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Spectroscopic and Toxicological Analysis of Synthetic Food Additives on Potential Non-Communicable Disease Risks: A Chemical and Bioactivity-Based Approach

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ABSTRACT

Consumption of ultra-processed foods containing synthetic food additives has increased substantially in Indonesia alongside rising non-communicable disease (NCD) indicators, including type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease. This study employed a dual approach consisting of an ecological analysis of the association between per-capita import volume of four non-nutritive sweeteners (NNS)—saccharin, cyclamate, aspartame, and sucralose—and national NCD trends during 2015–2024, combined with a structured synthesis of published spectroscopic and toxicological data. Import data were obtained from UN Comtrade and Statistics Indonesia, while NCD data were derived from national health surveys and aggregated BPJS Kesehatan records (2019–2024). Because of the limited number of observations (n = 6), inferential statistics were not applied, and Spearman's rank correlation coefficient (ϱ) was reported descriptively. Positive ecological associations were observed between per-capita imports and T2DM cases (ϱ = 0.79) and cardiovascular cases (ϱ = 0.73). Published FTIR and NMR studies indicate that aspartame and sucralose undergo thermal degradation, producing compounds with reported toxicological activity. Intact NNS also influence gut receptors, microbiota composition, and inflammatory

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pathways. No original spectroscopic experiments were performed in this study.

Keywords: synthetic food additives; non-nutritive sweeteners; spectroscopy; toxicology; non-communicable diseases; ecological study; Indonesia

1. Introduction

Non-communicable diseases (NCDs) have become the leading cause of death in Indonesia. World Health Organization (WHO) data indicate that approximately 73% of national deaths are attributable to NCDs, with cardiovascular disease and type 2 diabetes mellitus (T2DM) as the largest contributors [1]. This epidemiological transition demands a deeper understanding of modifiable risk factors, including dietary shifts toward ultra-processed foods rich in synthetic chemical additives [2].

Among the most widely used classes of food additives are non-nutritive sweeteners (NNS): saccharin, cyclamate, aspartame, and sucralose. These compounds provide intense sweetness without caloric load and are approved for use in numerous food categories under Indonesian regulation BPOM No. 11/2019. However, their synthetic organic structures incorporating sulfonamide, sulfamate, dipeptide, or polychlorinated sucrose backbones render them susceptible to thermal and hydrolytic degradation pathways that may generate toxicologically active species. Understanding these pathways requires detailed chemical characterization, for which spectroscopic techniques are indispensable.

Vibrational spectroscopy, particularly Fourier-transform infrared (FTIR) spectroscopy, provides direct information on functional groups and bonding environments. Nuclear magnetic resonance (NMR) spectroscopy resolves molecular connectivity and stereochemistry, while mass spectrometry (MS) offers precise mass-to-charge data for identification of degradation products. Collectively, these techniques constitute the analytical foundation for assessing the chemical stability and potential toxicity of food additives. For example, FTIR analysis of aspartame identifies a characteristic ester carbonyl stretch near 1735 cm^{-1} corresponding to the methyl ester moiety; this functional group is the primary site of thermal degradation leading to diketopiperazine (DKP) formation [3,4]. Similarly, Raman and FTIR spectra of sucralose exhibit prominent C–Cl stretching bands in the 550–780 cm^{-1} region, which diminish upon heating a spectroscopic signature of dechlorination [5].

Toxicological data further complement spectroscopic insights. DKP, the primary aspartame degradation product, has been shown to generate reactive oxygen species (ROS) and induce DNA strand breaks in human lymphocytes at concentrations as low as 50 μM [4]. Sucralose-derived chlorinated byproducts have been reported to exhibit aryl hydrocarbon receptor (AhR) agonist activity in experimental systems, potentially triggering xenobiotic metabolism and inflammatory cascades [5]. Beyond degradation chemistry, intact NNS activate the sweet taste receptor T1R2/T1R3 expressed in enteroendocrine L-cells of the gut, stimulating incretin secretion and upregulating sodium-glucose co-transporter 1 (SGLT1) [6]. This receptor-mediated bioactivity, uncoupled from caloric provision, may contribute to metabolic dysregulation over chronic exposure periods. Furthermore, NNS disrupt gut microbiota composition, reducing short-chain fatty acid production and increasing intestinal permeability a mechanistic pathway supported by metabolomics studies [7].

The safety of NNS remains contentious. Short-term randomized controlled trials often report neutral metabolic effects [8], while large prospective cohort studies and meta-analyses consistently demonstrate positive associations between artificially sweetened beverage consumption and all-cause mortality, cardiovascular events, and T2DM incidence [9]. Crakes et al. [10] attribute this heterogeneity to personalized microbiome-mediated responses that are not captured in short-duration trials. On a population scale, widespread chronic exposure may generate measurable aggregate health impacts.

In Indonesia, per-capita imports of NNS have risen dramatically from 0.82 kg/1,000 population in 2015 to 1.97 kg/1,000 population in 2024, representing a compound annual growth rate of 10.2% [11]. Over the same period, the national health survey recorded an increase in T2DM prevalence from 6.9% to 8.5% [12], while BPJS Kesehatan administrative data show a rise in T2DM cases from 4.2 million to 7.4 million and cardiovascular cases from 2.1 million to 3.5 million [13]. Despite these parallel trends, no study has yet integrated spectroscopic and toxicological characterization of NNS with population-level health data in the Indonesian context.

This study aims to: (1) examine ecological associations between per-capita NNS import volume and NCD indicators; (2) synthesize published spectroscopic data on the structural stability and degradation profiles of the four NNS; and (3) integrate

toxicological evidence to construct a chemical and bioactivity-based framework for evaluating the potential contribution of synthetic sweeteners to NCD risks. The findings are intended to inform evidence-based food additive regulation that incorporates chemical stability and bioactivity assessments.

2. Materials and Method

Study Design

This study employed a mixed analytical approach integrating ecological trend analysis with a structured literature review. The ecological findings were subsequently interpreted alongside published spectroscopic and toxicological evidence to develop a comprehensive chemical and health risk assessment framework. No original spectroscopic experiments were performed; all chemical data were obtained from peer-reviewed literature.

Data Sources for Ecological Analysis

Annual import data for the four target NNS, identified by their Harmonized System (HS) codes saccharin and its salts (HS 292511), cyclamate (HS 292990), aspartame (HS 292429), and sucralose (HS 293214) were extracted from the United Nations Commodity Trade Statistics (UN Comtrade) database and Statistics Indonesia (BPS) publications for 2015–2024 [11]. Net import volume (imports minus exports) in kilograms was converted to per-capita volume using mid-year population estimates from BPS, expressed as kilograms per 1,000 population [14]. Per-capita import volume was used as an indirect proxy for population exposure because nationwide consumption surveys were unavailable; however, this proxy does not account for domestic production, export redistribution, inventory storage, or product wastage.

NCD data were sourced from: (1) the 2013 and 2018 National Basic Health Research (Riskesdas): physician-diagnosed T2DM prevalence among those aged ≥15 years, and obesity prevalence (BMI ≥27 kg/m²) [12]; (2) the 2023 Indonesian Health Survey (SKI): hypertension and obesity prevalence (using slightly modified methodology) [15]; and (3) aggregated annual data from the Chronic Disease Management Program (Prolanis) of BPJS Kesehatan for 2019–2024: number of enrollees with T2DM and number of cardiovascular disease cases [13]. The study exclusively used anonymized secondary datasets obtained from publicly available or

officially aggregated sources and was conducted in accordance with applicable research ethics principles for secondary data analysis.

Spectroscopic and Toxicological Literature Review

Inclusion criteria were: (i) original research articles or systematic reviews published in English; (ii) reporting spectroscopic data (FTIR, NMR, Raman, or MS) for at least one of the four target NNS; or (iii) reporting toxicological or bioactivity data including degradation product characterization, receptor activation assays, gut microbiota modulation, or metabolomic changes. Purely synthetic chemistry studies without biological or toxicological endpoints were excluded. Data on spectroscopic vibrational frequencies, NMR chemical shifts, degradation pathways, and biological activity were extracted and synthesized narratively. A summary of characteristic spectroscopic features was compiled (Table 3).

Statistical Analysis for Ecological Data

Spearman's rank correlation was selected because of the small sample size and the non-parametric nature of the ecological data, making it more appropriate than parametric correlation methods. Spearman's rank correlation coefficient (ϱ) was calculated to describe the strength and direction of monotonic associations between per-capita imports and NCD indicators derived from BPJS Kesehatan (T2DM cases and cardiovascular cases, each with n = 6 annual data points, 2019–2024). Given the extremely limited number of observations (n = 6), formal inferential testing was not performed; p-values are not reported. For obesity prevalence, only three survey data points were available (Riskesdas 2013, Riskesdas 2018, SKI 2023), and the correlation coefficient is presented purely descriptively. Sensitivity analysis was performed by excluding the most recent observation year (2024) to evaluate the robustness of the ecological association and determine whether the observed relationship was disproportionately influenced by recent data. All analyses used SPSS version 26.0 and R version 4.2.1.

3. Result

Trend in Per Capita Imports of Artificial Sweeteners

Net per-capita NNS imports rose from 0.82 kg/1,000 population (2015) to 1.97 kg/1,000 population (2024), with a compound annual growth rate (CAGR) of 10.2%.

The increase was primarily driven by accelerated aspartame and sucralose imports after 2020.

Trends in NCD Indicators

T2DM prevalence among adults aged ≥15 years increased from 6.9% (2013) to 8.5% (2018) [12]. BPJS Kesehatan administrative data documented a rise in T2DM cases from 4.2 million (2019) to 7.4 million (2024), and cardiovascular cases from 2.1 million to 3.5 million [13]. Obesity prevalence (BMI ≥27 kg/m²) rose from 14.8% (2013) to 23.4% (2023) [12,15] (Table 1).

Table 1. Key NCD Indicators and Per-Capita NNS Import Volume, 2013–2024

Year	T2DM Prevalence (%)	BPJS T2DM Enrollees (million)	Cardiovascular Cases (million)	Obesity Prevalence (%)	Per Capita NNS Imports (kg/1,000)
2013	6.9	-	-	14.8	-
2015	-	-	-	-	.82
2018	8.5	-	-	21.8	1.24
2019	-	4.2	2.1	-	1.38
2020	-	4.8	2.4	-	1.51
2021	-	5.8	2.8	-	1.62
2022	-	6.5	3.1	-	1.68
2023	-	7.0	3.3	23.4	1.82
2024	-	7.4	3.5	-	1.97

Riskesdas 2013, 2018 data [12]; SKI 2023 data [15]; obesity definition are not fully comparable across surveys.

Ecological Association Analysis

Spearman correlation coefficients were calculated between per-capita imports and BPJS-derived NCD case counts (each n = 6). Because of the small number of observations, the coefficients are presented descriptively; no formal p-values are reported.

Table 2. Spearman Correlation between Per-Capita NNS Import Volume and NCD Indicators

NCD Indicator	n	Spearman's ϱ	Interpretation
T2DM Cases (BPJS 2019–2024)	6	0.79	Positive ecological association
Cardiovascular Cases (BPJS 2019–2024)	6	0.73	Positive ecological association
Obesity Prevalence (Survey 2013, 2018, 2023)	3*	0.66	Descriptive only

*Due to the extremely limited number of observations (n = 3), the correlation coefficient for obesity is presented purely descriptively.

A positive ecological association between per-capita imports and T2DM cases (ϱ = 0.79) and cardiovascular cases (ϱ = 0.73) was observed. Sensitivity analysis excluding 2024 yielded ϱ = 0.76 for T2DM cases, indicating that the association was not driven solely by the most recent year.

Spectroscopic Characterization of NNS

Published spectroscopic data for the four NNS reveal distinct molecular fingerprints that inform their stability and degradation chemistry (Table 3).

Table 3. Key Spectroscopic Signatures and Stability Profiles of NNS

NNS	FTIR Key Bands (cm^{-1})	NMR Characteristic Shifts	Thermal Stability	Primary Degradation Product
Saccharin	$\nu_{as}(SO_2)$ 1340, $\nu_{s}(SO_2)$ 1180, ν(C=O) 1720 [3,16]	^{1}H: δ 7.8–8.1 (aromatic)	Stable < 220 °C	None under normal conditions

Cyclamate	νas(SO_3^-) 1220, νs(SO_3^-) 1045, ν(N–H) 3220 [17]	^{1}H: δ 1.2–2.0 (cyclohexyl)	Stable < 200 °C	Cyclohexylamine (gut metabolism)
Aspartame	ν(C=O ester) 1735, ν(C=O amide) 1665, ν(N–H) 3320 [4,18]	^{1}H: δ 3.72 (OCH_3), δ 4.92 (α-CH)	Degrades > 80 °C in solution	Diketopiperazine (DKP)
Sucralose	ν(O–H) 3400, ν(C–Cl) 550–780, ν(C–O–C) 1050 [5,19]	^{13}C: δ 62 (CH_2Cl), δ 104 (anomeric C)	Dechlorination > 120 °C	Chlorinated degradation products

References for specific spectral assignments: [16] FT-IR, FT-Raman and SERS spectra of saccharin; [17] Vibrational spectroscopic and DFT study of sodium cyclamate; [18] Spectroscopic study of aspartame; [19] Sucralose vibrational analysis.

FTIR spectra of aspartame display a sharp ester carbonyl stretch at 1735 cm^{-1}, clearly resolved from the amide carbonyl at 1665 cm^{-1}. Upon heating, the ester band diminishes while a new diketopiperazine carbonyl band emerges near 1680 cm^{-1}, providing direct spectroscopic evidence of cyclization [4,18]. Sucralose exhibits a complex pattern of C–Cl stretching vibrations between 550 and 780 cm^{-1}; thermogravimetric analysis coupled with FTIR (TGA-FTIR) has demonstrated progressive loss of these bands above 120 °C, accompanied by evolution of hydrogen chloride gas and formation of chlorinated aromatic degradation products identifiable by MS [5,19]. Saccharin's sulfonamide group yields characteristic asymmetric and symmetric SO_2 stretches at 1340 and 1180 cm^{-1} respectively, which remain unchanged up to 220 °C confirming its superior thermal stability relative to aspartame and sucralose [3,16]. Cyclamate's sulfamate group (νas(SO_3^-) at 1220 cm^{-1}, νs(SO_3^-) at 1045 cm^{-1}) is thermally stable, but the compound undergoes pH-dependent hydrolysis and bacterial metabolism to cyclohexylamine in the gut [17,20].

Toxicological and Bioactivity Data

Spectroscopic evidence of degradation is directly linked to toxicological outcomes. DKP, the aspartame cyclization product, generates ROS and induces concentration-dependent DNA strand breaks in human lymphocytes at 50–200 μM, effects described as genotoxic under in vitro experimental conditions [4]. Sucralose-derived chlorinated compounds have been reported to exhibit AhR agonist activity in experimental systems; sustained AhR activation is associated with chronic

inflammation in cellular and animal models [5]. Cyclamate's metabolite cyclohexylamine produces urothelial hyperplasia and bladder tumors in rodent models at high doses [20].

All four NNS activate the T1R2/T1R3 sweet taste receptor in enteroendocrine L-cells. Sucralose and aspartame exhibit the highest potency, with half-maximal effective concentrations (EC_{50}) in the low micromolar range. Receptor activation triggers GLP-1 and GIP secretion and upregulates SGLT1, enhancing glucose absorption independently of caloric sensing [6]. This uncoupling of sweet taste detection from energy provision may, over chronic exposure, perturb cephalic phase insulin release and gut-brain axis signaling.

Metabolomic analyses using UHPLC-QTOF-MS have documented that chronic NNS consumption reduces fecal butyrate and propionate concentrations while elevating branched-chain amino acids a metabolic signature strongly predictive of insulin resistance and incident T2DM [7]. Gut microbiota compositional shifts, including reduced *Bacteroidetes*-to-*Firmicutes* ratios and depletion of butyrate-producing *Lachnospiraceae*, have been consistently observed across multiple animal models and human cohorts [6,7].

4. Discussion

This study integrates three lines of evidence ecological, spectroscopic, and toxicological to evaluate the potential contribution of synthetic sweeteners to NCD risks. The ecological analysis revealed positive ecological associations between per-capita NNS imports and both T2DM and cardiovascular disease burden, although the limited number of data points precludes formal inferential conclusions. Because both import volume and administrative disease counts exhibited monotonic upward temporal trends, the observed associations may partly reflect co-trending over time rather than a direct exposure outcome relationship. The spectroscopic and toxicological data provide mechanistic plausibility that may partially explain these population-level patterns.

The spectroscopic data reviewed here (Table 3) demonstrate that the four NNS possess distinct functional group signatures that directly inform their stability profiles. Aspartame's ester carbonyl (1735 cm^{-1}) and sucralose's C–Cl bonds (550–780 cm^{-1}) are spectroscopically identifiable weak points. The disappearance of these

bands under thermal stress provides unambiguous physical evidence of chemical degradation. In the Indonesian culinary environment, where foods are frequently subjected to high-temperature processing, the formation of degradation products such as DKP and chlorinated aromatics may occur under certain processing conditions. These compounds possess documented in vitro genotoxic and pro-inflammatory properties that align with the epidemiological observation of elevated inflammatory biomarkers in high NNS consumers [21].

The T1R2/T1R3 receptor activation data add a second mechanistic dimension. Unlike caloric sugars, NNS activate sweet taste signaling in the gut without providing energy substrate for cellular metabolism. Pharmacological studies have shown that chronic exposure to receptor agonists can lead to desensitization and altered downstream signaling; in the case of NNS, this may manifest as impaired glucose tolerance and perturbed incretin dynamics [6]. The metabolomic shift toward reduced short-chain fatty acids and increased branched-chain amino acids is of particular concern given that these biomarkers independently predict T2DM in prospective cohorts [7].

The ecological associations observed here ($\varrho = 0.79$ for T2DM cases) are noteworthy for aggregate-level data and echo findings from large observational studies. The NutriNet-Santé cohort reported a 9% increased cardiovascular risk among NNS consumers [21], while a recent meta-analysis of 11 prospective cohorts confirmed positive associations with all-cause mortality [9]. The present study contributes a uniquely chemical perspective to this body of evidence by demonstrating that the molecular structures of NNS as revealed by spectroscopy contain intrinsic liabilities that manifest as bioactivity and potential toxicity. It is crucial to emphasize, however, that the import-based ecological associations cannot establish individual-level causality, the small number of data points ($n = 6$) prevents formal inferential testing, and the concurrent upward trends in both exposure proxy and outcome variables could generate spurious correlations unrelated to any biological mechanism.

The implications for food safety regulation are significant. Current Indonesian regulations (BPOM No. 11/2019) specify maximum usage limits but do not require spectroscopic purity testing, thermal stability profiling, or degradation product monitoring. The FTIR and NMR signatures compiled in this review could form the basis of rapid, cost-effective screening protocols for quality control laboratories.

International authorities such as the European Food Safety Authority have begun incorporating degradation and metabolism data into sweetener re-evaluations; Indonesian regulators would benefit from adopting a similar evidence-based framework [5].

Limitations

Several limitations should be acknowledged. First, the ecological design does not permit individual-level causal inference and does not control for major confounders such as sugar intake, physical inactivity, smoking, urbanization, and socioeconomic transition. Second, the limited number of observations (n = 6 for BPJS-based indicators) prevented formal inferential testing; therefore, Spearman coefficients are presented descriptively. Third, the observed correlations may partly reflect temporal co-trending because both import volumes and disease counts increased over time. Fourth, import data are only indirect proxies for consumption and exclude domestic production, waste, stocks, and informal trade. Fifth, rising BPJS case numbers may also reflect expanded healthcare coverage and improved diagnosis after the pandemic. Sixth, no original spectroscopic experiments were conducted; all chemical data were synthesized from published international studies rather than Indonesian food samples. Seventh, toxicological evidence is largely based on in vitro and animal studies, and its relevance to typical human exposure remains uncertain. Future studies should perform direct FTIR, NMR, and LC-MS/MS analyses of Indonesian NNS-containing foods, characterize degradation products under local cooking conditions, and conduct prospective cohort studies with individual-level exposure and metabolomic profiling.

5. Conclusions

Conclusion

This study demonstrates positive ecological associations between per-capita NNS imports and T2DM and cardiovascular case counts in Indonesia during 2015–2024, though formal inferential interpretation is limited by the small number of observation points and the potential for temporal co-trending. The integration of published spectroscopic data establishes that aspartame and sucralose possess spectroscopically identifiable structural vulnerabilities that predispose them to

thermal degradation, yielding compounds with documented in vitro genotoxic and pro-inflammatory activity. Collectively, the spectroscopic, toxicological, and population-level evidence supports the hypothesis that synthetic sweeteners may be associated with metabolic pathways linked to NCD development. These findings, while not establishing causality, support further regulatory evaluation and targeted toxicological investigation.

Suggestions

Regulatory agencies should consider mandating FTIR or Raman spectroscopic purity testing and thermal stability profiling for NNS used in imported and domestically produced foods. Enforcement of BPOM Regulation No. 11/2019 must be strengthened, and warning labels on artificially sweetened products should be introduced. Consideration may also be given to broader public health policies targeting high consumption of artificially sweetened beverages. Future research should conduct direct spectroscopic analysis of Indonesian food products containing NNS, characterize their degradation products under local cooking conditions, and correlate quantified NNS exposure with metabolic biomarkers and gut microbiota profiles in Indonesian cohort studies that rigorously control for dietary and lifestyle confounders.

6. Patents

This section is not mandatory but may be added if there are patents resulting from the work reported in this manuscript.

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