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Relationship among nutrients, gut microbiota, and microRNAs for healthy weight loss: a systematic review

Luiz Gustavo Brandão de Proença[1*], Ana Carolina Gonçalves de Macedo[1]

[1]Clinic Luiz Gustavo Brandao de Proenca - Clinical Treatments for Obesity and Overweight. Avenue: Cândido Hartmann, 570, 181, Campo largo - Paraná, Brazil.

*Corresponding author: Dr. Luiz Gustavo Brandão de Proença.
Clinic Luiz Gustavo Brandao de Proenca - Clinical Treatments for Obesity and Overweight. Avenue: Cândido Hartmann, 570, 181, Campo largo - Paraná, Brazil.
E-mail: lgbrandao90@gmail.com

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Abstract

Introduction: In the context of chronic non-communicable diseases, obesity represents a pandemic represented as a long-term chronic imbalance between calorie intake and energy expenditure, resulting in more than 2.0 billion overweight and obese people worldwide. **Objective:** It was to present the major considerations and results of clinical studies on the relationship between nutrients, gut microbiota, and microRNAs for healthy weight loss through a systematic review. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from August to September 2024 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 142 articles were found, and 35 articles were evaluated in full and 28 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=72.4%>50%. It was concluded that diet is a determining factor for a healthy colonization of the gut microbiota. Adipose tissue hypertrophy causes metabolic and hemodynamic disorders through the production of several adipokines that play a role in the genesis of insulin resistance and atherosclerosis. Studies in humans with obesity have also found a lower proportion of Bacteroidetes compared to eutrophic individuals. Furthermore, when they lose weight, the proportion of Firmicutes decreases and becomes more similar to that of lean individuals. Maintaining a healthy metabolism depends on a symbiotic consortium between bacteria and other intestinal microorganisms. Furthermore, microRNAs regulate gene expression in adipose tissue, impact the regulation of metabolism and energy homeostasis, and regulate adipogenesis signaling pathways in white, beige, and brown adipose tissue. For example, microRNA (miR-143) promotes thermogenesis in brown adipose tissue and inhibits adipogenesis in white adipose tissue. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism, with crosstalk with the gut microbiota. Furthermore, an association was found between *B. eggerthi* abundance, miR-183-5p expression, and adiponectin levels. miR-15a-5p expression was found to be associated with *H. parainfluenza* abundance and insulin levels.

Keywords: Obesity. Nutrients. Gut microbiota. microRNAs. Healthy weight loss.

Introduction

In the context of chronic non-communicable diseases, obesity represents a pandemic represented as a long-term chronic imbalance between calorie intake and energy expenditure, which causes serious comorbidities **[1-3]**. Obesity is the result of complex and incompletely

understood pathological processes arising from crosstalk between environmental factors, genetic susceptibility, and epigenetic mechanisms, resulting in more than 2.0 billion overweight and obese people worldwide **[1]**.

In recent years, new technologies have allowed researchers to phylogenetically identify and/or quantify components of the gut microbiota by analyzing nucleic acids (DNA and RNA) directly extracted from feces. Most of these techniques are based on DNA extraction and amplification of the 16S ribosomal RNA (rRNA) gene. 16S rRNA sequencing has become the most useful technique to highlight the diversity and abundance of the microbiome. The 16S rRNA gene sequences can be explored with a polymerase chain reaction (PCR) and metagenomic sequencing to characterize the strains **[2]**.

In this scenario, the gut microbiota is essential for the host to ensure digestive and immunological homeostasis. However, in the presence of dysbiosis, the malfunctioning of the epithelial barrier leads to intestinal and systemic disorders, mainly obesity **[4,5]**. In this sense, microRNAs (miRNAs) stand out, which are a class of small non-coding RNAs that regulate gene expression **[4-6]**. These molecules have recognized roles in the regulation of several biological processes, regulating the expression of more than 60% of protein-coding genes, and alterations in their expression and functions have been associated with many diseases, including metabolic disorders and obesity **[7,8]**.

Furthermore, host miRNAs contribute to the regulation of the gut microbiota, or the gut microbiota affects the host through the induction of miRNA expression **[9]**. Evidence suggests that miRNAs produced by host intestinal epithelial cells (IECs) participate in the formation of the gut microbiota and affect bacterial growth. These miRNAs target bacterial mRNA, and then the host controls the gut microbiota through degradation of bacterial mRNA or inhibition of translation **[10]**.

The gut microbiota regulates miRNA expression in IEC subtypes, and this regulation may alter intestinal homeostasis **[11]**. In this sense, it has been shown that the expression of some miRNAs is different between IEC subtypes and the difference depends on microbial patterns **[12]**. Thus, studies provide clues that the gut microbiota regulates host gene expression through modulation of the host miRNA signature and that host metabolism may be influenced by this interaction. Also, miRNAs appear to play an important role in host-microbe interactions and could be considered molecular targets for the development of novel antimicrobial therapies. However, little is known about the interactions between miRNAs and the host microbiome in the context of obesity **[3]**.

Also, metabolic disorders are characterized by the inability to utilize and/or store energy adequately. There is growing concern about the dysregulation of miRNAs in metabolic diseases. Recent data show the potential involvement of miRNAs in metabolic diseases, particularly obesity and type 2 diabetes **[13]**. In addition, obesity is associated with chronic low-grade inflammation in adipose tissue. The resident immune microenvironment is not only responsible for maintaining homeostasis in adipose tissue but also plays a crucial role in combating obesity and its comorbidities. Increasing evidence suggests that obesity promotes the activation of resident T cells and macrophages. MicroRNAs contribute to the maintenance of the immune response and obesity in adipose tissue. Resident T cells, macrophages, and adipocytes secrete various miRNAs and communicate with other cells to create a potential effect on metabolic organ crosstalk. Resident macrophages and T cell-associated miRNAs play a prominent role in regulating obesity by targeting various signaling pathways **[14]**.

Therefore, the present study aims to present the key considerations and results of clinical studies on the relationship between nutrients, gut microbiota, and microRNAs for healthy weight loss through a systematic review.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 01/11/2025. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 01/11/2025.

Data Sources and Search Strategy

The literature search process was carried out in January 2025 and developed based on Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (MeSH Terms) were used: "Obesity. Nutrients. Gut microbiota. microRNAs. Healthy weight loss", and using the Boolean "and" between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

The quality was classified as high, moderate, low,

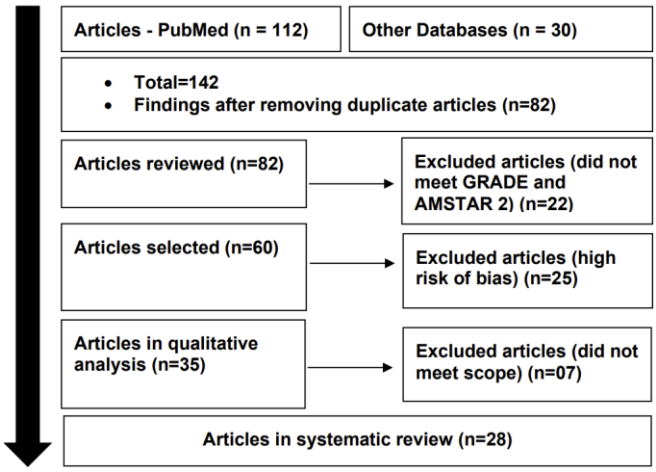
or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

142 articles were found that were submitted to eligibility analysis, and 28 final studies were selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=72.4%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 25 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

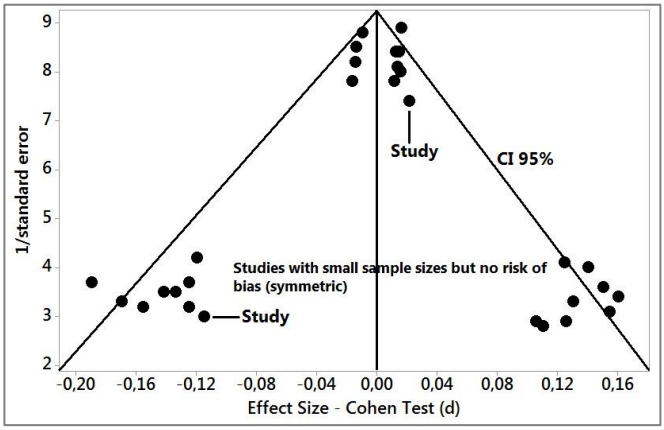
Figure 1. Screening of the articles.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using Cohen's Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

Figure 2. The symmetrical funnel plot suggests no risk of bias among the studies with small sample sizes that are shown at the bottom of the graph. Studies with high confidence and high recommendation are shown above the graph (n=28 studies).



Source: Own authorship.

Outcomes - Relationship Among Nutrients, Gut microbiota, microRNAs, and Healthy Weight loss

The maintenance of healthy metabolism depends on a symbiotic consortium of bacteria, archaea, viruses, fungi, and eukaryotic host cells throughout the human gastrointestinal tract. Microbial communities provide the enzymatic machinery and metabolic pathways that contribute to food digestion, xenobiotic metabolism, and the production of a variety of bioactive molecules. These include vitamins, amino acids, short-chain fatty acids, and metabolites, which are essential for the interconnected pathways of glycolysis, the tricarboxylic acid/Krebs cycle, oxidative phosphorylation, and amino acid and fatty acid metabolism **[15]**.

Studies have elucidated how nutrients that fuel metabolic processes impact how immune cells, particularly macrophages, respond to different stimuli under physiological and pathological conditions and become activated and acquire specialized functions. The two main inflammatory phenotypes of macrophages are controlled through differential consumption of glucose, glutamine, and oxygen. The M1 phenotype is triggered by the polarization signal of bacterial lipopolysaccharide (LPS) and pro-inflammatory Th1 cytokines such as interferon-γ, TNF-α, and IL-1β, or both, whereas the M2 phenotype is triggered by Th2 cytokines such as interleukin-4 and interleukin-13 as well as antiinflammatory cytokines IL-10 and TGFβ. Glucose utilization and production of chemical mediators including ATP, reactive oxygen species (ROS), nitric oxide (NO), and NADPH support effector activities of M1 macrophages **[15,16]**.

It is now known that gut microbiota-derived products induce low-grade inflammatory activation of tissue-resident macrophages and contribute to metabolic and degenerative diseases including diabetes, obesity, metabolic syndrome, and cancer. Furthermore, gut microbiota dysbiosis is closely related to the occurrence of many important chronic inflammation-related diseases. So far, traditionally prescribed probiotics and prebiotics have not shown a significant impact on improving these diseases in general **[17]**.

Thus, the development of next-generation prebiotics and probiotics designed to target specific diseases is greatly needed. Thus, under the situation of gut microbiota dysbiosis, the development of chronic inflammation occurs. These have resulted in the development of many important diseases, such as obesity, type 2 diabetes mellitus, liver inflammation, and other diseases, such as colorectal cancer, obesity-induced chronic kidney disease, impaired lung immunity, and some brain/neuro disorders. Although the efficacy of probiotics and/or prebiotics is promising, further studies are needed to establish recommendations for most clinical scenarios **[17,18]**.

Another study observed associations between phosphatidylglycerols (PG) and gut microbiota dysbiosis. Compared to other phospholipids, serum PG levels were highest in patients with low microbiota gene richness, which were normalized after a dietary intervention that restored gut microbial diversity **[17]**. Serum PG levels were positively correlated with metagenomic functional capacities for LPS synthesis. Experiments in mice and cultured human-derived macrophages demonstrated that LPS induces PG release. Acute PG treatment in mice altered adipose tissue gene expression toward remodeling and inhibition of lipolysis *ex vivo* in adipose tissue, suggesting that PGs favor lipid storage.

In this context, many efforts have been made to understand the link between gut microbiota composition and obesity, as well as the role of dietary ingredients, such as pro- and prebiotics, in modulating the gut microbiota. Studies involving the composition of the gut microbiota of obese individuals are still controversial, making the treatment of obesity difficult **[18]**.

It is also imperative to determine and understand how the behavior and changes that occur in Tregs and microRNAs interfere with the pathophysiological mechanisms of obesity through the action of probiotics on the gut microbiota, to evaluate the possibility of restoring normal metabolic function ("metabolic regeneration") and, thus, determine the existence of therapeutic or even preventive potential. The results in the literature suggest that probiotics bind to dendritic cells (DC) to stimulate Treg cells, together with microRNAs, to increase the concentration of interleukins (IL-10 and IL-35), TGF-β and positively regulate MHC class II **[19,20]**. In the global scenario, precision nutrition helps to develop personalized dietary plans and interventions and encompasses genomic (gene-nutrient interactions through microRNAs), epigenetic, gut microbiota, and environmental nutritional factors, in addition to seeking energy balance and adiposity **[21]**.

As an example, *Faecalibacterium prausnitzii* is one of the most prevalent intestinal bacterial species in healthy adults, being considered a beneficial bacteria and a butyrate producer. The ketone body β-hydroxybutyrate inhibits class I histone deacetylases to increase transcriptional activation of Notch signaling and maintain stem cell self-renewal, and B vitamins and short-chain fatty acids interact with microRNAs to influence obesity stem cell phenotypes **[22]**.

In this context, all cells in the human body secrete microRNAs and exosomes, with the largest producers being adipose tissue and mesenchymal stem cells. More than 60% of human protein-coding genes are modulated by microRNAs. MicroRNAs are also mediators between the gut microbiota and adipose tissue, impacting the regulation of metabolism and energy homeostasis, in addition to regulating adipogenesis signaling pathways in white, beige, and brown adipose tissue, and acting on the transcription and differentiation of adipocytes (mesenchymal stem cells) **[23]**.

In this sense, probiotics are closely related to the modulation of the gut microbiota and microRNAs, in addition to improving the intestinal mucosal barrier and preventing the passage of antigens into the bloodstream. Direct modulation of the immune system may be secondary to the induction of anti-inflammatory cytokines or increased production of secretory IgA. The presence of immunoregulatory mechanisms, such as microRNAs or exosomes, regulatory T cells (Tregs), interleukin-10 (IL-10), and apoptosis, among others, help to control pathological processes associated with excessive reactivity **[23]**.

Besides, IL-35 has been identified as a cytokine with possible implications in the regulatory function of Tregs, acting in the regulation of effector T cells as well as in the expansion of Tregs through the induction of Foxp3. They can also lead to the development of Foxp3- Tregs whose regulatory function depends on IL-35. Studies demonstrate that treatment of naïve T cells with IL-35 is capable of inducing the formation of a new population of regulatory T cells that do not express Foxp3 and whose suppressive activity is dependent on IL-35 **[24]**. Another study also showed the upregulation of surface MHC class II and B7-2 (CD86) by *Lactobacilli sp.* which is indicative of dendritic cell (DC) maturation **[25]**.

MicroRNAs hybridize to complementary sequences in mRNA and silence genes by destabilizing mRNA or preventing mRNA translation. Evidence suggests that microRNAs are not only endogenously synthesized but can also be obtained from dietary sources and that dietary compounds (e.g., plant foods and cow's milk) alter the expression of endogenous microRNA genes. Nutrition alters the expression of endogenous microRNA genes, thus compounding the effects of nutrition-microRNA interactions on gene regulation and disease diagnosis. MicroRNAs derived from diet and endogenous synthesis have been implicated in physiological and pathological conditions, including those linked to nutrition and metabolism **[26,27]**.

In this sense, a study showed that microRNAs regulate gene expression in adipose tissue, impact the regulation of metabolism and energy homeostasis, regulate adipogenesis signaling pathways in white, beige, and brown adipose tissue, and act on the transcription and differentiation of adipocytes (mesenchymal stem cells) **[28]**. In 2023, it was identified that microRNA (miR-143) also promotes thermogenesis in brown adipose tissue and inhibits adipogenesis in white adipose tissue **[29]**.

A study found 26 miRNAs differentially expressed in the plasma of individuals with obesity compared to individuals with normal weight. Furthermore, the expression of 14 miRNAs (miR-107, miR-103a-3p, miR-142-5p, miR-222-3p, miR-221-3p, miR-1835p, miR-183-5p, miR-130b-3p, miR-15a-5p, miR-33a-5p, miR-210-3p, miR-144-3p, miR-185-5p, miR-130a-3p and miR-21-5p) was linked to the relative abundance of 4 bacterial species that also differed significantly between cases and controls (*D. longicatena, B. intestinihominis, B. eggerthii and H. parainfluenzae*) **[3]**. These miRNAs that interact with obesity-associated bacteria regulate the expression of genes involved in several metabolic and obesity-related pathways, such as carbohydrate and lipid metabolism, and endocrine and inflammatory signaling pathways. Most miRNAs do not regulate a specific or individual target gene but rather modulate the expression of a large number of genes, demonstrating their importance in the regulation of several metabolic processes **[30]**.

In addition, studies are accumulating evidence that circulating miRNAs are associated with obesity **[31-33]**. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism **[34-36]**. miR-21-5p, miR-103a, and miR-221-3p were found to be downregulated in blood samples from individuals with obesity in a meta-analysis study **[37]**. Furthermore, miRNAs that were dysregulated in obesity are associated with several metabolic processes, such as glucose intolerance, maintenance of pancreatic beta cell mass, adipocyte development and adipose tissue physiology, inflammation pathways, and cardiomyocyte survival **[38-40]**.

An interaction between BMI levels, *B. eggerthii* abundance, and the expression of three miRNAs (miR-130b-3p, miR-185-5p, and miR-21-5p) was observed. *B. eggerthii* is one of the intestinal bacteria that metabolizes phenolic acids, which are considered beneficial for human health. In a recent study, *B. eggerthii* abundance was significantly higher in children with obesity and correlated positively with body fat percentage but negatively with insoluble fiber intake in Mexican children. On the other hand, this bacteria was found to be underrepresented after sleeve gastrectomy surgery **[41]**.

Of the three miRNAs associated with *B. eggerthii* abundance and BMI levels, miR-185-5p and miR-21-5p were also correlated with *D. longicatena* abundance. Furthermore, miR-185-5p has been reported to be involved in oxidative stress, obesity, and diabetes mellitus in many studies **[42]**. miR-185-5p has been identified as a regulator of de novo cholesterol biosynthesis and low-density lipoprotein uptake **[35]**. An association was found between *B. eggerthi* abundance, miR-183-5p expression, and adiponectin levels. Previous findings have demonstrated that miR-183 may contribute to adipocyte differentiation, adipogenesis, and adipose cell development **[36]**. Both gain-offunction and loss-of-function assays showed that miR-183 promoted 3T3-L1 adipocyte differentiation, lipid accumulation, and adipogenesis by increasing the expressions of peroxisome proliferator-activated receptor gamma (PPARγ), CCAAT enhancer-binding protein alpha (C/EBPα), adiponectin, and fatty acid synthase (FAS) **[42]**.

MiR-15a-5p expression was found to be associated with *H. parainfluenzae* abundance and insulin levels. miR-15a positively regulates insulin biosynthesis by inhibiting the expression of the endogenous uncoupling protein 2 (UCP2) gene, leading to higher islet ATP levels and improving glucose-stimulated insulin secretion. Furthermore, circulating miR-15a levels were found to be downregulated before the onset of type 2 diabetes (T2DM) and also in individuals with incident T2DM compared with controls **[3,4]**.

Although a hypothesis-driven approach was undertaken, selecting only miRNAs previously associated with obesity or metabolism leaves type I or type II errors possibly due to multiple comparisons. Although there are limitations in the current data, the patterns already discovered are important for understanding the contribution of miRNAs and gut microbiota in obesity **[3]**.

Conclusion

It was concluded that diet is a determining factor for a healthy colonization of the gut microbiota. Adipose tissue hypertrophy causes metabolic and hemodynamic disorders through the production of several adipokines that play a role in the genesis of insulin resistance and atherosclerosis. Studies in humans with obesity have also found a lower proportion of Bacteroidetes compared to eutrophic individuals. Furthermore, when they lose weight, the proportion of Firmicutes decreases and becomes more similar to that of lean individuals. Maintaining a healthy metabolism depends on a symbiotic consortium between bacteria and other intestinal microorganisms. Furthermore, microRNAs regulate gene expression in adipose tissue, impact the regulation of metabolism and energy homeostasis, and regulate adipogenesis signaling pathways in white, beige, and brown adipose tissue. For example, microRNA (miR-143) promotes thermogenesis in brown adipose tissue and inhibits adipogenesis in white adipose tissue. Some miRNAs have been implicated in the control of body weight gain, glucose homeostasis, insulin resistance, and lipid metabolism, with crosstalk with the gut microbiota. Furthermore, an association was found between *B. eggerthi* abundance, miR-183-5p expression, and adiponectin levels. miR-15a-5p expression was found to be associated with *H. parainfluenza* abundance and insulin levels.

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Author contributions **Conceptualization**- Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo; **Data curation -** Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo; **Formal Analysis-** Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo; **Investigation-** Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo; **Methodology -** Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo; **Project administration-** Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo**; Supervision:** Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo; **Writing - original draft-** Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo; **Writing-review & editing-** Luiz Gustavo Brandão de Proença, Ana Carolina Gonçalves de Macedo.

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Data Sharing Statement

No additional data are available.

Conflict of Interest

The authors declare no conflict of interest.

Similarity Check

It was applied by Ithenticate®.

Application of Artificial Intelligence (AI)

Not applicable.

Peer Review Process

It was performed.

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