

Alterations in the intestinal microbiota through the administration of guarana (Paullinia cupana) extract: a review study

Alterações na microbiota intestinal através da administração do extrato de guaraná (Paullinia cupana): um estudo de revisão

Alteraciones en la microbiota intestinal mediante la administración del extracto de guaraná (Paullinia cupana): un estudio de revisión

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ABSTRACT

Guarana (*Paullinia cupana*) is a plant native to South America, traditionally used by Indigenous populations since before colonization and widely consumed today. Despite its well-known stimulant effects, little is known about the relationship between its extract and the intestinal microbiota, which plays a key role in nutrient absorption and the regulation of energy metabolism and is significantly altered in obesity. This study aimed to review the effects of guarana extract on the intestinal microbiota and its possible implications in the context of obesity. A bibliographic review was conducted in the PubMed, Google Scholar, Virtual Health Library, and SciELO databases, selecting articles published between 2009 and 2025 in English, Portuguese, and Spanish, based on originality, relevance, and methodological rigor. Studies in animal models indicated favorable effects on intestinal microbiota modulation and metabolic changes associated with obesity. In humans, however, results were less consistent due to factors such as difficulty in controlling intake, limited study duration, metabolic differences, and variations in lifestyle. It is concluded that guarana may promote health due to therapeutic effects mainly related to caffeine, representing a complementary alternative to conventional therapies. Nevertheless, further long-term studies are needed to confirm its potential in obesity treatment.

Keywords: guaraná, obesity, phytotherapeutics.

RESUMO

O guaraná (*Paullinia cupana*) é uma planta nativa da América do Sul, utilizada por populações indígenas desde antes da colonização e amplamente consumida atualmente. Apesar de seus conhecidos efeitos estimulantes, pouco se sabe sobre a relação entre seu extrato e a microbiota intestinal, a qual desempenha papel fundamental na absorção de nutrientes e na regulação do metabolismo energético, sendo significativamente alterada na obesidade. Objetivou-se, portanto, revisar estudos que abordam os efeitos do extrato de guaraná sobre a microbiota intestinal e suas possíveis implicações no contexto da

obesidade. Para tanto, foi realizada uma revisão bibliográfica nas bases PubMed, Google Acadêmico, Biblioteca Virtual em Saúde e SciELO, selecionando-se artigos publicados entre 2009 e 2025 nos idiomas inglês, português e espanhol, considerando originalidade, relevância e adequação metodológica. Os estudos com modelos animais indicaram efeitos favoráveis na modulação da microbiota intestinal e nas alterações metabólicas associadas à obesidade. Em humanos, entretanto, os resultados foram menos consistentes, devido a fatores como dificuldade no controle da ingestão, duração limitada dos estudos, diferenças metabólicas e variações no estilo de vida. Conclui-se que o guaraná pode favorecer a saúde graças aos efeitos terapêuticos relacionados à cafeína, representando uma alternativa complementar às terapias convencionais. Contudo, são necessários estudos adicionais e de maior duração para confirmar seu potencial no tratamento da obesidade.

Palavras-chave: guaraná, obesidade, fitoterápicos

RESUMEN

El guaraná (*Paullinia cupana*) es una planta nativa de América del Sur, utilizada tradicionalmente por poblaciones indígenas desde antes de la colonización y ampliamente consumida en la actualidad. A pesar de sus conocidos efectos estimulantes, se sabe poco sobre la relación entre su extracto y la microbiota intestinal, la cual desempeña un papel fundamental en la absorción de nutrientes y en la regulación del metabolismo energético, y se ve significativamente alterada en la obesidad. El objetivo de este estudio fue revisar los efectos del extracto de guaraná sobre la microbiota intestinal y sus posibles implicaciones en el contexto de la obesidad. Se realizó una revisión bibliográfica en las bases de datos PubMed, Google Académico, Biblioteca Virtual en Salud y SciELO, seleccionando artículos publicados entre 2009 y 2025 en inglés, portugués y español, considerando originalidad, relevancia y rigor metodológico. Los estudios realizados en modelos animales mostraron efectos favorables en la modulación de la microbiota intestinal y en los cambios metabólicos asociados con la obesidad. En humanos, sin embargo, los resultados fueron menos consistentes debido a factores como la dificultad para controlar la ingesta, la corta duración de los estudios, las diferencias metabólicas y las variaciones en el estilo de vida. Se concluye que el guaraná puede favorecer la salud gracias a sus efectos terapéuticos relacionados principalmente con la cafeína, representando una alternativa complementaria a las terapias convencionales. No obstante, se requieren estudios adicionales y de mayor duración para confirmar su potencial en el tratamiento de la obesidad.

Palabras clave: guaraná, obesidad, fitoterapéuticos

1 INTRODUCTION

Guarana (*Paullinia cupana*) is a climbing plant native to the Amazon basin, particularly in Brazil and Venezuela, and has been traditionally used by Indigenous populations for centuries due to its stimulant and medicinal properties (Salomão-Oliveira et al., 2018). In recent decades, guarana extract has gained increasing global attention as a natural ingredient in functional foods, dietary supplements, and weight management products, primarily attributed to its high caffeine content and thermogenic potential (Marques et al., 2019). Beyond its recognized stimulant effects, guarana is emerging as a promising bioactive compound with potential roles in modulating the gut microbiota, a key regulator of metabolic homeostasis.

The intestinal microbiota, composed of trillions of microorganisms that inhabit the human gastrointestinal tract, plays an essential role in nutrient absorption, immune regulation, and energy

metabolism. Dysbiosis, an imbalance in the composition or function of the gut microbiota, has been strongly associated with the development of metabolic disorders such as obesity, diabetes, and cardiovascular diseases (Lynch; Pedersen, 2016; Gilbert et al., 2016; Tremaroli; Bäckhed, 2012). As obesity affects more than one billion people worldwide and contributes significantly to global morbidity and mortality, identifying effective, safe, and natural therapeutic strategies to support its prevention and management has become a major public health priority. In this context, exploring the relationship between guarana extract and gut microbiota modulation addresses both a significant scientific gap and a pressing clinical need.

From a theoretical perspective, this study contributes to advancing scientific understanding of how plant-derived bioactive compounds influence gut microbial diversity and metabolic functions. By synthesizing existing evidence on guarana's effects on microbial composition, short-chain fatty acid production, and systemic metabolic regulation, this work enriches the conceptual framework linking phytochemicals, microbiota dynamics, and host metabolism. Furthermore, by identifying methodological limitations and knowledge gaps in current research, the study lays the groundwork for future investigations aimed at unraveling the mechanisms through which guarana exerts its microbiota-modulating effects.

From a practical perspective, the findings of this review hold potential for the development of novel strategies in clinical and nutritional interventions. If guarana can indeed modulate gut microbiota and improve metabolic outcomes, it could serve as a complementary or alternative therapeutic tool for obesity prevention and treatment. Such knowledge could guide the formulation of functional foods, nutraceuticals, and dietary interventions tailored to improve metabolic health and support precision nutrition approaches targeting specific microbial pathways. Additionally, understanding guarana's bioactive properties may inform policies and practices in public health nutrition, contributing to cost-effective and sustainable strategies against obesity and related metabolic disorders.

Given these considerations, the present study aims to provide a comprehensive literature review of the effects of *Paullinia cupana* extract on the intestinal microbiota and its potential implications in the context of obesity. Specifically, it seeks to (i) synthesize current scientific evidence on the interaction between guarana and gut microbial composition and function, (ii) evaluate metabolic outcomes associated with guarana consumption in animal and human models, and (iii) highlight existing methodological limitations and propose directions for future research. By integrating theoretical insights with potential real-world applications, this review aspires to contribute both to the scientific understanding and to the practical utilization of guarana in metabolic health management.

2 THEORETICAL FRAMEWORKS

The gut microbiota is a complex and dynamic community of microorganisms that plays a fundamental role in nutrient absorption, metabolic regulation, and immune function (Lynch; Pedersen, 2016). Alterations in its composition known as dysbiosis are closely linked to metabolic disorders such as obesity, diabetes, and cardiovascular diseases (Tremaroli; Bäckhed, 2012). Obesity, a multifactorial and globally prevalent condition, is influenced not only by lifestyle and genetics but also by changes in the gut microbiota. Research shows that obese individuals frequently present reduced microbial diversity and altered bacterial populations, which can affect energy harvest and fat storage (Turnbaugh et al., 2006).

Given the importance of microbiota in metabolic health, natural products capable of modulating it have gained scientific interest. Among them, guarana (*Paullinia cupana*) stands out due to its high caffeine content and potential metabolic effects. Beyond its traditional use as a stimulant, guarana holds significant agricultural and economic relevance in Brazil, especially in the states of Amazonas and Bahia, where it is widely cultivated (Meneghetti et al., 2021). According to a review published in the *Brazilian Journal of Animal and Environmental Research*, the growing production and socioeconomic value of guarana reinforce its potential not only as an agricultural commodity but also as a bioactive resource for health research.

This scientific relevance extends to metabolic research. Experimental studies indicate that guarana can influence gut microbial composition and improve metabolic outcomes in animal models (Bortolin et al., 2019; Silveira et al., 2018). However, evidence in humans remains scarce and inconclusive, highlighting the need for further investigation (Torres et al., 2022). Based on these findings and the importance of guarana as both an agricultural product and a bioactive compound, this review aims to synthesize current evidence on its effects on gut microbiota and its potential role in obesity management.

3 METHODOLOGIES

This study is a narrative literature review with a broad scope, aiming to describe the development of the topic from a theoretical and contextual perspective through the analysis and interpretation of existing scientific production. The guiding question was: “What has the scientific literature from 2009 to 2025 reported regarding the effects of *Paullinia cupana* (guarana) extract on gut microbiota and its potential role in obesity?”

A bibliographic search was conducted in PubMed, SciELO, Google Scholar, and the Virtual Health Library (VHL), covering the period from 2009 to 2025. The search strategy used the descriptors: *Paullinia cupana*, guarana, gut microbiota, obesity, phytotherapeutics, probiotic, and

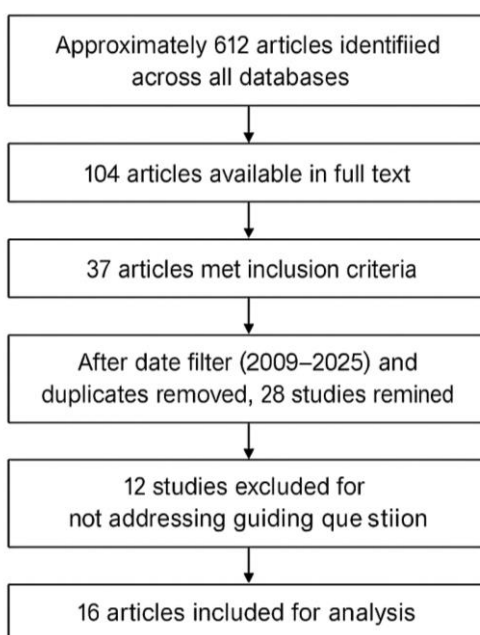
prebiotic. Publications in English, Portuguese, and Spanish were considered, including journal articles, dissertations, theses, and conference proceedings available electronically, free of charge, and in full text.

Inclusion criteria comprised studies that directly addressed the relationship between guarana, gut microbiota, and metabolic outcomes. Exclusion criteria included works published before 2009, lacking scientific references, duplicates, derived from non-scientific websites, or unrelated to the topic.

Initially, approximately 612 articles were identified across all databases. Of these, 104 were available in full text, and 37 met the inclusion criteria. After applying the publication date filter and removing duplicates, 28 studies remained. Following title and abstract screening, 12 were excluded for not addressing the guiding question, resulting in a final sample of 16 articles selected for analysis.

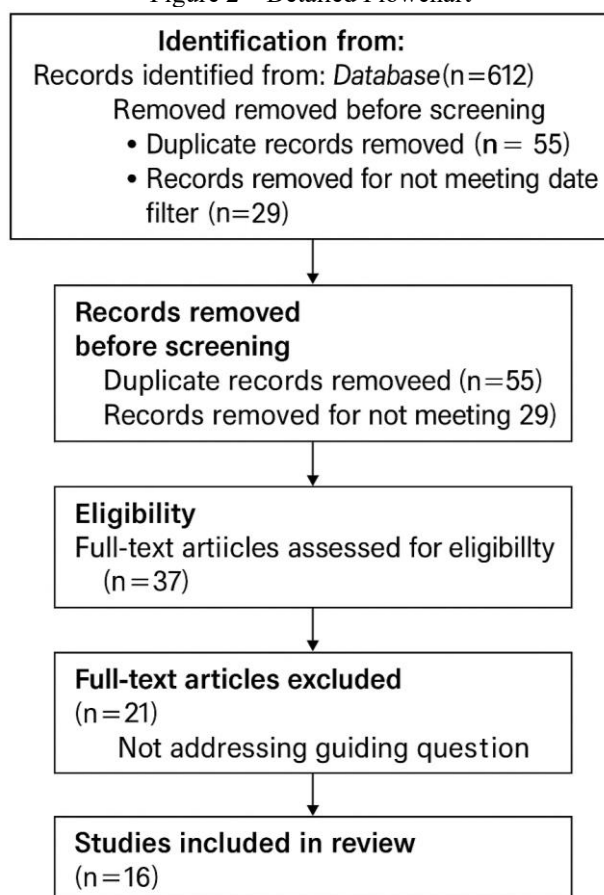
The selection process is summarized in Figure 1, which presents the overall flow from identification to final inclusion. A more detailed breakdown is provided in Figure 2, showing how the final sample of 16 studies was reached. The selected articles were then read and critically analyzed, catalogued, and organized into thematic categories. Finally, the findings were interpreted to identify convergences, divergences, and knowledge gaps in the literature regarding guarana, gut microbiota, and obesity.

Figure 1 – Overall Article Selection Process



Source: Prepared by the authors.

Figure 2 – Detailed Flowchart



Source: Prepared by the authors.

4 RESULTS AND DISCUSSIONS

This review analyzed and synthesized the available scientific literature from 2009 to 2025 regarding the effects of *Paullinia cupana* (guarana) extract on the gut microbiota, its metabolic implications, and its potential role in obesity. Following the application of inclusion and exclusion criteria, 16 relevant studies were selected, including in vitro experiments, animal models, and human clinical trials. The integration of these findings reveals significant evidence supporting the biological effects of guarana, while also highlighting substantial knowledge gaps that must be addressed by future research.

4.1 SEARCH STRATEGY AND STUDY SELECTION

The literature search was conducted in the PubMed, SciELO, Google Scholar, and Virtual Health Library (BVS) databases, using the descriptors: *Paullinia cupana*, guarana, gut microbiota, obesity, herbal medicine, probiotic, and prebiotic. Articles published between 2009 and 2025 in English, Portuguese, and Spanish were considered.

After the initial screening of 612 articles, 104 were available in full text. Of these, 37 met the inclusion criteria. After removing duplicates and applying eligibility filters, 28 remained. Finally,

16 articles were selected for qualitative analysis and categorized according to title, objectives, methodological approach, and main findings.

4.2 CHARACTERIZATION OF INCLUDED STUDIES

Table 1 presents the characterization of the studies included in this review, organized according to title, objectives, and methodological approach. This table provides an overview of scientific production on the topic and serves as the basis for the discussion of the results that follow.

Table 1 – Characterization of studies on *Paullinia cupana*, gut microbiota, and obesity (2009–2025)

Article	Objective	Key Findings	Model	Approach
Bortolin et al. (2019)	Assess metabolic effects and gut microbiota in rats on a Western diet	↓ Weight gain, ↑ insulin sensitivity, improved adipokines, minor microbiota changes	Wistar rats	In vivo
Silveira et al. (2018)	Investigate guarana and caffeine impact on microbiota and redox status	Altered microbiota without loss of diversity; improved redox balance	Wistar rats	In vivo
Lima et al. (2019)	Evaluate maternal guarana effects on offspring metabolism	Attenuated metabolic and inflammatory alterations	Pregnant mice	In vivo
Santos et al. (2025)	Test guarana effects on SCFA and metabolic markers	↑ SCFA (acetate), ↓ glucose and total cholesterol	Young rats	In vivo
Portella et al. (2013)	Study antioxidant effects in habitual consumers	↓ LDL oxidation; confirmed antioxidant activity	Elderly humans	Observational + in vitro
da Costa Krewer et al. (2014)	Evaluate cytokine modulation by guarana	↓ IL-6, TNF- α ; ↑ IL-10	Humans / PBMC	Clinical + in vitro
Torres et al. (2022)	Review metabolic and microbiota effects in humans	Variable metabolic benefits; scarce microbiota data	Humans	Review
Teixeira et al. (2024)	Summarize preclinical guarana evidence	Improved metabolic and inflammatory markers	Animal models	Systematic review

Source: Prepared by the author (2025).

The analysis of titles and objectives revealed that most studies address gut microbiota modulation and its metabolic impacts as the central focus. The methods used were predominantly experimental (*in vivo* and *in vitro*), representing about 75% of the studies. Clinical trials and narrative reviews make up 25% of the sample, highlighting the scarcity of controlled human trials.

4.3 TEMPORAL DISTRIBUTION, LOCATION, AND MAIN FINDINGS

To complement the analysis, Table 2 presents the distribution of the articles by year, location, model used, and main findings, allowing for the identification of patterns in scientific production and accumulated evidence.

Table 2 – Distribution of studies by year, location, model, and main findings

Article	Year	Location	Model	Main Findings
Silveira et al.	2018	Brazil	Wistar rats	Guarana altered the gut microbiota composition and modulated redox status, partially mediated by caffeine, without loss of diversity (Silveira et al., 2018).
Bortolin et al.	2019	Brazil	Wistar rats	Guarana supplementation prevented weight gain and insulin resistance and activated brown adipose tissue (↑UCP-1, ↑mitochondrial biogenesis), with minor changes in gut microbiota (Bortolin et al., 2019).
Lima et al.	2019	Brazil	Pregnant mice	Guarana attenuated metabolic and inflammatory changes in offspring programmed by maternal obesity (Lima et al., 2019).
Santos et al.	2025	Brazil	Young Wistar rats	Daily guarana powder increased SCFA levels (total and acetate) and reduced serum glucose and total cholesterol after 7 days (Santos et al., 2025).
Portella et al.	2013	Brazil	Humans (elderly habitual consumers) + in vitro	Habitual guarana consumption was associated with reduced LDL oxidation; antioxidant activity was confirmed in vitro (Portella et al., 2013).
Torres et al.	2022	Brazil/Chile	Humans (narrative review)	Human evidence shows variable benefits on lipid profile and oxidative stress, but direct effects on human gut microbiota remain scarce (Torres et al., 2022).

Source: Prepared by the author (2025).

Analysis of Table 2 shows that most studies were conducted in Brazil, the country of origin and main producer of guarana (Meneghetti et al., 2021). There is also a noticeable increase in publications in the past decade, reflecting growing scientific interest in guarana's effects on metabolic health.

Moreover, the most robust results come from animal models, which demonstrated significant alterations in gut microbiota, improved insulin sensitivity, and reduced body weight (Bortolin et al., 2019; Silveira et al., 2018). In contrast, clinical trials in humans remain scarce and present heterogeneous results, often attributed to variability in dose, duration of intervention, and individual factors such as diet and lifestyle (Torres et al., 2022).

4.4 IDENTIFIED THEMATIC CATEGORIES

The thematic analysis of the literature allowed the identification of four major discussion axes that structure the present review:

- Modulation of gut microbiota and bacterial composition
- Metabolic effects and physiological mechanisms
- Experimental evidence: in vitro studies and animal models
- Clinical evidence in humans

These categories provide a comprehensive overview of guarana's effects and facilitate a critical interpretation of the findings presented

4.5 IN VITRO EVIDENCE: MICROBIAL INTERACTIONS AND INITIAL MECHANISMS

In vitro studies are fundamental for elucidating the direct interactions between guarana (*Paullinia cupana*) bioactive compounds and the gut microbiota, providing mechanistic insights that form the foundation for subsequent vivo and clinical research. Polyphenols, saponins, catechins, and particularly caffeine present in guarana extract have demonstrated significant antimicrobial and prebiotic potential. These compounds modulate bacterial growth dynamics and influence the synthesis of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate, which play crucial roles in maintaining epithelial barrier integrity, regulating energy metabolism, and promoting metabolic homeostasis (Silveira et al., 2018).

A notable feature observed in these studies is the selective modulation of microbial populations. Guarana extract has been shown to inhibit the proliferation of pathogenic species such as *Clostridium perfringens* and *Escherichia coli*, while simultaneously promoting the growth of beneficial genera such as *Bifidobacterium* and *Lactobacillus*.

These genera contribute to SCFA production, reinforce intestinal barrier function, and modulate immune responses, thereby supporting host metabolic health (Silveira et al., 2018; Pasinato et al., 2025). Furthermore, guarana bioactives may also regulate microbial metabolic pathways beyond growth modulation, including enhanced carbohydrate fermentation efficiency and improved redox balance within the gut environment. Collectively, these effects initiate metabolic cascades that contribute to the prevention of obesity and metabolic syndrome.

4.6 EVIDENCE FROM ANIMAL MODELS

Animal model studies form the backbone of current research on the therapeutic potential of *Paullinia cupana* (guarana) in modulating gut microbiota and improving metabolic health. They offer controlled conditions to explore physiological effects and uncover molecular and microbiological mechanisms that are often difficult to investigate in humans.

One of the most consistent findings is guarana's ability to counteract diet-induced metabolic disturbances. Bortolin et al. (2019) demonstrated that rats fed a high-fat diet and supplemented with guarana showed significant reductions in weight gain, visceral adiposity, and insulin resistance, as well as improved glucose tolerance and lipid profiles. These metabolic improvements correlated with notable shifts in gut microbiota, including an increased relative abundance of *Akkermansia muciniphila*, a bacterium associated with enhanced intestinal barrier integrity, reduced endotoxemia, and lower chronic inflammation. Additionally, guarana lowered the Firmicutes/Bacteroidetes ratio, a microbial marker commonly linked to obesity and excessive energy extraction, suggesting a restoration of microbial balance (Silveira et al., 2018).

Beyond compositional changes in the microbiota, guarana influences host metabolism directly. Lima et al. (2005) showed that supplementation improved lipid metabolism, enhanced fatty acid oxidation, and modulated key metabolic enzymes, indicating that guarana interacts with both microbial-derived metabolites such as short-chain fatty acids (SCFAs) and host metabolic pathways. Guarana bioactives, particularly polyphenols and saponins, also reduce oxidative stress, regulate inflammatory cytokines like TNF- α and IL-6, and enhance antioxidant enzyme activity, collectively mitigating obesity-associated inflammation and improving insulin sensitivity (Pasinato et al., 2025).

Intriguingly, guarana's effects may extend across generations. Maternal supplementation during gestation reversed metabolic and inflammatory disturbances in offspring induced by maternal obesity, suggesting a role in metabolic programming through changes in maternal microbiota and epigenetic regulation (Bortolin et al., 2019). Moreover, emerging evidence indicates that guarana may modulate the gut-brain axis, influencing appetite regulation and energy expenditure via changes in SCFA production and gut-derived hormones such as GLP-1 and PYY, which are critical for satiety and glucose homeostasis (Silveira et al., 2018).

In summary, animal studies demonstrate that guarana exerts multifaceted metabolic benefits through complementary mechanisms: reshaping gut microbial communities, enhancing intestinal barrier function, reducing inflammation and oxidative stress, improving lipid and glucose metabolism, and potentially modulating epigenetic and neuroendocrine pathways. These preclinical findings provide a robust foundation for future clinical research and the development of guarana-based interventions for obesity prevention and metabolic health improvement.

4.7 CLINICAL EVIDENCE IN HUMANS

Although still limited compared to preclinical research, clinical studies provide valuable insights into the translational potential of guarana (*Paullinia cupana*) as a functional dietary component for metabolic regulation and gut microbiota modulation in humans. These studies, though often characterized by smaller sample sizes, short intervention durations, and heterogeneous methodologies, suggest that guarana can exert beneficial systemic effects even in complex human metabolic contexts.

One of the most consistent findings is guarana's anti-inflammatory and antioxidant potential in human populations. Pasinato et al. (2025) demonstrated that supplementation with guarana, selenium, and L-carnitine improved oxidative profiles in rats with osteoarthritis, supporting the compound's systemic antioxidant activity. While this study was conducted in an animal model, its outcomes parallel findings from human trials showing reduced circulating pro-inflammatory cytokines such as TNF- α and IL-6 and improved lipid metabolism following guarana consumption.

These anti-inflammatory effects are of relevance in the context of obesity, where chronic low-grade inflammation plays a central role in the development of insulin resistance and metabolic syndrome.

In addition to modulating inflammatory markers, guarana has been associated with improvements in lipid profiles, including reductions in total cholesterol and low-density lipoprotein (LDL) and increases in high-density lipoprotein (HDL) levels (Silveira et al., 2018). These findings suggest a potential cardiometabolic benefit, especially when guarana is incorporated into dietary interventions for obesity or metabolic syndrome. Some studies also report mild improvements in glucose homeostasis, although these effects are less consistent and often depend on the duration of intervention and the metabolic status of participants.

However, the impact of guarana on the gut microbiota in humans remains less pronounced than in animal models. Variability in diet, lifestyle, baseline microbiota composition, and genetic background across populations introduces significant interindividual differences in response to guarana supplementation. Moreover, most available studies feature relatively short intervention periods (typically <12 weeks), which may not be sufficient to observe robust microbial changes. Methodological heterogeneity including differences in guarana formulation, dosage, and bioactive compound concentration further complicates the interpretation and comparison of results across studies.

To overcome these limitations, future clinical research should focus on larger, randomized, controlled trials with standardized guarana preparations, extended intervention periods, comprehensive microbiota and metabolomic profiling. Integrating multi-omics approaches and stratifying participants based on baseline microbiota composition or metabolic status may help clarify the variability observed and uncover more precise relationships between guarana, gut microbial dynamics, and host metabolic outcomes.

4.8 KEY BACTERIA AND THEIR METABOLIC ROLES

The modulation of the gut microbiota by guarana involves profound shifts in microbial diversity and function, with several taxa playing pivotal roles in metabolic regulation, immune modulation, and energy homeostasis. These changes are integral to the metabolic improvements observed in both preclinical and clinical contexts.

Table 3 – Main bacterial genera modulated by guarana and their physiological roles

Bacterial genus	Main physiological role	Relationship with obesity
<i>Akkermansia muciniphila</i>	Degrades mucin, enhances intestinal barrier integrity, reduces inflammation	Inversely associated with weight gain
<i>Bifidobacterium</i> spp.	Produces SCFAs, strengthens the intestinal barrier, modulates immune response	Promotes insulin sensitivity
<i>Lactobacillus</i> spp.	Produces lactic acid, stimulates immune function, inhibits pathogens	Reduces intestinal inflammation and obesity risk
<i>Bacteroides</i> spp.	Participates in polysaccharide digestion, energy regulation, and bile acid metabolism	Altered proportions linked to metabolic dysfunction
<i>Clostridium</i> spp.	Includes butyrate-producing and pathogenic species	Dysbiosis contributes to obesity and inflammation
<i>Escherichia coli</i>	Certain strains increase inflammation and intestinal permeability	Overgrowth linked to insulin resistance

Source: Prepared by the author (2025).

Among these, *Akkermansia muciniphila* has emerged as a key taxon consistently associated with improved metabolic outcomes. Its mucin-degrading capacity strengthens the intestinal mucus layer, reduces systemic endotoxemia, and lowers inflammation, ultimately improving insulin sensitivity (Bortolin et al., 2019). Likewise, *Bifidobacterium* and *Lactobacillus* spp. contribute significantly to SCFA production, enhancing energy homeostasis, epithelial health, and host immune modulation (Silveira et al., 2018).

Modulation of the Firmicutes/Bacteroidetes ratio is another critical mechanism underlying guarana's metabolic benefits. A lower ratio has been linked to decreased energy harvest and improved metabolic outcomes, while suppression of potentially pathogenic taxa such as *Clostridium perfringens* and *Escherichia coli* reduces inflammation and metabolic endotoxemia. Together, these shifts reflect a transition toward a eubiotic gut state, characterized by balanced microbial interactions that support metabolic health and protect against obesity.

4.9 PHYSIOLOGICAL MECHANISMS AND METABOLIC IMPLICATIONS

Guarana's anti-obesogenic effects are closely tied to its capacity to modulate metabolic pathways and systemic physiological processes. Caffeine, one of its primary bioactive constituents, plays a central role in stimulating lipolysis and enhancing energy expenditure through activation of thermogenic pathways mediated by the sympathetic nervous system (Lima et al., 2005). These effects contribute to increased basal metabolic rate and improved fat oxidation, both of which are essential for weight regulation.

Polyphenols and saponins in guarana exhibit potent antioxidants and anti-inflammatory properties, reducing levels of pro-inflammatory cytokines such as TNF- α and IL-6 and modulating key regulatory pathways such as AMP-activated protein kinase (AMPK) signaling. AMPK serves as a critical energy sensor in cells, and its activation leads to enhanced glucose uptake, increased fatty acid oxidation, and improved insulin sensitivity (Silveira et al., 2018).

Moreover, guarana-induced shifts in the gut microbiota led to increased production of SCFAs, which exert far-reaching metabolic effects. SCFAs regulate appetite through gut-brain axis signaling, modulate hepatic gluconeogenesis, and improve peripheral insulin sensitivity. They also influence the release of enteroendocrine hormones such as GLP-1 and PYY, which regulate satiety and glucose homeostasis. Together, these mechanisms highlight guarana's potential as a multifaceted modulator of metabolic function.

4.10 LIMITATIONS AND KNOWLEDGE GAPS

Despite significant progress, the current body of literature on guarana and gut microbiota still faces notable limitations:

- A scarcity of robust, large-scale clinical trials with extended intervention durations.
- High methodological heterogeneity across studies, including variations in dosage, formulation, and extract characterization.
- Predominance of preclinical studies, limiting the direct extrapolation of findings to human populations.
- Limited exploration of synergistic interactions among guarana's diverse bioactive compounds.
- A lack of standardized protocols for microbiota and metabolomic analyses, hindering data comparability.

Addressing these limitations will require multicenter, randomized, and controlled trials designed to elucidate molecular mechanisms and validate preclinical findings in diverse human populations. Integration of multi-omics approaches, including metagenomics, metabolomics, and transcriptomics, will be essential for capturing the full complexity of guarana's effects on host-microbiota interactions and metabolic pathways.

4.11 FUTURE PERSPECTIVES

The current evidence positions guarana as a promising natural compound for modulating gut microbiota and as an adjuvant in the prevention and management of obesity and metabolic disorders. Future research should prioritize several key areas:

- Long-term clinical trials with larger and more representative populations, incorporating rigorous control of dietary and lifestyle variables.
- Application of multi-omics approaches to unravel the complex interactions between guarana bioactives, gut microbiota, and host metabolic responses.

- Standardization of guarana formulations to ensure reproducibility and consistency across studies, enabling clearer comparisons and meta-analyses.
- Exploration of synergistic interventions, combining guarana with probiotics and prebiotics to potentiate its microbiota-modulating and metabolic effects.

Advancing research in these areas will be critical to fully understanding guarana's therapeutic potential and translating preclinical findings into effective clinical applications.

5 CONCLUSIONS

This review synthesized current scientific evidence on the effects of *Paullinia cupana* (guarana) extract on the gut microbiota and its potential role in the prevention and management of obesity. The studies analyzed, ranging from in vitro experiments to preclinical animal models and human clinical trials, consistently demonstrate that guarana exerts significant biological effects on microbial composition, metabolic regulation, and systemic physiological pathways.

Evidence from in vitro studies shows that guarana's bioactive compounds—particularly polyphenols, saponins, catechins, and caffeine—selectively modulate microbial growth, inhibit pathogenic bacteria, and stimulate beneficial taxa such as *Bifidobacterium* and *Lactobacillus*. These changes enhance short-chain fatty acid production, improve intestinal barrier integrity, and support immune modulation, contributing to metabolic homeostasis. Animal model studies provide the most robust evidence to date, revealing that guarana supplementation mitigates diet-induced metabolic disturbances, reduces weight gain and adiposity, improves insulin sensitivity, and lowers systemic inflammation. These effects are closely linked to shifts in gut microbiota, including an increase in *Akkermansia muciniphila* and a reduction in the *Firmicutes/Bacteroidetes* ratio. Furthermore, evidence suggests guarana's impact may extend to epigenetic regulation, metabolic programming, and gut–brain axis modulation, highlighting its multifaceted biological activity.

While clinical studies remain limited and present heterogeneous results, they indicate that guarana may improve lipid profiles, reduce pro-inflammatory cytokines, and exert antioxidant effects. However, consistent effects on gut microbiota composition in humans have yet to be firmly established, underscoring the need for more comprehensive, long-term, and standardized clinical trials.

Collectively, the findings reviewed here highlight guarana as a promising natural compound with the potential to modulate gut microbiota, regulate metabolic pathways, and contribute to obesity prevention and treatment. Importantly, the implications of this research extend beyond laboratory and clinical outcomes. From a societal perspective, the evidence suggests that guarana-

based interventions could serve as low-cost, sustainable, and culturally accepted strategies to combat obesity and metabolic diseases, which are major global public health challenges. This could lead to improved population health, reduced healthcare costs, and increased accessibility to preventive therapies, especially in regions with limited medical resources. From an academic and scientific perspective, these findings advance the understanding of plant–microbiota interactions and provide a foundation for developing new therapeutic approaches. They also encourage interdisciplinary collaboration across fields such as microbiology, nutrition, pharmacology, and clinical medicine, while guiding future investigations into bioactive natural compounds and their translational potential in human health.

Future research should prioritize large-scale, randomized, and controlled clinical trials, integration of multi-omics approaches, and exploration of combined interventions with probiotics and prebiotics. Addressing these gaps will be essential for translating preclinical findings into clinical applications and for fully harnessing guarana’s potential as a functional dietary component in metabolic health strategies.

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