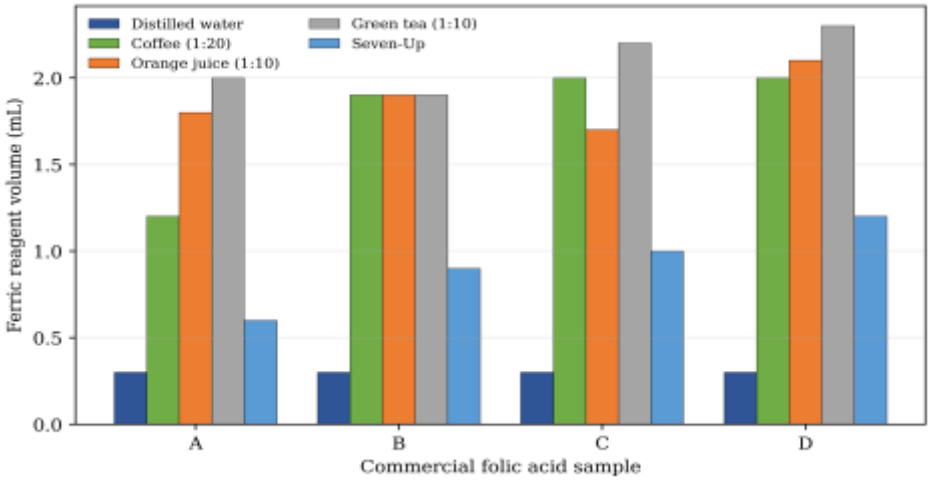


Figure 8. Ferric reagent volume recorded by sample and beverage medium.

Apparent concentrations

Apparent folic acid concentrations varied by both sample and medium (Table 2; Fig. 9). In distilled water, values ranged from 1.174 µg/mL (D) to 21.170 µg/mL (A). The lowest beverage-matrix value was 3.697 µg/mL (C in Seven-Up), whereas the highest was 12.109 µg/mL (B in green tea). Product D increased from 1.174 µg/mL in water to 10.364 µg/mL in green tea and 9.866 µg/mL in Seven-Up, demonstrating that the observed differences cannot be uniformly interpreted as beverage-induced degradation.

Table 2. Apparent folic acid concentration by commercial sample and medium.

Sample	Water	Coffee 1:20	Orange 1:10	Green tea 1:10	Seven-Up
A	21.170	9.180	9.056	8.370	5.177
B	8.152	8.168	3.900	12.109	4.227
C	12.186	11.953	4.679	12.077	3.697
D	1.174	7.778	3.915	10.364	9.866

Values are apparent concentrations (µg/mL) calculated with the aqueous calibration curve. They are not corrected for dilution, recovery, labeled strength, or beverage-matrix effects.

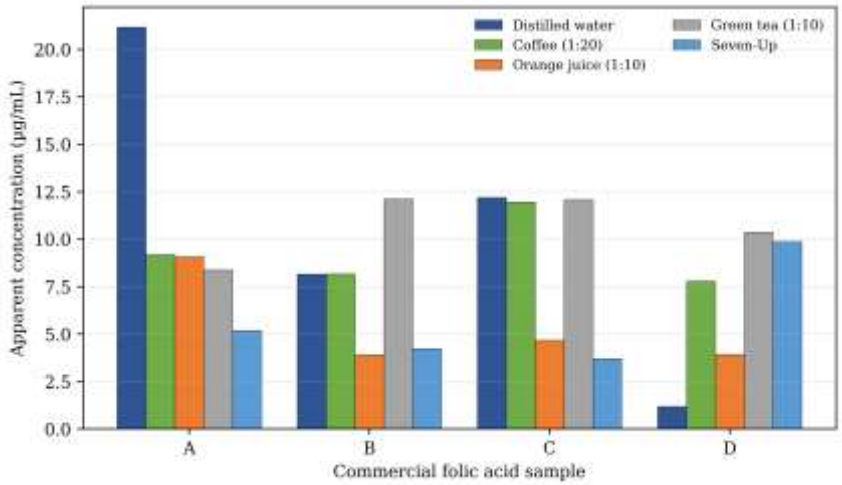


Figure 9. Apparent folic acid concentration by sample and beverage medium.

Questionnaire findings

Among 66 participants, 78.78% had heard of folic acid, 60.60% reported understanding its importance, and 51.51% reported having taken supplements. The source record stated that 29.16% of married women planned pregnancies, but the denominator for this subgroup was not available (Fig. 10). The awareness-to-use gradient is consistent with systematic-review evidence that knowledge is associated with better iron–folic acid adherence, but causality cannot be inferred from this survey (Saragih et al., 2022).

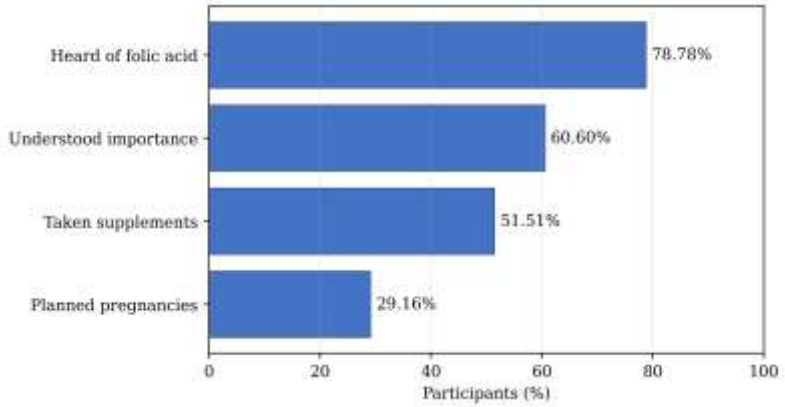


Figure 10. Descriptive folic acid awareness and reported practices in the academic convenience sample (n = 66).

Discussion

The main laboratory finding was pronounced product-by-medium variation in apparent folic acid concentration. An aqueous measurement of 21.170 µg/mL for sample A and 1.174 µg/mL for sample D suggests either true product-content differences, unequal preparation relative to label strength, incomplete extraction, calculation or transcription error, or formulation-specific interference. Without labeled strengths, replicate preparations, recovery experiments, and an independent assay, these alternatives cannot be distinguished. Recent validated RP-HPLC-PDA and UPLC/PDA methods incorporate specificity, recovery, repeatability, limits of detection and quantification, robustness, and system suitability, providing a stronger basis for pharmaceutical quality assessment (Alshehri et al., 2023; Lusi et al., 2025).

The beverage results should not be described as direct evidence that coffee, green tea, orange juice, or Seven-Up destroys folic acid or reduces its absorption. The ferric-bipyridine method depends on redox chemistry, and beverage constituents can independently reduce Fe(III), chelate iron, contribute color or turbidity, or shift pH. The strong increase for sample D in several beverages directly contradicts a simple universal degradation model. A 2024 comprehensive review concluded that food matrices affect folate liberation and stability but emphasized limited molecular-level evidence and scant information on interconversion and degradation during digestion (Liu et al., 2024).

Nevertheless, folic acid is susceptible to environmental conditions. Alginate-pectin and related carriers improved retention under pH, temperature, and light challenges in a 2020 primary study, while encapsulation increased photo- and thermal stability in a fortified pineapple beverage in 2021 (Črnivec et al., 2020; Pamunuwa et al., 2021). These studies support controlled stability experiments, but they cannot validate the current beverage observations because the formulations, matrices, exposure conditions, and analytical methods differ.

The questionnaire showed high awareness but lower reported use and pregnancy planning. This direction is plausible: a systematic review and meta-analysis found that knowledge of iron and folic acid supplementation was positively associated with adherence (Saragih et al., 2022), while the 2025 sub-Saharan African meta-analysis documented very low preconception use overall (Aweke et al., 2025). However, the present convenience sample was small, lacked participant characteristics and a validated questionnaire, and did not preserve the subgroup denominator; generalization to women of reproductive age in Libya is not justified.

The clinical importance of reliable products and timely use remains strong. The 2026 umbrella review found robust evidence for prevention of NTDs and megaloblastic anaemia (Yoo et al., 2026), and the 2023 USPSTF evidence review supported benefit without evidence of the harms examined (Viswanathan et al., 2023). Safety claims require nuance: the EFSA systematic assessment retained an adult tolerable upper intake level of 1000 µg/day for supplemental folate forms, primarily to protect individuals with vitamin B12 deficiency, while finding insufficient evidence for a causal relationship with cognitive decline or colorectal and prostate cancer at the population level (EFSA NDA Panel et al., 2023).

Strengths and limitations

Strengths include evaluation of multiple commercial products, use of an explicit calibration curve, comparison across common beverage matrices, inclusion of original laboratory photographs, and triangulation with a descriptive awareness survey. The revised interpretation separates measured assay response from chemical stability and in-vivo bioavailability.

Major limitations are absence of product label strengths and batch information; unclear tablet-equivalent calculations; no independent sample replicates; no beverage-matched calibration or standard-addition recovery; no pH, time, temperature, or light controls; no validated stability-indicating chromatographic method; no identification of degradation products; and no inferential statistics. For the survey, the sampling frame, demographics, instrument validity, response rate, ethics approval, consent process, and subgroup denominator were unavailable. The clinician interview in the original draft was excluded from evidentiary analysis because it was anecdotal and not collected under a defined qualitative protocol.

Conclusion

Four commercial folic acid tablet products produced markedly different spectrophotometric responses, and the apparent concentrations changed substantially across water, coffee, orange juice, green tea, and Seven-Up. These findings demonstrate matrix sensitivity of the indirect ferric chloride–2,2′-bipyridyl assay but do not establish pharmaceutical non-compliance, chemical degradation, reduced absorption, or a clinically relevant beverage interaction. The awareness survey suggests a gap between having heard of folic acid and reported supplement use, but its convenience design precludes population inference. A confirmatory study should normalize results to labeled strength, use independent replicate preparations, validate accuracy and precision, apply beverage-specific

blanks and standard additions, control pH and exposure, and compare results with a stability-indicating HPLC/UPLC method.

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Conflict of interest
The author declares no conflict of interest.

Data availability
Aggregate data used in this article are presented in Tables 1 and 2 and Fig. 10. Replicate-level laboratory data and the individual questionnaire dataset were unavailable.

Ethics statement

Formal ethical approval was not obtained for this questionnaire-based study prior to data collection. Participation was voluntary, and informed consent was obtained from all participants before completion of the questionnaire. Participants were informed about the purpose of the study, the voluntary nature of participation, their right to decline participation or withdraw without consequences, and the intended use of the collected information. No personally identifiable information was collected or reported. All questionnaire responses were treated confidentially, anonymized where applicable, securely stored, and accessed only by the research team. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Author Contributions

Faraj Rabeh led the study design, methodology, supervision, resources, project administration, validation, and manuscript review.

Seraj Abbas contributed to study conceptualization, data collection and management, statistical/formal analysis, figure preparation, first-draft writing, and manuscript revision.

Hajir Husayn, Faraj Aljibali, Emraga Lashhab, Khadija Muhammad, Naday Faraj, Safaa Amrajia, and Manal Momen contributed to data collection, data management, validation, and manuscript review.

All authors contributed substantially to the study, reviewed and approved the final manuscript, accept responsibility for its accuracy and integrity, and confirm that it has not been published or submitted elsewhere.

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Appendix A. Reference audit

Reference	Verified DOI	Evidence type	Indexing checked
Yoo et al. (2026)	10.7189/jogh.16.04014	Systematic umbrella review	PubMed/PMC
Abate et al. (2025)	10.1159/000539803	Umbrella review/meta-analysis	PubMed
Aweke et al. (2025)	10.1371/journal.pone.0318422	Systematic review/meta-analysis	MEDLINE/PubMed; Scopus

Reference	Verified DOI	Evidence type	Indexing checked
Viswanathan et al. (2023)	10.1001/jama.2023.9864	Systematic evidence review	MEDLINE/PubMed; Scopus/WoS
Huo et al. (2024)	10.1016/j.eclinm.2023.102366	Systematic review	MEDLINE/PubMed; Scopus
Bo et al. (2020)	10.3389/fpubh.2020.550753	Umbrella review/meta-analysis	PubMed/PMC; Scopus
EFSA NDA Panel et al. (2023)	10.2903/j.efsa.2023.8353	Systematic safety assessment	PubMed/PMC; Scopus
Saragih et al. (2022)	10.1016/j.midw.2021.103185	Systematic review/meta-analysis	MEDLINE/PubMed; Scopus
Liu et al. (2024)	10.1111/1541-4337.13328	Comprehensive review	MEDLINE/PubMed; Scopus/WoS
Črnivec et al. (2020)	10.1039/C9FO02419K	Primary experimental study	MEDLINE/PubMed; Scopus/WoS
Pamunuwa et al. (2021)	10.1155/2021/9913884	Primary experimental study	Scopus (journal status should be rechecked at submission)
Modupe et al. (2020)	10.1016/j.jafr.2020.100060	Primary analytical validation	PubMed/PMC; Scopus
Naji et al. (2020)	10.1016/j.heliyon.2020.e03162	Primary analytical validation	PubMed/PMC; Scopus
Sager et al. (2023)	10.24996/ijs.2023.64.8.2	Primary analytical study	DOAJ; indexing should be rechecked
Alshehri et al. (2023)	10.1016/j.heliyon.2023.e20282	Primary analytical validation	PubMed/PMC; Scopus
Lusi et al. (2025)	10.1093/jaoacint/qsaf014	Primary analytical validation	MEDLINE/PubMed; Scopus/WoS

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