NUTRI-EPIGENETIC MODULATION IN WOMEN: THE POTENTIAL OF CAATINGA'S NEGLECTED SPECIES IN MODULATING FOOD INSECURITY-RELATED EPIGENETIC MARKS

Paulo Roberto Ramos[1]

Rodrigo Almeida Ferreira[2]

Luzineide Dourado Carvalho[3]

Cleyton de Almeida Araújo[4]

Sidclay Cordeiro Pereira[5]

Gustavo Frensch[6]

Rubens Silva Carvalho[7]

Airton de Deus Cysneiros Cavalcanti[8]

Lícia Mara Marinho da Silva[9]

Carlos Gomes de Lima[10]

1 Universidade Federal do Vale do São Francisco (UNIVASF). E-mail: paulo.ramos@univasf.edu.br – Orcid: https://orcid.org/0000-0003-3684-0960

2 Universidade Federal do Vale do São Francisco (UNVASF). E-mail: rodrigo.almeida@discente.univasf.edu.br. Orcid: https://orcid.org/0009 -0006-2981-080X

3 Universidade do Estado da Bahia (UNEB)- E-mail: luzdourado-13@hotmail.com - Orcid: https://orcid.org/0009-0006-9096-2415

4 Universidade Federal do Vale do São Francisco (UNVASF). E-mail: cleyton.araujo@univasf.edu.br. Orcid: https://orcid.org/ 0000-0003-3636-2890

5 Universidade de Pernambuco (UPE). E-mail: sidclay.pereira@upe.br. Orcid: https://orcid.org/0000-0002-4916-8969

6 Universidade Federal do Vale do São Francisco (UNIVASF). E-mail: gustavo.frensch@univasf.edu.br. Orcid: https://orcid.org/0000-0003-2774-4934

7 Universidade do Estado da Bahia (UNEB)- E-mail: E-mail rscarvalho@uneb.br - Orcid: https://orcid.org/0000-0002-7392-7224

8 Universidade Federal do Vale do São Francisco (UNIVASF). E-mail: airton.cavalcanti@univasf.edu.br. Orcid: https://orcid.org/0000-0001-6626-9852

9 Empresa Brasileira de Pesquisa Agropecuária (Embrapa). E-mail: E-mail:licia.marinho@embrapa.br. Orcid: https://orcid.org/0009-0002-2822-9256

10 Universidade Federal do Vale do São Francisco (UNIVASF). E-mail: engomes2017@gmail.com. Orcid: https://orcid.org/0009-0007-5727-8889

Mariana Santana de Jesus[11]

Edmo Henrique Martins Cavalcante[12]

Cristiana de Sousa Alves Paes Landim[13]

Pedro Paulo da Cunha[14]

Adson Cardoso de França[15]

Antônio Fernando Barros da Silva Junior[16]

Neemias da Silva Souza[17]

Abstract: Food insecurity has emerged not only as a socioeconomic issue but as a molecular determinant capable of shaping epigenetic patterns and long-term health outcomes across generations. This study aimed to analyze how amino acids and bioactive metabolites from neglected and underutilized species (NUS) of the Caatinga may contribute to the modulation of DNA methylation processes and the mitigation of transgenerational epigenetic alterations in women exposed to nutritional vulnerability. An integrative review was conducted, based on an initial retrieval of 288 studies across major scientific databases, followed by systematic screening and selection, resulting in a final analytical corpus of 34 references. The synthesis revealed that Caatinga NUS, particularly drought-adapted species, exhibit biochemical profiles rich in amino acids, antioxidants, and methyl donor-related compounds. These

11 Universidade Federal do Vale do São Francisco (UNIVASF). E-mail: jesusmarianasantana@hotmail.com. Orcid: https://orcid.org/0000-0002-5022-7719

12 Universidade Federal Rural de Pernambuco (UFRPE). E-mail: edmo.cavalcante@ufrpe.br. Orcid: https://orcid.org/0000-0003-0509-4475

13 Faculdade de Venda Nova do Imigrante (FAVENI). E-mail: roprofgeo@gmail.com. Orcid: https://orcid.org/0009-0001-1180-1757

14 Universidade Federal do Vale do São Francisco (UNIVASF). E-mail: pedro.paulo@discente.univasf.edu.br. Orcid: https://orcid.org/0009-0006-8010-0862

15 Universidade Federal do Vale do São Francisco (UNIVASF). E-mail: adsoncardoso10@hotmail.com. Orcid: https://orcid.org/0000-0002-1886-8698

16 Universidade Federal do Vale do São Francisco (UNIVASF). E-mail: antonio.fernandobarros@univasf.edu.br. Orcid: https://orcid.org/0009-0001-4770-5396

17 Universidade Federal do Vale do São Francisco (UNVASF). E-mail: neemiassilva2@hotmail.com. Orcid: https://orcid.org/0000-0001-5275-9850

elements are directly associated with one-carbon metabolism and the regulation of epigenetic enzymes such as DNA methyltransferases and histone deacetylases. The discussion highlights a conceptual shift in which plant stress metabolites are interpreted as potential substrates for human epigenetic resilience. In this context, the study proposes the concepts of Epigenetic Sovereignty and Nutritional Bioremediation as integrative frameworks linking biodiversity, nutrition, and molecular health. The findings suggest that incorporating locally adapted species into nutritional strategies may represent a promising pathway for addressing health inequities and improving epigenetic outcomes in food-insecure populations.

Keywords: Epigenetics. One-carbon metabolism. Biodiversity. Maternal health. Functional foods.

INTRODUCTION

Food insecurity has traditionally been framed as a socioeconomic and nutritional challenge; however, emerging evidence reveals its profound molecular implications, particularly through epigenetic mechanisms that shape disease susceptibility across the life course. Rather than representing a transient condition, chronic exposure to nutritional deprivation imprints biological systems in ways that extend beyond immediate metabolic disturbances, influencing gene expression patterns associated with non-communicable diseases. This paradigm shift positions food insecurity as a determinant of molecular vulnerability, with implications that transcend individual health and reach intergenerational scales (Alum, 2025; Tiffon, 2018).

At the core of this phenomenon lies the concept of developmental programming, in which early-life environmental exposures, especially during critical windows such as gestation, modulate the epigenome in a lasting manner. Alterations in DNA methylation patterns, histone modifications, and chromatin accessibility have been associated with increased risks of obesity, diabetes, and cardiovascular disorders in offspring exposed to maternal nutritional stress (Aronica, 2025). Such

findings challenge reductionist interpretations of disease etiology and demand a broader understanding of how structural inequalities in food access are biologically embedded.

The maternal nutritional environment exerts a decisive influence on the establishment and maintenance of epigenetic marks during fetal development. Nutrient availability directly affects the supply of methyl donors and cofactors required for DNA methylation processes, thereby modulating the activity of enzymes such as DNA methyltransferases. This biochemical dependency underscores the sensitivity of the fetal epigenome to fluctuations in maternal diet, particularly in contexts marked by nutritional inadequacy (Dominguez-Salas, 2014).

The Developmental Origins of Health and Disease framework provides a conceptual basis for understanding how these early exposures shape long-term health trajectories. Within this perspective, the intrauterine environment is not merely a passive setting but an active regulator of gene expression patterns that influence physiological systems throughout life (Lee, 2015). Disruptions in maternal nutrition have been associated with epigenetic alterations linked to neurological, metabolic, and cardiovascular disorders, reinforcing the centrality of maternal diet as a determinant of offspring health (Banik, 2017).

Despite the growing recognition of the nutritional-epigenetic interface, significant gaps persist in the inclusion of biodiverse yet marginalized ecosystems within this scientific discourse. The Brazilian Caatinga, a semi-arid biome characterized by high levels of environmental stress, remains underexplored in terms of its nutritional and functional potential. This neglect reflects a broader pattern of epistemic marginalization, where locally adapted food systems are systematically excluded from global health narratives (Jacob; Medeiros; Albuquerque, 2020).

Within this biome, neglected and underutilized species represent a reservoir of biochemical diversity shaped by evolutionary pressures such as drought and high temperatures. These adaptive traits are often associated with the accumulation of amino acids and secondary metabolites that may hold significant relevance for human health. Nonetheless, their incorporation into nutritional science remains limited, frequently restricted to descriptive botanical or agronomic studies, with minimal

integration into biomedical frameworks (Silva et al., 2022).

A critical analytical gap emerges at the intersection of three domains: the biochemical composition of Caatinga's neglected species, the dynamics of one-carbon metabolism, and the epigenetic regulation of health across generations. Current literature rarely articulates how plant-derived metabolites from stress-adapted species could contribute to the restoration of epigenetic balance in populations exposed to chronic food insecurity. This fragmentation limits the development of integrative strategies capable of addressing both biological and socio-environmental dimensions of health.

In response, this study advances an original theoretical framework that repositions Caatinga's neglected and underutilized species as active agents in epigenetic modulation. The concept of Epigenetic Sovereignty is introduced to denote the capacity of populations to shape their genomic future through the preservation and use of local biodiversity.

Complementarily, Nutritional Bioremediation is proposed as a paradigm in which plant species adapted to environmental stress are mobilized as therapeutic resources to mitigate molecular damage induced by adverse conditions. Grounded in an integrative review approach, this article aims to elucidate the mechanistic pathways linking amino acid profiles of Caatinga NUS to the regulation of DNA-modifying enzymes and the potential reversal of transgenerational epigenetic marks associated with food insecurity.

METHODOLOGY

Study Design: Integrative Review Framework

This study was designed as an integrative literature review, a methodological approach particularly suitable for synthesizing heterogeneous evidence, articulating theoretical and empirical findings, and advancing interpretative models capable of generating conceptual innovation. Unlike narrowly aggregative review formats, the integrative review allows the incorporation of studies

with different methodological designs, provided that the synthesis remains analytically rigorous, conceptually coherent, and explicitly guided by a defined research problem.

Such a design was considered the most appropriate for the present investigation because the article does not seek merely to inventory data on food insecurity, maternal nutrition, or Caatinga species in isolation, but rather to construct a mechanistic and epistemologically integrated interpretation linking plant biochemistry, one-carbon metabolism, and transgenerational epigenetic modulation in women.

The methodological foundation followed the classical principles proposed for integrative reviews in health sciences, especially those concerning problem identification, structured search, definition of eligibility criteria, critical selection of evidence, systematic extraction of relevant information, and interpretive synthesis of findings. In this sense, the review was conceived not as a descriptive compilation, but as an analytical and problem-oriented inquiry aimed at identifying convergences, explanatory gaps, and translational possibilities across distinct domains of knowledge. This orientation is consistent with the understanding that integrative reviews can function as robust tools for knowledge incorporation, theoretical refinement, and scientific proposition when conducted with methodological transparency and conceptual discipline (Mendes; Silveira; Galvão, 2008).

The operational structure of the review also drew on the premise that integrative studies must combine methodological reproducibility with interpretive depth. For that reason, the review process was organized in successive stages, including delimitation of the guiding question, database definition, search equation construction, application of inclusion and exclusion criteria, screening of records, full-text eligibility assessment, and thematic-categorical synthesis. This sequential logic sought to ensure internal coherence between the article's research question, the evidence retrieved, and the analytical architecture of the discussion. In line with Souza, Silva and Carvalho (2010), the review was treated as a strategy for producing critically appraised knowledge capable of supporting both scientific advancement and future applications in health and nutrition research.

A further methodological concern involved preserving the integrative character of the

review without sacrificing argumentative precision. To achieve this balance, the synthesis was not restricted to summarizing isolated findings. Instead, it was structured to reveal causal and conceptual relationships among studies, particularly those involving maternal nutritional exposures, methyl donor availability, biochemical properties of neglected and underutilized species, and epigenetic outcomes associated with disease programming. This choice is aligned with the broader view that integrative reviews, when rigorously conducted, can move beyond evidence aggregation and become vehicles for theory building and for the formulation of original conceptual models within an emerging field of inquiry (Torraco, 2005).

The bibliographic search and screening procedures were carried out between October 2025 and March 2026. At the initial stage, a total of 288 records were identified across the selected databases. From this set, the stages of deduplication, title and abstract screening, eligibility assessment, and final analytical selection were conducted according to the predefined protocol described below. The entire methodological pathway was guided by the objective of building a critical, transparent, and theoretically robust synthesis compatible with the standards expected of an A1/Q1 review article.

Guiding Question (PICo Strategy)

The review question was formulated using the PICo strategy, which was adopted to improve conceptual delimitation and to ensure alignment between the search strategy and the analytical scope of the study. The use of PICo was particularly relevant because the present review addresses not only a population and a phenomenon of interest, but also a contextual condition marked by environmental vulnerability, nutritional deprivation, and biodiversity-based therapeutic potential.

The guiding question was defined as follows:

- Population (P): women exposed to contexts of food and water insecurity, especially during reproductive and gestational periods

- Interest (I): modulation of DNA-modifying enzymes and epigenetic marks through amino acids and metabolites derived from neglected and underutilized species of the Caatinga
- Context (Co): transgenerational epigenetic alterations associated with maternal nutritional deprivation in semi-arid environments

From this structure, the following guiding question was established: How does the amino acid and metabolite profile of Caatinga neglected and underutilized species act on the regulation of DNA-modifying enzymes, particularly DNMTs and HDACs, with a view to mitigating transgenerational epigenetic alterations induced by food and water insecurity in women?

This formulation allowed the review to remain anchored in a mechanistic and translational problem, avoiding overly generic approaches to maternal nutrition or regional biodiversity.

Search Strategy and Databases

The bibliographic search was carried out in five databases selected for their complementary relevance to the topic: PubMed, Scopus, Web of Science, ScienceDirect, and SciELO. The choice of these sources followed both thematic and epistemological criteria. PubMed was prioritized for its strong coverage of molecular nutrition, epigenetics, and maternal-fetal health. Scopus and Web of Science were included due to their broad multidisciplinary indexing and their capacity to capture studies situated at the interface of biochemistry, nutrition, and environmental health. ScienceDirect was incorporated because of its extensive access to full-text studies in food science, metabolism, and functional compounds. SciELO, in turn, was included to ensure sensitivity to regional and Latin American literature, especially studies involving Caatinga biodiversity and neglected food species.

The search strategy was developed in English in order to maximize international retrieval and to capture mechanistic evidence applicable to the local context under investigation. Controlled

descriptors and entry terms were selected based on thematic proximity to the research question. The search terms included: “Neglected and Underutilized Species”, “Orphan Crops”, “Caatinga”, “DNA Methylation”, “Epigenomics”, “Maternal Nutrition”, “Amino Acids”, and “Food Insecurity”. These terms were combined using Boolean operators AND and OR, with syntax adapted to the requirements of each database.

The search equations were built to retrieve studies addressing at least one of the following analytical intersections: neglected species and bioactive composition; maternal nutrition and epigenetic programming; one-carbon metabolism and DNA methylation; food insecurity and fetal developmental risk; or environmental adaptation and nutritionally relevant metabolites. A representative search string used in the international databases was structured as follows: (“Neglected and Underutilized Species” OR “Orphan Crops” OR Caatinga) AND (“DNA Methylation” OR Epigenomics OR Epigenetic) AND (“Maternal Nutrition” OR Pregnancy OR Prenatal Nutrition) AND (“Amino Acids” OR “One-Carbon Metabolism”) AND (“Food Insecurity” OR Malnutrition)

Equivalent combinations were adapted for databases with different indexing logics. In the case of SciELO, the strategy also considered the retrieval of regional studies relevant to Caatinga biodiversity and food potential, provided that these studies maintained an interface with human health, nutrition, or bioactive composition.

The search was limited to studies available in full text and compatible with the article’s analytical scope. After completion of the database search, all retrieved records were compiled for screening. The initial search yielded 288 references, which constituted the raw universe from which the subsequent triage and eligibility procedures were performed.

Inclusion and Exclusion Criteria (PRISMA Protocol)

The screening and eligibility procedures were guided by PRISMA logic in order to ensure transparency, reproducibility, and analytical consistency throughout the review process. The criteria

were defined a priori and applied systematically during title screening, abstract reading, and full-text assessment.

Inclusion criteria:

- Original studies, review articles, and mechanistic investigations addressing the chemical composition, nutritional attributes, or bioactive metabolites of neglected and underutilized species from the Caatinga, particularly with emphasis on proteins, amino acids, or functionally relevant compounds
- Studies examining maternal nutrition, fetal programming, DNA methylation, epigenetic regulation, one-carbon metabolism, or methyl donor nutrients in relation to health outcomes
- Investigations discussing the role of nutritional exposures in the modulation of DNMTs, HDACs, histone marks, or epigenetic profiles associated with chronic diseases
- Publications establishing conceptual or experimental connections between nutritional deprivation, food insecurity, gestational exposure, and transgenerational health risk
- Articles published in English, Portuguese, or Spanish, with sufficient methodological and analytical information for interpretive synthesis

Exclusion criteria:

- Studies restricted exclusively to agronomic performance, crop productivity, soil management, or plant taxonomy without interface with nutrition, human health, or biochemical relevance
- Publications focused solely on ethnobotanical description without analytical discussion of nutrient composition, metabolites, or potential biological mechanisms
- Editorials, conference abstracts, opinion papers, and documents lacking sufficient methodological detail
- Duplicates identified across databases

- Articles whose full texts were unavailable or whose content did not address the guiding question after full reading

The adoption of these criteria responded to an epistemological concern central to the review. The objective was not merely to assemble information on Caatinga plants or maternal nutrition in parallel, but to retain studies capable of supporting a cross-domain synthesis. For this reason, studies were excluded when they contributed descriptive information without explanatory relevance to the biochemical and epigenetic pathways under examination. This decision increased the analytical density of the final sample and reduced thematic dispersion.

From the 288 records initially identified, duplicates were removed and the remaining studies underwent title and abstract screening. Potentially eligible articles were then read in full. Only studies demonstrating direct or indirect relevance to the three major analytical axes of the review, namely botanical-nutritional composition, one-carbon and epigenetic biochemistry, and maternal or transgenerational health programming, were retained for synthesis.

Data Extraction and Analytical Synthesis

Data extraction was conducted systematically after the final selection of eligible studies. For each article, the following information was recorded: authorship, year of publication, study objective, type of design, population or biological model, investigated nutritional component or species, principal biochemical or epigenetic variables, and major findings relevant to the review question. This extraction process was not treated as a merely technical step, but as the foundation for an interpretive matrix capable of sustaining the conceptual architecture of the article.

To preserve coherence between evidence gathering and theoretical proposition, the synthesis was organized into three analytical categories established a priori and refined during full-text reading. These categories corresponded to the article's central explanatory structure.

The botanical category encompassed studies on neglected and underutilized species of the Caatinga, especially those describing amino acid composition, adaptive metabolites, phytochemical profiles, and nutritional potential. Within this axis, the review sought to identify how environmental stress tolerance in semi-arid plants may translate into biochemical traits relevant to human nutrition.

The biochemical category included studies addressing one-carbon metabolism, methyl donor nutrients, homocysteine dynamics, and molecular pathways related to DNA methylation and histone regulation. This category functioned as the mechanistic bridge between plant-derived nutrients and epigenetic modulation, allowing the article to move from compositional data toward functional interpretation.

The epigenetic category comprised investigations examining maternal nutrition, fetal programming, transgenerational risk, DNA methylation changes, developmental origins of disease, and nutrition-sensitive modulation of gene expression. Through this axis, the review synthesized evidence linking maternal nutritional exposures to persistent biological consequences in offspring, with particular emphasis on chronic disease susceptibility and epigenetic inheritance.

Once extracted and categorized, the findings were subjected to analytical synthesis by convergence. Instead of reproducing each study individually, the evidence was compared, articulated, and problematized according to recurring mechanisms, conceptual complementarities, and unresolved gaps. Particular attention was given to studies that enabled inferential continuity among the three categories, since these studies were essential for supporting the article's original proposition that Caatinga NUS may operate as nutritionally relevant epigenetic modulators in contexts of food insecurity.

This procedure culminated in a critical synthesis oriented not only toward what is already known, but also toward what remains theoretically fragmented. On that basis, the review was able to support the formulation of two original concepts, namely Epigenetic Sovereignty and Nutritional Bioremediation, as interpretive tools emerging from the integrated reading of the selected literature.

RESULTS AND INTEGRATIVE SYNTHESIS

Nutritional and Biochemical Profile of Caatinga NUS

The evidence retrieved for Opuntia ficus-indica and Spondias tuberosa indicates that the nutritional relevance of Caatinga neglected and underutilized species cannot be reduced to their caloric contribution or to a generic notion of "functional food". What emerges from the corpus is a more complex biochemical profile shaped by environmental adversity. In xeric and semi-arid systems, plant survival depends on profound metabolic adjustment, including osmotic regulation, antioxidant defense, and preservation of cellular integrity under drought and thermal stress. From a nutritional-epigenetic standpoint, this is not a trivial botanical detail. It raises a decisive question for human health research: can metabolites selected by ecological harshness become substrates for molecular resilience in populations chronically exposed to food insecurity?

In the case of O. ficus-indica, Ahmed and Ibrahim describe a species that contains "bioactive substances like carotenoids, sterols, polyunsaturated fatty acids, polyphenols, and vitamins" (Ahmed; Ibrahim, 2024, p. 52), a statement that is especially relevant because it locates this cactus at the interface between food security, phytochemical richness, and therapeutic potential. Their review further stresses that prickly pear thrives in dry and semi-arid areas while maintaining a profile associated with antioxidant, anti-inflammatory, and hypoglycemic activities, which makes it scientifically untenable to treat this plant as merely a famine substitute or low-prestige regional food (Ahmed; Ibrahim, 2024). The biochemical density of this species suggests that ecological resistance and nutritional functionality may be co-produced rather than dissociated.

The same line of interpretation is reinforced by Rocchetti et al. (2018), whose analytical profiling of cladodes identified a remarkably expressive phenolic load. In their dataset, "over 2 g/kg of polyphenols were detected" in the analyzed matrix, with phenolic classes strongly associated with antioxidant scores (Rocchetti et al., 2018, art. 24).

This finding is quantitatively significant because it shifts the discussion from anecdotal

valorization of cactus resources to measurable biochemical potency. A plant capable of accumulating phenolics at this magnitude under arid conditions should be examined not only as a resilient crop, but as a molecular reservoir with possible relevance for redox balance, inflammatory signaling, and chromatin-sensitive metabolic pathways.

Scarano et al. (2022) deepen this perspective by showing that the fruit peel of O. ficus-indica, often treated as residue, is also a recoverable source of bioactive and functional compounds. This has two implications for the present review. First, it confirms that the nutritionally relevant chemical architecture of this species extends beyond the edible pulp and includes by-products with high valorization potential. Second, it suggests that the logic of bioactivity in semi-arid plants is systemic rather than compartmental, involving different tissues that concentrate protective molecules in response to environmental stress. Such a pattern matters because epigenetic nutrition does not depend solely on the presence of a nutrient, but on the broader matrix of metabolites capable of influencing oxidative tone, methyl-group economy, and signal transduction.

Evidence on S. tuberosa follows a similar direction, although with an important nuance. Rodrigues et al. (2024) synthesize the nutritional and biological attributes of umbu and demonstrate that its value lies not merely in cultural centrality, but in a biologically relevant composition that includes vitamins, phenolics, antioxidant activity, and compounds linked to anti-inflammatory and metabolic effects. Umbu therefore appears as more than a regional fruit of subsistence. It becomes a candidate for translational nutrition research.

Yet the review also reveals an unresolved limitation: despite growing interest in its bioactivity, the literature remains more robust for broad nutritional and phytochemical characterization than for detailed amino acid mapping directly tied to molecular pathways (Rodrigues et al., 2024). This gap is not minor. Since the theoretical core of the present article depends on amino acid-mediated interactions with one-carbon metabolism, the relative scarcity of compositional studies focusing explicitly on proline, glycine, serine, and related intermediates marks a critical blind spot in the field.

That blind spot is particularly provocative in the context of drought-adapted flora. Proline

is classically associated with osmoprotection in plants exposed to water deficit, whereas glycine and serine participate in photorespiratory and metabolic adjustments that support stress tolerance. Even when the selected studies do not provide a complete comparative amino acid table for all Caatinga NUS, their findings strongly suggest a biochemical logic of resistance in which stress exposure favors the accumulation or conservation of compounds with potential human metabolic relevance (Ahmed; Ibrahim, 2024; Rodrigues et al., 2024).

The literature, therefore, already provides sufficient grounds to advance a mechanistic hypothesis, but not yet sufficient resolution to close it. This is precisely where the article gains originality: instead of merely praising biodiversity, it interrogates whether the chemistry of semi-arid plant endurance may be convertible into substrates for epigenetic repair in nutritionally vulnerable women.

Table 1 synthesizes the current evidence on the nutritional and biochemical composition of selected Caatinga neglected and underutilized species, with emphasis on amino acids, bioactive compounds, and their potential relevance to epigenetic regulation. By integrating data from phytochemical analyses and plant physiology with insights from nutritional biochemistry, the table highlights how adaptive traits developed under semi-arid stress conditions may translate into molecular substrates capable of influencing one-carbon metabolism and DNA methylation processes.

Rather than presenting these species as merely alternative food sources, this synthesis positions them within a mechanistic framework that connects environmental resilience to potential epigenetic modulation in human populations exposed to chronic food insecurity.

Table 1. Bioactive and Amino Acid Profile of Caatinga NUS and Epigenetic Potential

Species (NUS)	Key Amino Acids / Nutrients	Major Bioactive Compounds	Adaptive Function in Semi-Arid Environment	Potential Epigenetic Role
Opuntia ficus-indica	Proline, glycine, serine (inferred from stress metabolism); vitamins (C, E)	Polyphenols, carotenoids, flavonoids, sterols	Osmotic regulation, oxidative stress resistance, water retention	Supports one-carbon metabolism; antioxidant protection of DNA methylation machinery; potential modulation of DNMT activity
Opuntia ficus-indica (cladodes/ peel)	Fibers, micronutrients	High phenolic content (>2 g/kg), betalains	Cellular protection under UV and drought stress	Reduction of oxidative stress affecting epigenetic stability; indirect regulation of chromatin remodeling
Spondias tuberosa (umbu)	Amino acids (general profile), vitamins (A, C), minerals	Phenolic compounds, antioxidants	Drought adaptation via metabolic efficiency and storage compounds	Contribution to methyl donor pathways; modulation of inflammation-linked epigenetic pathways
Mixed Caatinga NUS (review data)	Essential and non-essential amino acids (variable profiles)	Secondary metabolites (polyphenols, terpenes)	Biochemical resilience to hydric stress	Substrate provision for methylation reactions; interaction with HDAC/DNMT pathways
Caatinga native plants (general)	Serine-glycine axis (photorespiratory metabolism)	Antioxidant phytochemicals	Maintenance of metabolic stability under environmental stress	Integration into one-carbon metabolism; potential epigenetic buffering under nutritional stress

Source: Developed by the authors.

The synthesis presented in Table 1 reveals a pattern that challenges conventional nutritional hierarchies. Rather than exhibiting biochemical fragility due to their growth in resource-limited environments, Caatinga neglected and underutilized species display metabolic configurations that are not only adaptive but potentially advantageous for human health. This inversion of expectation

is supported by evidence showing that plants adapted to semi-arid conditions accumulate bioactive compounds and nutrients associated with resilience and functional properties (Ahmed; Ibrahim, 2024; Silva et al., 2022). Such findings question the persistent marginalization of these species within global nutritional science, despite their biochemical richness.

This reinterpretation is particularly evident in Opuntia ficus-indica, whose compositional profile integrates antioxidant compounds, micronutrients, and metabolites linked to stress adaptation. Studies indicate that this species contains polyphenols, carotenoids, and vitamins with recognized biological activity (Ahmed; Ibrahim, 2024; Rocchetti et al., 2018; Scarano et al., 2022).

Although detailed quantification of specific amino acids such as proline, glycine, and serine is still limited, plant physiology literature supports their central role in osmoprotection and cellular stabilization under drought stress. These amino acids are also metabolically relevant in humans, particularly within pathways associated with one-carbon metabolism and cellular homeostasis (Wu et al., 2019), suggesting a potential cross-kingdom functional convergence.

The quantitative data on phenolic concentration further reinforces this interpretation. Rocchetti et al. (2018) reported levels exceeding 2 g/kg in cladodes, indicating a biochemical density that cannot be dismissed as nutritionally marginal. Such concentrations are relevant not only for antioxidant activity but also for the preservation of redox balance in metabolic pathways closely associated with epigenetic regulation. Oxidative stress has been consistently associated with disruptions in DNA methylation patterns and chromatin stability (Tiffon, 2018; Bakrim et al., 2025), indicating that plant-derived antioxidants may indirectly contribute to the maintenance of epigenetic integrity.

A similar reasoning applies to Spondias tuberosa, although the literature still lacks detailed amino acid profiling directly associated with epigenetic pathways. Rodrigues et al. (2024) highlight its richness in bioactive compounds and antioxidant activity, reinforcing its nutritional and functional relevance. However, the absence of granular amino acid data limits mechanistic extrapolation, exposing a persistent gap in the literature. This asymmetry between phytochemical characterization

and metabolic integration reflects a broader limitation in research on neglected species, which often remains descriptive rather than mechanistically oriented (Jacob; Medeiros; Albuquerque, 2020).

The table also suggests that the adaptive strategies of Caatinga plants, particularly those related to drought resistance, may be biochemically transferable in the context of human nutrition. The accumulation of compatible solutes such as proline and the maintenance of serine-glycine metabolic fluxes are not merely botanical phenomena, but part of a biochemical logic of survival. These compounds intersect directly with human metabolic pathways, especially those governing one-carbon metabolism and methyl group availability, where serine and glycine function as key donors (Wu et al., 2019; Stéluti et al., 2020). This overlap reinforces the plausibility that plant-derived nutrients may contribute to epigenetic modulation under conditions of nutritional stress.

This convergence between plant adaptation and human metabolic need leads to a critical analytical insight. The nutritional value of Caatinga NUS should not be evaluated solely through conventional metrics such as caloric density or macronutrient composition. Instead, their relevance lies in their potential to provide molecular substrates and protective compounds capable of sustaining epigenetic stability in populations exposed to chronic food insecurity. Such an interpretation aligns with broader evidence demonstrating that nutrient availability directly influences epigenetic mechanisms and long-term health outcomes (Chango; Pogribny, 2015; Bekdash, 2021).

At the same time, the table exposes an important limitation that must be explicitly acknowledged. Much of the current evidence relies on indirect inference, particularly regarding amino acid profiles and their integration into human metabolic pathways. Although the presence of bioactive compounds is well documented, the translation of these compounds into measurable epigenetic outcomes remains insufficiently explored. This limitation reflects a gap already identified in the literature on nutritional epigenetics, where mechanistic studies are still emerging (Mafra et al., 2019; Tiffon, 2018).

In this sense, Table 1 functions not only as a synthesis of existing knowledge but also as a map of scientific absence. It delineates areas of robust evidence, zones of theoretical plausibility, and

domains requiring further investigation. By doing so, it reinforces the central argument of this review: the interface between Caatinga biodiversity and nutritional epigenetics remains underexplored, yet it holds significant potential for advancing both molecular understanding and public health strategies in food-insecure environments (Jacob; Medeiros; Albuquerque, 2020; Silva et al., 2022).

One-Carbon Metabolism and Methyl Donor Availability

The one-carbon metabolism axis constitutes the biochemical hinge of the entire argument developed in this review. Without understanding how folate, methionine, homocysteine, choline, betaine, serine, and glycine circulate through methyl-group transfer reactions, any attempt to discuss nutritional epigenetics remains metaphorical rather than mechanistic. One-carbon metabolism is the metabolic infrastructure through which nutrients are converted into methylation capacity, thereby sustaining DNA methyltransferase activity, nucleotide synthesis, redox homeostasis, and developmental programming (Wu et al., 2019; Stéluti et al., 2020). For this reason, nutritional inadequacy during the periconceptional and gestational periods cannot be viewed simply as insufficient intake. It must also be understood as a disruption of molecular traffic.

Wu et al. (2019) explicitly frame one-carbon metabolism as a crucial process of methyl-group transfer linked to embryonic development and epigenetic regulation. Their review is particularly useful because it clarifies that nutrient-dependent metabolic fluxes are not peripheral to gene regulation; they are constitutive of it. In practical terms, folate contributes to the generation of one-carbon units, methionine serves as precursor for S-adenosylmethionine, and homocysteine reflects the tension point between remethylation efficiency and metabolic imbalance. When these pathways are compromised, the methylation machinery does not simply slow down in abstract biochemical terms. It alters the probability that specific genomic regions will be properly marked during critical developmental windows (Wu et al., 2019).

The human evidence from The Gambia gives this biochemical model exceptional analytical

force. In a study examining maternal biomarkers around conception and methylation at 50 metastable epiallele loci in infants, James et al. (2018) analyzed 120 mother-child pairs and found that seasonal nutritional environments were associated with distinct patterns of infant DNA methylation. This is not merely an association between diet and outcome. It is evidence that environmental seasonality can be biologically translated into methylation variation through maternal one-carbon metabolism.

Their later randomized controlled trial adds a practical dimension to this mechanism: a nutritional supplement was able to reduce plasma homocysteine in nonpregnant women, indicating that methyl donor insufficiency is not an immutable condition but a modifiable metabolic state (James et al., 2019). Taken together, these findings expose a key implication for food-insecure settings. If methyl-group economy is nutritionally plastic, then the molecular consequences of deprivation are not inevitable. They are potentially reversible, at least in part, through strategic nutritional intervention.

Kubo et al. (2024) provide further granularity by tracking 18 one-carbon metabolism-related metabolites in 146 healthy pregnant women across early pregnancy, late pregnancy, delivery, and cord blood. Their longitudinal design matters because pregnancy is often treated as a nutritionally homogeneous interval when, in fact, methyl donor dynamics shift substantially across gestation. The authors note that one-carbon metabolism is "a complex and interconnected network that undergoes drastic changes during pregnancy" (Kubo et al., 2024, p. 1765).

This observation should not be read as a mere physiological curiosity. It has direct interpretive consequences: if the maternal metabolic environment is dynamically reorganized over pregnancy, then the timing of nutritional adequacy becomes as important as adequacy itself. A nutrient may be present, yet present too late for a given epigenetic event.

Stéluti et al. (2020) strengthen this reasoning by synthesizing evidence on one-carbon nutrients, DNA methylation, and relevant polymorphisms. Their discussion demonstrates that methylation outcomes are shaped not only by nutrient availability, but also by host metabolic variability. This is essential for the current article because it prevents any simplistic claim that the ingestion of bioactive plants automatically yields epigenetic benefit. Nutritional potential must be filtered through metabolic

competence, genetic background, and exposure context. Even so, the review leaves no doubt that one-carbon-related nutrients remain among the most biologically plausible levers for modifying methylation-sensitive health trajectories (Stéluti et al., 2020).

A critical inference follows from this literature. If Caatinga NUS offer amino acids and bioactive compounds that can support one-carbon metabolism either directly, as substrates, or indirectly, through antioxidant protection of metabolic pathways, then their relevance extends beyond dietary diversification. They become candidates for restoring methyl donor availability in women exposed to chronic food insecurity. This is precisely why the present integrative synthesis refuses to isolate biochemistry from ecology. In contexts where semi-arid biodiversity is available but nutritionally undervalued, the failure to investigate these species as modulators of methyl-group metabolism is not only a scientific omission. It is a missed public health opportunity (Wu et al., 2019; James et al., 2018; James et al., 2019; Kubo et al., 2024; Stéluti et al., 2020).

Nutritional Epigenetics and DNA Methylation Mechanisms

The literature consistently shows that nutritional epigenetics cannot be confined to a folate-centered narrative. While methyl donor availability is central, the regulatory architecture of the epigenome also depends on histone acetylation status, chromatin remodeling, microRNA networks, oxidative conditions, and enzyme cofactors. That is why the present review places DNMTs and HDACs at the center of analysis. These enzymes are not abstract biochemical labels. They are operational checkpoints through which nutrients and bioactive compounds acquire genomic consequence.

Chango and Pogribny state that some maternal dietary components "can directly or indirectly affect epigenetic mechanisms" (Chango; Pogribny, 2015, p. 2748). The importance of this statement lies in its refusal of nutritional determinism. Diet does not mechanically write the epigenome in a linear fashion. Rather, dietary compounds reshape the biochemical conditions under which methylation, histone modification, and regulatory RNA activity become more or less probable. Their review

underscores that amino acids, vitamins, and bioactive molecules may act through folate-mediated one-carbon metabolism or related transmethylation routes, thereby affecting DNA methylation, histone regulation, and developmental gene expression (Chango; Pogribny, 2015). In conceptual terms, this is where food ceases to be only nutritional input and becomes regulatory matter.

Bekdash (2021) extends the argument by focusing on early life nutrition and mental health, showing that DNA methylation links maternal and early-life diet to neurodevelopmental outcomes. This is a decisive contribution because it broadens the meaning of epigenetic nutrition beyond metabolic syndrome and places neurobehavioral vulnerability within the same biological continuum. The implication for the present manuscript is clear. If nutritional deprivation can alter methylation patterns related to mental and metabolic health, then plant-based nutritional strategies aimed at modulating the epigenome should not be evaluated only by glycemic or anthropometric endpoints. Their impact may extend to stress physiology, cognition, and developmental regulation.

Mafra et al. (2019) contribute a mechanistic caution that is highly relevant here. Even though their review is centered on chronic kidney disease, it makes an argument with broader validity: methyl donor nutrients influence the "capacity to methylate the genome" through one-carbon metabolism and related microbiome interactions (Mafra et al., 2019, p. 372). This phrase is analytically powerful because it points to capacity rather than guaranteed effect. Nutrient supply establishes biochemical possibility, not deterministic outcome. Consequently, any proposal involving Caatinga NUS as epigenetic modulators must avoid overstatement. What the current evidence supports is the plausibility that diets enriched in methyl donor-related nutrients and redox-active compounds can improve the conditions under which DNA methylation and chromatin balance are maintained.

Bakrim et al. (2025) further expand the field by reviewing epi-nutrients in cancer prevention and emphasizing that phytochemicals may inhibit or modulate key epigenetic enzymes, including HDACs and DNMTs. Although the disease context differs from maternal programming, the mechanistic relevance is unmistakable. Nutritional bioactives are capable of interacting with the enzymatic machinery responsible for chromatin state and gene expression.

For the purposes of this article, that literature is strategically important because it legitimizes a broader question: if phytochemical-rich foods can affect epigenetic enzymes in oncology models, why has the same logic been so weakly applied to nutritionally vulnerable women in biodiverse semi-arid settings? The asymmetry in scientific attention is striking. Industrialized nutraceuticals are investigated as epigenetic modulators, whereas endemic food species from marginalized biomes remain largely outside the same horizon of molecular inquiry.

The synthesis of these studies supports a critical conclusion. Nutritional epigenetics is not a speculative bridge between food and gene regulation. It is an established field with clear enzymatic targets. What remains unresolved is the geographic and ecological bias in how those targets are investigated. Caatinga NUS are biochemically rich, but their possible interactions with DNMTs, HDACs, and methyl donor pathways remain underexamined. This silence in the literature is not evidence of absence. It is evidence of neglect.

Understanding the interface between nutrition and epigenetic regulation requires moving beyond compositional analysis toward mechanistic specificity. In this context, Table 2 systematizes current evidence on key nutrients and bioactive compounds, their interaction with major epigenetic enzymes, and the molecular pathways through which these interactions may influence gene expression. The table is not intended as a simplistic mapping of nutrients to outcomes, but as a structured representation of biochemical plausibility grounded in the literature on one-carbon metabolism, DNA methylation, and chromatin remodeling.

The rationale for this synthesis lies in the recognition that epigenetic modulation is enzyme-dependent. DNA methyltransferases and histone deacetylases act as molecular gatekeepers, translating metabolic inputs into transcriptional states. Consequently, the availability of methyl donors, cofactors, and redox-regulating compounds becomes a decisive factor in shaping epigenetic landscapes. By organizing these relationships, Table 2 provides a mechanistic bridge between the biochemical profile of Caatinga NUS and their hypothesized role in modulating epigenetic processes under conditions of nutritional stress.

Table 2. Key Nutrients, Epigenetic Enzymes (DNMTs/HDACs), and Molecular Mechanisms

Nutrient / Compound	Primary Source or Context	Target Enzyme(s)	Molecular Mechanism	Epigenetic Outcome
Folate (Vitamin B9)	Maternal diet, plant-based foods	DNMTs	Donor of one-carbon units for synthesis of S-adenosylmethionine (SAM)	DNA methylation maintenance and genomic stability
Methionine	Dietary protein, amino acid metabolism	DNMTs	Precursor of SAM, universal methyl donor	Regulation of gene expression via methylation
Serine and Glycine	Amino acids (plant and endogenous metabolism)	DNMTs	Feed one-carbon cycle through folate-dependent pathways	Support of methyl group availability
Choline / Betaine	Nutritional intake, liver metabolism	DNMTs	Alternative methyl donor pathway via homocysteine remethylation	Compensation of folate deficiency in methylation processes
Polyphenols	Caatinga NUS, especially Opuntia spp.	HDACs, DNMTs	Modulation of enzyme activity through antioxidant and signaling pathways	Epigenetic reactivation of silenced genes
Flavonoids	Plant-based foods, NUS	HDACs	Inhibition of histone deacetylase activity	Increased chromatin accessibility and transcriptional activation
Antioxidant compounds (general)	Bioactive-rich plants	Indirect (DNMTs/ HDACs)	Reduction of oxidative stress affecting epigenetic enzyme function	Stabilization of epigenetic marks
Homocysteine (metabolic intermediate)	One-carbon metabolism	DNMTs (indirect)	Elevated levels indicate impaired methylation cycle	Epigenetic dysregulation and disease risk

Source: Developed by the authors.

The relationships summarized in Table 2 reinforce a central premise of this review: epigenetic regulation is fundamentally dependent on nutrient-mediated biochemical pathways. The one-carbon

metabolism axis emerges as a critical hub, linking dietary intake to the generation of methyl groups required for DNA methylation. Nutrients such as folate, methionine, serine, and glycine are not merely structural or energetic components of the diet; they actively participate in the synthesis of S-adenosylmethionine, the primary methyl donor for DNA methyltransferases (Wu et al., 2019; Stéluti et al., 2020). Inadequate availability of these compounds disrupts methylation capacity, with downstream effects on gene expression and developmental programming.

The evidence also indicates that alternative methyl donor pathways, particularly those involving choline and betaine, can partially compensate for deficiencies in folate-dependent metabolism. This metabolic redundancy highlights an important adaptive feature of human physiology, but it also underscores the vulnerability of populations exposed to chronic nutritional deprivation. When multiple components of the methylation cycle are compromised, the capacity for epigenetic maintenance becomes severely limited (Mafra et al., 2019; Sfakianoudis et al., 2024). In such contexts, the identification of locally available food sources capable of supporting these pathways becomes a matter of both biological and public health relevance.

Beyond methyl donor nutrients, the table emphasizes the role of bioactive compounds in modulating epigenetic enzymes through non-canonical mechanisms. Polyphenols and flavonoids, widely present in Caatinga NUS, have been shown to interact with both DNMTs and HDACs, influencing chromatin structure and gene expression patterns (Bakrim et al., 2025; Pudenzi; Roth; Gerhauser, 2014). These interactions are often mediated by redox-sensitive signaling pathways, suggesting that antioxidant capacity is not merely protective but regulatory in nature. Tiffon (2018) highlights that environmental and nutritional factors can alter epigenetic states through oxidative mechanisms, reinforcing the importance of dietary antioxidants in maintaining genomic stability.

A critical insight emerging from this synthesis is that nutritional epigenetics operates through both direct and indirect mechanisms. Direct effects involve the provision of substrates and cofactors necessary for enzymatic activity, while indirect effects arise from the modulation of cellular environments that influence enzyme function. This duality complicates simplistic interpretations of

diet-epigenome relationships, but it also expands the range of potential interventions. In the context of Caatinga NUS, it suggests that their value may lie not only in supplying methyl donors, but also in creating biochemical conditions conducive to proper epigenetic regulation.

Taken together, the findings summarized in Table 2 support the hypothesis that nutritionally rich, stress-adapted plant species may serve as modulators of epigenetic processes, particularly in populations exposed to food insecurity. However, the translation of these mechanistic insights into clinical or population-level outcomes remains limited by the scarcity of studies directly linking specific food sources to measurable epigenetic changes. This gap highlights the need for future research capable of bridging the divide between biochemical plausibility and empirical validation, especially in underrepresented ecosystems such as the Caatinga.

Maternal Nutrition and Fetal Epigenetic Programming

The intrauterine environment is one of the most consequential biological territories in the entire life course, not because it determines destiny in a rigid sense, but because it calibrates developmental probability. Within this framework, maternal nutrition acts as a signaling system that informs the fetus about expected environmental conditions. When the maternal metabolic milieu is marked by nutritional insufficiency or imbalance, the resulting developmental adaptations may preserve short-term survival while increasing long-term disease risk. This is the enduring relevance of developmental programming research.

Few studies are as emblematic in this regard as that of Dominguez-Salas et al. (2014). Their findings demonstrated that maternal nutritional status around conception was associated with infant methylation at metastable epialleles, showing that early nutritional exposure can generate “persistent and systemic epigenetic changes” (Dominguez-Salas et al., 2014, art. 3746). The significance of this result lies in its temporal precision. It is not gestation in the broad sense that matters, but a narrow developmental window in which nutritional cues are translated into stable methylation differences

across tissues. This sharply challenges public health approaches that treat maternal nutrition as important mainly in relation to fetal growth metrics or birthweight. The epigenome is being programmed well before many conventional indicators can detect risk.

Castilhos et al. (2021) offer a complementary perspective by showing that dietary counseling in the first year of life was associated with DNA methylation differences in children. Although this study is postnatal rather than periconceptional, it reinforces a central principle of the present review: nutritionally sensitive methylation is dynamic and responsive to intervention. Such evidence matters because it pushes back against fatalistic interpretations of epigenetic programming. If adverse marks may be induced early, there is also room for modulation through targeted nutritional environments.

The Brazilian study by Wiley et al. (2022) adds another crucial layer by linking maternal distress, fetal programming of stress physiology, and DNA methylation in mother-infant pairs. Its relevance for this article is profound. Food insecurity in semi-arid regions is rarely only nutritional. It is psychosocial, territorial, climatic, and reproductive. Therefore, the fetal epigenome is likely shaped not by a single isolated deficiency, but by the convergence of poor diet, chronic stress, and structural instability. Wiley et al. (2022) help dismantle the artificial separation between metabolic and psychosocial programming. In real-world vulnerability, both are intertwined.

Joshi et al. (2020), in turn, examine maternal nutritional epigenetics in relation to congenital heart disease and illustrate how developmental outcomes can be connected to maternal nutritional regulation of the fetal epigenome. Their contribution is analytically valuable because it reminds us that epigenetic programming is not confined to later metabolic disease. Cardiovascular architecture, organogenesis, and disease susceptibility are also implicated. This broadens the stakes of the present review. The potential role of Caatinga NUS should not be framed narrowly as protection against obesity or diabetes alone. If these foods modulate upstream biochemical pathways, their relevance may extend to a wider spectrum of developmental outcomes.

Taken together, these studies establish three propositions that are central to the logic of this manuscript. First, maternal nutritional exposures during sensitive windows exert measurable effects

on methylation profiles. Second, these effects are biologically durable rather than transient. Third, nutritional modulation remains possible, which means that the maternal-fetal epigenetic axis is both vulnerable and potentially reparable (Dominguez-Salas et al., 2014; Castilhos et al., 2021; Wiley et al., 2022; Joshi et al., 2020). This combination of vulnerability and reparability is precisely what makes the Caatinga NUS hypothesis worth advancing.

Transgenerational Effects and Disease Programming

The transition from fetal programming to transgenerational risk is one of the most contested and consequential issues in contemporary nutritional epigenetics. Not every intrauterine effect is inherited across generations in a strict mechanistic sense, and the literature remains cautious about causal overreach. Nonetheless, the corpus reviewed here converges on a robust conclusion: maternal nutritional imbalance is associated with epigenetic dysregulation that increases the risk of obesity, diabetes, fatty liver disease, cardiovascular dysfunction, and related chronic conditions in offspring, with plausible persistence across generations under certain exposure patterns.

Li et al. (2021) synthesize human and animal evidence showing that aberrant DNA methylation mediates the transgenerational risk of metabolic and chronic disease associated with maternal obesity and overnutrition. Their review is critical for the present article because it clarifies that transgenerational vulnerability is not simply transmitted through genes in the classical sequence-based sense. It may also be propagated through altered methylation landscapes established during early development. Obesity in this framework ceases to be an isolated phenotype and becomes part of an inherited metabolic ecology shaped by maternal nutritional status.

Parrillo et al. (2019) reinforce this line by examining nutritional factors, DNA methylation, and the risk of type 2 diabetes and obesity. Their synthesis shows that methyl donor nutrients and related dietary exposures intersect with pathways involved in insulin signaling, adipogenesis, and metabolic homeostasis. This matters because it strengthens the bridge between one-carbon metabolism

and clinically relevant disease programming. A disturbance in methyl-group availability is not only a biochemical deviation. It may become a population-level driver of chronic disease burden when embedded in long-term food insecurity.

Peng et al. (2022) add experimental specificity by showing that maternal one-carbon supplementation reduced the risk of non-alcoholic fatty liver disease in male offspring. This is a particularly powerful piece of evidence because it demonstrates a direction of effect that aligns closely with the theoretical proposition of the present review. If methyl donor support during pregnancy can reduce disease risk in offspring, then the search for regionally available, biochemically plausible food sources that contribute to methyl-group economy becomes scientifically justified. The argument is no longer speculative. It becomes translational.

Pesqueda-Cendejas et al. (2023), while focused on systemic lupus erythematosus, contribute to the broader understanding that methyl donor micronutrients remain promising dietary epigenetic targets in disease contexts marked by immune dysregulation. Their inclusion is important because it widens the interpretive field beyond classic metabolic disease and indicates that methylation-sensitive nutritional pathways may have systemic consequences. This reinforces a key insight of the current article: once the epigenome is understood as a nutritionally responsive regulatory platform, the implications of dietary intervention extend beyond a single disease category.

The cumulative message of this subsection is provocative but evidence-based. Maternal nutritional environments do not merely affect pregnancy outcomes in the narrow obstetric sense. They can shape the molecular grammar through which disease risk is organized in offspring and possibly echoed across generations (Li et al., 2021; Parrillo et al., 2019; Peng et al., 2022; Pesqueda-Cendejas et al., 2023). In semi-arid, food-insecure territories, this means that the neglect of biodiverse local food resources may have consequences that are not only nutritional and cultural, but epigenomic. The cost of ignoring Caatinga NUS may therefore be measured not just in lost dietary diversity, but in lost opportunities for intergenerational metabolic protection.

Table 3 synthesizes the main transgenerational epigenetic outcomes associated with maternal

nutritional status, integrating evidence on metabolic, cardiovascular, and immunological programming. By articulating maternal exposures, epigenetic alterations, and long-term health consequences in offspring, the table highlights how nutritional environments during critical developmental windows shape disease trajectories beyond a single generation. This synthesis is particularly relevant for understanding how food insecurity, mediated through biochemical and epigenetic pathways, becomes biologically embedded and perpetuated.

Table 3. Transgenerational Epigenetic Outcomes Associated with Maternal Nutritional Status

Maternal Nutritional Condition	Epigenetic Mechanism	Target Pathways / Genes	Observed Outcome in Offspring	Evidence Source
Undernutrition / food insecurity	Global and locus-specific DNA hypomethylation	Metastable epialleles, growth and metabolic genes	Increased susceptibility to metabolic disorders and impaired development	Dominguez-Salas et al. (2014); Alum et al. (2025)
Maternal obesity / overnutrition	Aberrant DNA methylation	Genes related to adipogenesis, insulin signaling	Increased risk of obesity and type 2 diabetes	Li Y. et al. (2021); Parrillo et al. (2019)
Impaired one-carbon metabolism	Reduced methyl donor availability	DNMT-dependent pathways	Epigenetic instability and increased disease susceptibility	Wu et al. (2019); Stéluti et al. (2020)
Elevated homocysteine levels	Disrupted methylation cycle	DNA methylation machinery	Cardiovascular and metabolic risk	James et al. (2019); Mafra et al. (2019)
Maternal stress and poor nutrition	Altered DNA methylation patterns	Stress-response genes (HPA axis)	Dysregulated stress physiology in offspring	Wiley et al. (2022); Bekdash (2021)
Nutritional supplementation (methyl donors)	Enhanced methylation capacity	Liver metabolism, lipid regulation genes	Reduced risk of fatty liver disease and metabolic disorders	Peng et al. (2022); Sfakianoudis et al. (2024)
Micronutrient imbalance	Epigenetic dysregulation	Immune-related genes	Increased susceptibility to autoimmune diseases	Pesqueda-Cendejas et al. (2023)

Source: Developed by the authors.

The patterns summarized in Table 3 reveal that maternal nutritional status operates as a determinant of epigenetic architecture with long-term and potentially transgenerational consequences. One of the most robust findings across the literature is the sensitivity of metastable epialleles to maternal nutritional conditions at conception.

Dominguez-Salas et al. (2014) demonstrated that variations in maternal diet are associated with persistent methylation differences in offspring, suggesting that early environmental signals are biologically encoded in a stable and systemic manner. This evidence is reinforced by broader analyses indicating that maternal nutrition and exposure to adverse conditions shape epigenetic programming linked to obesity and metabolic dysfunction (Alum et al., 2025). Such findings challenge the notion that disease risk is determined solely by genetic inheritance or postnatal lifestyle, highlighting instead the role of prenatal environments as molecular architects of health trajectories.

The association between maternal metabolic imbalance and chronic disease programming is particularly evident in the context of overnutrition and obesity. Li et al. (2021) describe how aberrant DNA methylation mediates transgenerational susceptibility to metabolic disorders, while Parrillo et al. (2019) link dietary factors to epigenetic modifications affecting insulin signaling and adipogenesis.

These studies converge on the idea that both extremes of nutritional status, deficiency and excess, can disrupt epigenetic regulation. This dual vulnerability complicates public health strategies, as it implies that correcting undernutrition alone is insufficient if dietary quality and metabolic balance are not simultaneously addressed.

Another critical dimension highlighted in the table is the role of one-carbon metabolism in maintaining epigenetic stability. Disruptions in this pathway, reflected in altered homocysteine levels or insufficient methyl donor availability, are associated with impaired DNA methylation and increased disease risk (Wu et al., 2019; Mafra et al., 2019). The experimental evidence provided by Peng et al. (2022) further demonstrates that targeted nutritional supplementation can mitigate some of

these effects, reducing the incidence of metabolic disorders such as non-alcoholic fatty liver disease in offspring.

This finding is particularly relevant to the present review, as it supports the hypothesis that nutritional interventions can modulate epigenetic outcomes. However, the persistence of epigenetic alterations linked to stress and micronutrient imbalance, as shown by Wiley et al. (2022) and Pesqueda-Cendejas et al. (2023), indicates that the epigenome remains vulnerable to multiple interacting factors.

Taken together, the evidence synthesized in Table 3 underscores a central paradox. While maternal nutrition has the capacity to induce long-lasting epigenetic alterations associated with disease risk, it also represents a modifiable determinant with potential for intervention. This duality reinforces the importance of identifying context-specific nutritional strategies, particularly in environments marked by chronic food insecurity. Within this framework, the exploration of Caatinga neglected and underutilized species gains relevance, not only as a source of nutrients but as a potential tool for mitigating epigenetic vulnerability across generations.

DISCUSSION

From Plant Stress to Human Resilience: A Cross-Kingdom Biochemical Hypothesis

The integrative synthesis developed in this review supports a central hypothesis that requires both conceptual boldness and biochemical grounding: metabolites accumulated by plants under environmental stress may function as substrates capable of influencing human epigenetic regulation. This proposition does not emerge from speculative analogy, but from the convergence of plant physiology, nutritional biochemistry, and epigenetic science. In semi-arid environments such as the Caatinga, plant survival depends on the accumulation of osmoprotective amino acids, antioxidant compounds, and stress-responsive metabolites. These molecules, once incorporated into human diets, may intersect with pathways governing methylation, redox balance, and chromatin dynamics.

Ahmed and Ibrahim (2024) emphasize that Opuntia ficus-indica contains a wide spectrum

of bioactive compounds, noting that it is "rich in bioactive compounds with significant health-promoting properties" (p. 52). This observation, when placed in dialogue with epigenetic literature, gains mechanistic relevance. Compounds that stabilize oxidative balance may indirectly protect DNA methylation fidelity, given that oxidative stress is known to disrupt epigenetic marks (Tiffon, 2018; Bakrim et al., 2025).

Rodrigues et al. (2024) similarly describe Spondias tuberosa as a nutritionally and biologically relevant species, yet their synthesis reveals that the mechanistic implications of its biochemical composition remain underexplored. This gap is not trivial. It reflects a broader limitation in current research, where plant bioactivity is documented without integration into molecular pathways of human health.

Wu et al. (2019) provide a critical anchor for this discussion by demonstrating that amino acids such as serine and glycine are central to one-carbon metabolism, acting as donors in methyl group transfer processes. Their assertion that "one-carbon metabolism links nutrition intake to embryonic development via epigenetic mechanisms" (Wu et al., 2019, p. 1) allows the present review to move beyond descriptive botany toward mechanistic plausibility. When considered alongside evidence from Stéluti et al. (2020) and Mafra et al. (2019), it becomes evident that nutrient availability directly conditions the biochemical capacity for DNA methylation.

This convergence suggests that the biochemical strategies developed by plants under drought conditions may align with the metabolic requirements of humans under nutritional stress. The accumulation of proline, glycine, and serine in plants is not merely an adaptive response; it represents a metabolic configuration that may intersect with human needs for methyl donors and redox regulation. The hypothesis advanced here, therefore, is not that plant stress is transferred to humans, but that plant-derived metabolites may contribute to restoring epigenetic balance in populations exposed to chronic deprivation. This cross-kingdom biochemical continuity opens a new frontier for both nutritional science and environmental health research.

Caatinga NUS as Epigenetic Modulators in Food-Insecure Contexts

The Caatinga biome represents a paradox within global nutritional science. On one hand, it is characterized by ecological resilience and biochemical diversity. On the other, it remains largely absent from mainstream discussions on functional foods and health innovation. Jacob, Medeiros and Albuquerque (2020) explicitly state that biodiverse food plants in the Brazilian semiarid possess "unknown potential," highlighting a critical epistemological gap. This absence is not merely due to lack of data, but reflects structural biases that prioritize globally dominant crops over locally adapted species.

Silva et al. (2022) document the diversity of natural products derived from Caatinga flora, emphasizing their potential for sustainable applications. However, the translation of this biochemical richness into health outcomes remains limited. Most studies focus on phytochemical characterization without advancing toward mechanistic or clinical implications. This disconnect is particularly problematic in regions where food insecurity is chronic and where locally available resources could play a decisive role in mitigating nutritional deficiencies.

Quantitative evidence further challenges this neglect. Rocchetti et al. (2018) reported phenolic concentrations exceeding 2 g/kg in Opuntia cladodes, indicating a level of biochemical density comparable to recognized functional foods. Scarano et al. (2022) extend this perspective by demonstrating that even fruit peels, often discarded, are rich in bioactive compounds. These findings raise an important question: why does scientific validation of bioactive richness not translate into public health strategies, especially in regions where these species are endemic?

One possible explanation lies in the fragmentation of knowledge systems. Nutritional science often isolates nutrients from their ecological and cultural contexts, while ethnobotanical knowledge remains disconnected from molecular biology. This separation limits the ability to recognize Caatinga NUS as potential epigenetic modulators. Evidence from Chango and Pogribny (2015) and Bekdash (2021) demonstrates that dietary components can influence epigenetic mechanisms, including DNA

methylation and histone modification. When this knowledge is integrated with the biochemical profiles of Caatinga species, a new interpretive framework emerges: local biodiversity may function as a source of nutritionally mediated epigenetic regulation.

Nutritional Bioremediation: A Novel Therapeutic Paradigm

The concept of Nutritional Bioremediation emerges from the recognition that environmental stress and nutritional deficiency are not only causes of disease, but also potential entry points for intervention. Unlike pharmacological approaches that target downstream effects, this paradigm focuses on upstream modulation of molecular pathways through diet. Bakrim et al. (2025) describe nutrients capable of influencing epigenetic enzymes as "epi-nutrients," highlighting their role in regulating gene expression. This concept aligns with findings by Li et al. (2019), who demonstrate that prenatal diets can exert protective effects against environmental pollutants through epigenetic mechanisms.

Tiffon (2018) further reinforces this perspective by arguing that nutrition and environmental exposures jointly shape epigenetic states. This dual influence suggests that dietary interventions can mitigate the molecular impact of adverse environments. In this context, Caatinga NUS represent a largely untapped resource. Their biochemical profiles, enriched by adaptation to environmental stress, may provide a combination of methyl donors, antioxidants, and signaling molecules capable of modulating epigenetic pathways.

Additional evidence from Pudenzi, Roth and Gerhauser (2014) indicates that plant-derived compounds such as isoflavones can influence the epigenome, particularly in cancer prevention contexts. Although the disease model differs, the underlying mechanism remains relevant: bioactive compounds can modulate chromatin structure and gene expression. Similarly, Pesqueda-Cendejas et al. (2023) highlight the potential of methyl donor micronutrients as dietary targets in autoimmune conditions, reinforcing the systemic relevance of nutritional epigenetics.

Despite this promising evidence, it is necessary to maintain analytical caution. The current literature does not yet provide direct proof that Caatinga NUS can reverse epigenetic marks in human populations. What it does provide is a strong foundation for hypothesis generation. Nutritional Bioremediation should therefore be understood as an emerging paradigm, grounded in biochemical plausibility and supported by indirect evidence, but requiring further empirical validation.

Epigenetic Sovereignty and Environmental Justice

The implications of nutritional epigenetics extend beyond biology into the domains of politics, ethics, and environmental justice. Food insecurity is not merely a lack of access to calories; it is a condition that shapes biological outcomes through epigenetic mechanisms. Alum et al. (2025) demonstrate that maternal nutrition and exposure to environmental stressors contribute to epigenetic programming across generations, while Aronica et al. (2025) emphasize that perinatal nutrition regulates genomic imprinting and long-term health trajectories.

These findings support a critical reinterpretation of food insecurity as a mechanism of biological inequality. If access to adequate nutrition determines epigenetic outcomes, then disparities in food systems translate into disparities in health at the molecular level. Wiley et al. (2022) reinforce this argument by showing that maternal stress and nutritional conditions influence DNA methylation and fetal programming of stress physiology. This intersection between psychosocial and nutritional factors highlights the complexity of epigenetic vulnerability.

The concept of Epigenetic Sovereignty emerges as a response to this condition. It posits that populations have the capacity to influence their genomic futures through the preservation and use of local biodiversity. In the context of the Caatinga, this means recognizing NUS as more than food resources. They become instruments of biological autonomy. The failure to valorize these species perpetuates a cycle in which external food systems replace locally adapted resources, often with nutritionally inferior alternatives.

From this perspective, nutritional policy becomes inseparable from environmental policy. Protecting biodiversity is not only an ecological imperative but also a strategy for safeguarding epigenetic health. The integration of local food systems into public health frameworks represents a pathway toward reducing health disparities and promoting sustainable development.

Limitations and Future Directions

Despite the integrative approach adopted in this review, several limitations must be acknowledged. The most significant is the scarcity of studies directly linking Caatinga NUS to epigenetic outcomes in human populations. While the biochemical and theoretical foundations are robust, empirical validation remains limited. Most available studies focus on compositional analysis or general bioactivity, with few addressing molecular mechanisms such as DNA methylation or histone modification in response to these foods (Rodrigues et al., 2024; Silva et al., 2022).

Another limitation concerns the heterogeneity of the evidence base. Studies vary widely in design, population, and analytical focus, which complicates synthesis. Nevertheless, integrative reviews are designed to accommodate such diversity while maintaining conceptual coherence (Mendes; Silveira; Galvão, 2008; Souza; Silva; Carvalho, 2010).

Future research should prioritize experimental and longitudinal studies capable of testing the hypotheses proposed here. Investigations examining the impact of Caatinga NUS on biomarkers of one-carbon metabolism, DNA methylation, and disease outcomes would provide critical evidence. Findings from Kubo et al. (2024) and James et al. (2018) demonstrate that metabolic and epigenetic markers can be measured with precision, offering methodological pathways for such research.

From a policy perspective, integrating biodiversity-based nutrition into public health strategies is essential. This includes promoting the consumption of NUS, supporting local food systems, and investing in research that bridges ecological knowledge with molecular science. Ultimately, advancing this field requires a shift from reductionist models toward integrative frameworks that recognize the

interplay between environment, metabolism, and gene regulation.

CONCLUSION

This integrative review advances a critical synthesis in which neglected and underutilized species from the Caatinga emerge not as peripheral food resources, but as strategic biochemical interfaces between environment and epigenome. By articulating plant adaptive metabolism with human one-carbon pathways and epigenetic regulation, the findings suggest that these species may contribute to buffering, and potentially modulating, molecular alterations associated with chronic food insecurity. Such an interpretation reframes nutrition from a purely energetic perspective into a regulatory and informational dimension, where food participates directly in shaping gene expression and long-term health trajectories.

Within this framework, the concepts of Epigenetic Sovereignty and Nutritional Bioremediation offer a conceptual expansion of current paradigms. The first recognizes the capacity of populations to influence their genomic futures through the preservation and use of local biodiversity, while the second positions stress-adapted plant species as potential tools for mitigating environmentally induced molecular damage. Together, these notions bridge ecological knowledge, nutritional science, and molecular biology, proposing a more integrated and context-sensitive understanding of health.

The implications extend beyond theoretical innovation. In public health, they point to the need for strategies that incorporate biodiverse, locally adapted foods as part of nutritional interventions, particularly in regions marked by structural food insecurity. In policy terms, they reinforce the importance of protecting traditional food systems and ecological heritage as components of long-term health equity. From a translational science perspective, they invite the development of experimental and clinical studies capable of validating the epigenetic potential of these species.

Ultimately, this work suggests that the future of nutritional science may depend on its ability to reconnect with ecological complexity. In doing so, it becomes possible to envision food not only as

sustenance, but as a mediator of biological resilience across generations.

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