Pertanika J. Trop. Agric. Sci. 48 (2): 393 - 409 (2025)

PERTANIKA JOURNALS

TROPICAL AGRICULTURAL SCIENCE

Journal homepage: http://www.pertanika.upm.edu.my/

Review Article

Tea Polyphenols and Iron Oxide Nanoparticles: Therapeutic Benefits, Microbiota Interactions, and Proteomic Perspectives

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ABSTRACT

Combining green tea polyphenols (GTPs) in iron oxide nanoparticles (IONPs) has attracted significant interest due to its potential therapeutic implications. This review investigates the beneficial effects of conjugating IONPs with polyphenols, highlighting their enhanced bioavailability and efficacy. The relationship between tea polyphenols and intestinal microbiota has been clarified by metagenomics research, highlighting how these relationships improve bioavailability. Moreover, studies elucidating the impact of metallic and magnetic nanoparticles on the composition of the gut microbiota provide insight into their function in regulating microbial diversity. Proteomic analyses have provided valuable insights into the molecular mechanisms underlying polyphenol-metallic nanoparticle interactions, offering a comprehensive understanding of their biological processes at the protein level. The study of polyphenol-nanoparticle interactions using metagenomics and proteomic approaches provides a promising direction for further research into possible medicinal uses and therapeutic applications.

Keywords: Iron oxide, metagenomics, nanoparticles, polyphenols, proteomics

ARTICLE INFO

Article history:
Received: 01 July 2024
Accepted: 14 August 2024
Published: 17 February 2025

DOI: https://doi.org/10.47836/pjtas.48.2.04

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INTRODUCTION

Numerous studies have shown that the bioactive polyphenols present in tea plants confer significant nutritional and health benefits (Li et al., 2022). Tea polyphenols are a complex set of compounds that consist of approximately 30 types of phenols, with catechins consisting around 30 to 42% of the total polyphenol content (Zhang, Zhang

ISSN: 1511-3701
e-ISSN: 2231-8542

et al., 2021). Among these, green tea polyphenols (GTPs) are of great significance due to their strong antioxidant potential and a number of noteworthy chemical and biological properties (Li et al., 2019). One of the main polyphenolic catechins found in green tea, epigallocatechin gallate (EGCG), has drawn interest for its wide range of bioactive characteristics, which include antiviral, antitumorigenic, anti-inflammatory, antibacterial, antioxidative, and antiproliferative effects (Chacko et al., 2010). Furthermore, theaflavins (TFs) and their derivatives have many biological activities, including antibacterial, antiviral, antitumor, and anti-inflammatory qualities (Mhatre et al., 2021).

The presence of galloyl and gallic moieties in the catechin structure has also been associated with specific cytotoxicity towards cancer cells (Karas et al., 2017). Despite promising therapeutic potential, the efficiency of these compounds is not fully evaluated, with occasional pro-oxidant effects and potential medication interactions via enzymatic and microbiota-mediated processes (Galati & O'Brien, 2004). In recent years, nano-delivery systems have gained traction for their capacity to enhance the stability and targeted delivery of bioactive compounds (Zhang, Qiu et al., 2021). Particularly, metal nanoparticles have garnered interest because of their special qualities, which include a high specific surface area and adjustable size and shape, which may improve the bioavailability of bioactive compounds (Meena et al., 2020). However, significant gaps persist in understanding the biological implications of nanomaterials despite their widespread application in various products (Barreto et al., 2020).

Over time, proteomics has seen a steady increase in the application of nanotechnology (Agrawal et al., 2013). The impact of nanoparticles (NPs) on various cells can be seen clearly, simply, accurately, and valuably through proteomics analysis (Abdelhamid & Wu, 2015). As a result, proteomics and nanotechnology have come together to form nanoproteomics, which offers a reliable, real-time analytical platform for sensitively identifying low-abundance proteins (Matarraz et al., 2011). Additionally, alterations in microbial communities are tracked through metagenomics analysis, which examines modifications in various metrics such as microbial biomass, microbial activity rates, or microbial community composition (Lynch et al., 2012). Quantifying community composition is essential for determining how NPs affect the environment, creating toxicity detection tools, and enhancing bioremediation techniques (Afzal & Singh, 2022). The main objective of this review is to thoroughly investigate the current state of science regarding green tea polyphenols iron oxide nanoparticles' advantages in terms of bioavailability. The study focuses on metagenomics insights into the interactions between intestinal microbiota and tea polyphenols, highlighting how these relationships improve bioavailability. In addition, the review explores proteomic issues, thoroughly examining the effects of associations between tea polyphenols and iron oxide nanoparticles on biological systems. Figure 1 highlights the key ideas presented in this review, from the potential medicinal uses

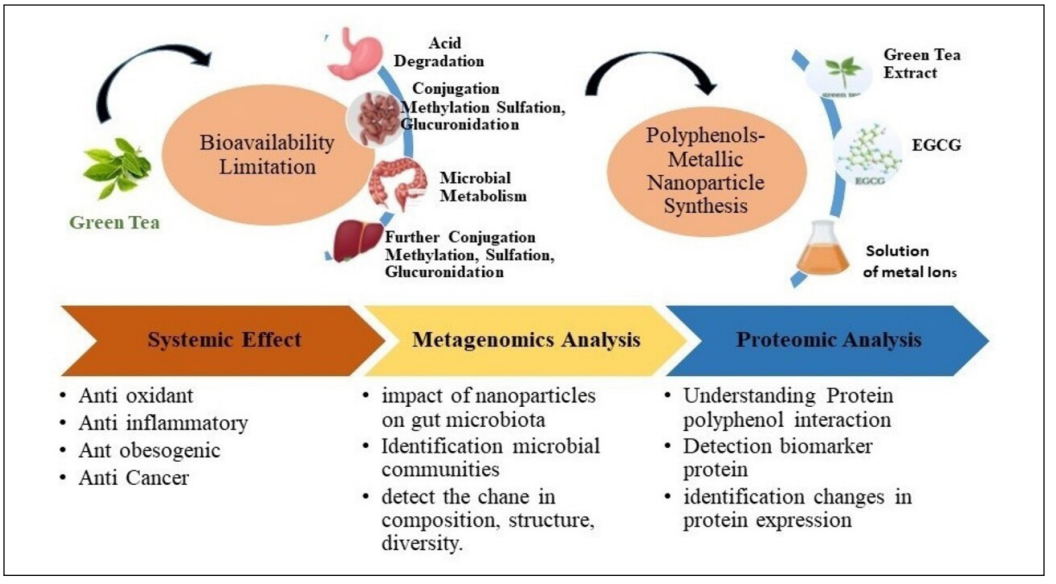

Figure 1. Summary of the key points presented in this review from the potential medicinal uses of tea polyphenols, its bioavailability limitation to nanocarriers using metagenomics and proteomics approaches

of tea polyphenols and their bioavailability limitation to nanocarriers using metagenomics and proteomic approaches.

Green Tea Polyphenols and Iron Oxide Nanoparticles

Tea is one of the most popular beverages made from the leaves of the *Camellia sinensis* plant. Tea has become one of the most widely consumed drinkables in the world for enjoyment and health (Meegahakumbura et al., 2018). Green tea, which is high in polyphenols, has attracted the attention of researchers and scientists for its consumption. Green tea is generally favored over black tea in terms of health benefits (Pasrija & Chinnaswamy, 2015). Green tea also contains a high concentration of flavonoids, amino acids, caffeine, phenolic acids, carbohydrates, and volatile constituents, which exist in their biomolecular form (Mujtaba et al., 2023). A high proportion of the constituents of green tea are catechins, consisting of 80–90% of the total polyphenols. Among the various catechins reported in green tea, epigallocatechin gallate (EGCG) constitutes more than 50% of total catechins. Other green tea polyphenol constituents are flavonols, phenolic acids, and alkaloids such as caffeine (Sinija & Mishra, 2008; Venkata et al., 2018). Due to the beneficial effects of caffeine, flavonoids, and catechins on health, this beverage has been used in natural medicine for thousands of years (Almeida & Figueira, 2013). However, some issues, including low solubility, poor permeability, instability, rapid release, susceptibility to environmental influences and low bioavailability, restrict the use of phenolic compounds in humans (Li et al., 2015).

Encapsulating chemically labile bioactive agents in nanoparticles enhances *in vivo* performance, providing enhanced absorption, decreased toxicity, extended circulation times, and controlled release of bioactive compounds (Li, Jin et al., 2018). Metal nanoparticles have drawn attention due to their large specific surface area, shape, controllable size and enhanced bioavailability of polyphenolic compounds (Sahraeian et al., 2024). Metal oxide and magnetic nanoparticles are utilized in various biomedical applications, including gene therapy, photodynamic therapy, drug delivery, medical imaging, dentistry and wound healing (Zhao et al., 2021). Therapeutic and diagnostic agents can be encapsulated, covalently attached, or adsorbed using iron oxide nanoparticles (IONPs) (Low et al., 2022). IONPs exhibit promising potential as effective drug delivery systems owing to their expansive surface area and diminutive size (Sankaranarayanan et al., 2022). IONPs provide several advantages over free drugs when iron oxide is integrated into drug delivery systems. The conjugated drug can effectively accumulate in tumor sites due to the notable ability of IONPs to be localized (Alphandéry, 2019). For instance, the immobilization nanocarrier of epigallocatechin-3-gallate (EGCG) and iron oxide nanoparticles (Maghemite) is far from auto-oxidation and degradation. With remarkable protein kinase CK2 inhibition, this composite can deliver EGCG to cancer cells (Saha et al., 2023).

IONPs are usually considered biocompatible and widely used in biomedical applications (Mollarasouli et al., 2021). Furthermore, magnetic nanoparticles possess unique characteristics, such as the ease of modification of their surface chemistry to achieve better compatibility and selectivity. Vast amounts of biomolecules aid in capping the metal salts' surfaces and turning them into metallic nanoparticles (NPs) (Sidhu et al., 2022). It has been possible to successfully create different metal oxide nanoparticles through green synthesis using a variety of bio-sources, such as plant extracts and microorganisms like bacteria, fungi, and algae (Chugh et al., 2021). As shown in Table 1, numerous studies are concentrated on synthesizing IONPs using particular bioactive molecules from polyphenols (Jamwal et al., 2018).

Table 1
Synthesis of magnetic nanoparticles using specific bioactive molecules from polyphenols

Polyphenolic compound	Metal nanoparticle	Improved target properties	References
Green tea extracts	Iron oxide (FeONPs)	Synergetic removal of melanoidin from ethanol distillery simulated model wastewater	Akhtar et al. (2023)
Polyphenols in the leaf extract (*Canthium coromandelicum*)	IONPs	Antibacterial activity against *Staphylococcus aureus* and *Salmonella typhi*.	Sudhakar et al. (2021)
Green tea	FeNPs	Removal of metal (loids) in acid mine drainage	Pan et al. (2023)
Tea polyphenols	Zero-valent iron NPs	Electrochemical determination of Hg2+	Bao et al. (2022)

Table 1 *(continue)*

Polyphenolic compound	Metal nanoparticle	Improved target properties	References
Green tea extract	FeNPs	Low ecotoxicological risks and the suitability of these green-synthesized FeNPs for environmental remediation purposes	Plachtová et al. (2018)
Green tea polyphenols	Fe3O4 NPs	Removal of dye pollutants from aqueous solution	Singh et al. (2017)
EGCG	FeNPs	Enhanced photothermic/chemodynamic cancer combination therapy	Su et al. (2023)
Polyphenols and caffeine	FeNPs	Selective removal of cationic dyes	Xiao et al. (2020)

The Beneficial Effects of Iron Oxide Nanoparticle Conjugation with Polyphenol

By using IONPs, a number of polyphenols have been used to boost their efficacy. A study found that the bioavailability of quercetin-conjugated dextran-coated Fe3O4 nanoparticles in the brain is about ten times that of free quercetin (Enteshari Najafabadi et al., 2018). Another study shows that encapsulation of catechin as a potent polyphenol drug in IONPs enhances its bioavailability, suggesting that NPs are an effective vehicle for targeted drug delivery in cancer therapy (Nobahari et al., 2023). EGCG was utilized to synthesize IONPs. These nanoparticles demonstrated minimal organ toxicity and were efficient for combined hyperthermia, drug delivery, and real-time magnetic resonance imaging (MRI) in mice tumor models (Yin et al., 2017). Additionally, dendrimerized magnetic nanoparticles have been created as EGCG delivery vehicles. EGCG-loaded nanoparticles induced human cervical cancer cells to undergo controlled cell death (Aggarwal et al., 2022). Research revealed a robust interaction between the iron oxide nanoparticles and curcumin. It was discovered that curcumin-capped magnetic nanoparticles and blue light irradiation could inhibit *Staphylococcus aureus* up to 60% of inhibition (Cañon-Ibarra et al., 2023).

Metagenomics Reveals Tea Polyphenols' Association with Intestinal Microbiota and Enhanced Bioavailability

Tea polyphenols (TPs) have limited intestinal absorption, contributing to low systemic bioavailability (Liu et al., 2018). In contrast, TPs are highly concentrated in the gastrointestinal tract (GIT), where the intestinal microbiota catabolizes them to phenolic acid (Stalmach et al., 2010). The numerous health advantages and varied bioactivities linked to green tea's polyphenols have led to the application of a number of techniques to study their biochemical mechanisms. Metagenomics has become a prominent method (Garza & Dutilh, 2015). The metagenomics approach includes a sequence of stages, starting with environmental sample collection, then metagenomics deoxyribonucleic acid (DNA) isolation, metagenomics library

creation, screening, and library modification. This technique uses 16S rRNA gene sequencing and whole-genome shotgun sequencing (Ilett et al., 2019).

Green tea supplements high in polyphenols can alter the gut microbiota's composition, increasing beneficial bacteria abundance, particularly *Bifidobacterium* and *Lactobacillus*, highlighting the positive impact of polyphenols on gut microbiota (Yuan et al., 2018). Polyphenols' effects on the gut microbiota of healthy individuals have been clarified by recent clinical interventions using metagenomics technology Table 2.

Gut microbiota can break down the heterocyclic structures of catechins into smaller compounds like phenylvalerolactones (PVLs) and phenylvalericacids (PVLa) through C-ring fission, glyosidic connections and A-ring fission. It is possible for these recently formed microbial metabolites to eventually cross the colon's epithelium and enter the systemic bloodstream (Chen, Zhu, et al., 2020). As main reaction products from catechins, valerolactone and phenolic acids increase, so does their absorption through the intestinal wall. Consequently, these compounds have improved bioavailability and are easier for the large intestine to absorb (Liu et al., 2018). Therefore, it is critical to consider how colonic metabolites and gut microbiota metabolism influence the bioavailability of TPs. According to earlier research on humans, 39% of TPs flavan-3-ol were bioavailable. Nevertheless, the bioavailability rose to 62% when colonic metabolites were taken into account (Calani et al., 2012).

As illustrated in Figure 2, TPs have the potential to improve metabolic health by promoting commensal abundance, decreasing pathobionts, and enhancing the diversity, richness, and metabolic processes of gut microbiota. Gut microbes are essential to maintaining optimal health by promoting healthy digestion, controlling the immune system and averting opportunistic infections (Dey et al., 2021). The catechins in tea polyphenols have been demonstrated to have antimicrobial properties against gut pathobionts and to promote the growth of beneficial bacteria, such as *Lactobacillus/Enterococcus* groups and *Bifidobacterium* spp., while inhibiting the growth of pathogenic bacteria such as *Eubacterium-Clostridium* groups, *Bacteroides-Prevotella*, and *Clostridium histolyticum*. The health advantages could be attributed to the interaction between EGCG and gut flora (Bond & Derbyshire, 2019).

Table 2
Summary of polyphenols' effects on the gut microbiota using metagenomics approach

Polyphenol	Technology used	Objective	Target (Result)	Reference
Oolong tea (OT)	16S rRNA gene sequencing	To examine the interventive effect of daily OT intake on body composition, gut microbiota, metabolic profile, and gastrointestinal functions of healthy subjects.	Changed microbial diversity in the gut. Enhanced the growth of *Bacteroides* and *Prevotella*, reduced the number of Megamonas, and enhanced digestive health.	Li et al. (2023)

Table 2 *(continue)*

Polyphenol	Technology used	Objective	Target (Result)	Reference
Tea polyphenol (TP) and epigallocatechin gallate (EGCG)	16S rRNA	To study how TP and EGCG affect liver fat accumulation and hyperlipidemia using physiology, genomics, and metabolomics.	TP enhanced the number of good bacteria (*Faecalibacterium*, *Parabacteroides*, *Akkermansia*, and *Bacteroides*), and EGCG encouraged the growth of bacteria that produce acid (*Desulfovibrio*, *Butyricimonas*).	Wen et al. (2023)
Dried black raspberry polyphenols	16S rRNA gene	To analyze how polyphenols and gut microbiotas from different sources interact bilaterally.	Identifying the essential bacterial species involved in synthesizing bioactive phenolic metabolites for colonic absorption, such as *B. vulgatus, E. rectale, and F. prausnitzi*i. Furthermore, certain phenolics, such as gallic acid, 3-(4-hydroxyphenyl) propionic acid, and 5-(3,4-dihydroxyphenyl) valeric acid, were able to suppress pathogenic genera while enhancing beneficial ones.	Chan et al. (2023)
Polyphenols from *Gnetum gnemon* Linn. leaves	Next generation sequencing (NGS)	The effects of vacuum-dried *Gnetum gnemon* var. tenerum leaf powder on the characteristics of gut health.	Elevated Bacteroides levels and significantly higher *Bifidobacterium* numbers	Anisong et al. (2023)
Mulberry leaf extracts	16 S rRNA	A multi omics approach that included gut microbiota, transcriptional analysis, and SCFA composition analysis was applied to clarify the precise mechanisms through which particular MLEs affect female obesity models.	Modulatory effects on obesity-related gut microbiota (*Firmicutes*-to-*Bacteroidetes ratio*)	Zhao et al. (2024)
Green tea extract	16S ribosomal RNA	To understand the impact of green tea extract on the composition and metabolism of gut microbiota from people with metabolic syndrome.	According to bioinformatics analysis, *Escherichia* and *Klebsiella*'s relative abundance was generally higher, while *Bacteroides*, *Citrobacter*, and *Clostridium*'s relative abundance was significantly lower.	Zhang, Xu, et al. (2022)

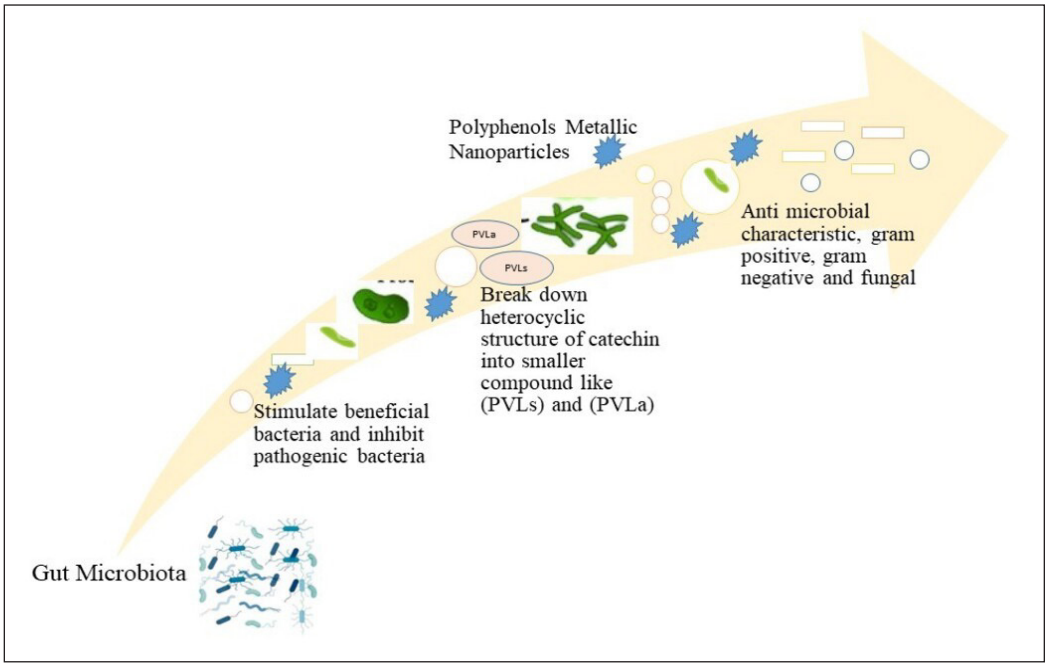

Figure 2. Interaction between polyphenol metallic nanoparticles and gut microbiota

Exploring the Influence of Metallic Nanoparticles on Gut Microbiota

The metagenomics approach has been used to investigate the impact of nanoparticles on gut microbiota, providing enhanced awareness of these particles' effects on microbial communities (Ma et al., 2023). Most nanomaterials possess antibacterial characteristics that effectively protect against common bacteria. As demonstrated in Table 3, metal oxide

Table 3
The effect of metallic nanoparticles on gut microbiota

Metallic nanoparticles	Gut microbiota	Effect	Reference
Titanium Dioxide (TiO_2 NPs)	*Lactobacillus*, *Firmicutes*, and *Proteobacteria*	Microbiota diversity and composition	Sohm et al. (2015)
TiO_2 NPs	*Proteobacteria*	Microbiota composition and structure	Li, Yang, et al. (2018)
Silver Nanoparticles (Ag NPs)	*Lactobacillus and E. coli*	Microbiota diversity and composition	Williams et al. (2015)
Zinc Oxide Nanoparticles (ZnO NPs)	*Lactobacillus*	Microbiota diversity and composition	Zhu et al. (2023)
Copper-loaded chitosan nanoparticles (CNP-Cu)	*Bifidobacterium and Lactobacillus*	Microbiota abundancy	Han et al. (2010)
Nano-Al(2)O(3)	*Firmicutes, Proteobacteria* and *Bacteroidetes*	Microbiota structure	Zhang, Li, et al. (2022)

nanomaterials such as nano-TiO_2, ZnO, and Ag_2O have the capability to inhibit common bacteria such as *Staphylococcus aureus*, *Bacillus subtilis*, and *E. coli* (Hajipour et al., 2012). Gram-positive, Gram-negative, and fungal microorganisms are poisoned by nano-TiO_2 and ZnO (Daou et al., 2018).

Investigating the Impact of Polyphenol-Metallic Nanoparticle Interaction from a Proteomic Perspective

Recent developments in proteomics have resulted in the identification of numerous biomolecules, primarily proteins, as disease markers for diagnosing and detecting infectious diseases, autoimmune disorders, and cancer (Mazzara et al., 2015). Research on tea has extensively used metabolomics and proteomics techniques, which can offer a thorough understanding of biological processes at the "protein-metabolite" level (Chen, Shi, et al., 2020) for instance, applying a proteomic approach allowed for identifying changes in the expression of multiple tumor-associated proteins in A549 cells following treatment with green tea (Lu et al., 2009; Singh et al., 2010). Additionally, a study was carried out employing mass spectrometry and a 2D gel-based proteomic analysis to examine the effects of green tea polyphenols (GTPs) on ovariectomized rats. The results demonstrated the potential estrogenic effects of GTPs and their antioxidant qualities, as demonstrated by the downregulation of catechol-O-methyl transferase and the upregulation of adenosine triphosphate synthase and superoxide dismutase-1 (Shao et al., 2011). Furthermore, mass spectrometry and two-dimensional gel electrophoresis were used to measure colon protein expression. Protein identification in response to green tea polyphenols revealed a decreased abundance of transcripts and proteins linked to fibrinogenesis and immune and inflammatory response pathways (Barnett et al., 2013).

Over the years, there has been a steady increase in nanotechnology applications in proteomics (Li et al., 2013). By using nanoparticles in proteomics (nanoproteomics), the proteome could be explored, which could provide the basis for the identification of biomarkers and result in the identification of numerous proteins in intricate biological materials (Abdelhamid & Wu, 2015). The research employed proteome modulation caused by curcumin nanoformulation was investigated using quantitative proteomic methods based on Sequential Window Acquisition of All Theoretical Mass Spectra (SWATH-MS). The result confirmed that curcumin nanoformulation positively influenced the expression of several proteins involved in TGF-β-mediated fibrosis (Ceccherini et al., 2023).

In addition, several studies have used proteomic analysis to examine cellular response to metal nanoparticles. For instance, there was significant deregulation of different pathways related to protein homeostasis, namely eIF2, eIf4/p70S6K, and unfolded protein response signaling after exposure to ZnONPs (Doumandji et al., 2020). Moreover, proteomic information on silver nanoparticles exposed HepG2 cells verifies that these metallic

nanoparticles caused changes in inflammatory responses, mitochondrial dysfunction, posttranslational protein modification, redox stress, and other cellular parameters (Braeuning et al., 2018; Gao et al., 2022). Similarly, using *Withania coagulans* plant extract for the biological synthesis of the Fe2O3NP, proteomic analysis revealed that chemical Fe2O3NPs produced 41 differentially expressed proteins, compared to 103 produced by biological Fe2O3NPs. These proteins could be used in therapeutic and diagnostic approaches (Hasan et al., 2023).

Limited proteomic studies have focused on green tea and metallic nanoparticles. A study confirmed that green tea-synthesized magnetic nanoparticles accelerate the microwave digestion of proteins, as analyzed by MALDI-TOF-MS (Sharma & Tapadia, 2016). One intriguing aspect of green synthesis and outer layer covering in nanoparticles (NPs) is that the metallic core is hidden by the organic corona in the NPs, making the metallic core biocompatible (Spagnoletti et al., 2021).

CONCLUSION

This review emphasizes various advantages and possible synergies of iron oxide nanoparticles and green tea polyphenols combination. This conjugation offers enhanced therapeutic potential owing to its targeted delivery and increased bioavailability. Furthermore, metagenomics research highlights the connection between intestinal microbiota and tea polyphenols, indicating possible consequences for improved bioavailability and gut health. Studies on how the makeup of the gut microbiota is affected by metallic nanoparticles provide more illumination on how these particles affect microbial diversity. The biological processes of polyphenol-metallic nanoparticle interactions have been comprehensively understood at the protein level through proteomic analyses, yielding valuable insights into the molecular mechanisms underlying these interactions. Developing new therapeutic approaches may be aided by additional research using proteomics and metagenomics techniques, which may offer deeper insights into the molecular pathways underlying interactions between polyphenols and metallic nanoparticles.

ACKNOWLEDGEMENTS

The authors acknowledge the Universiti Putra Malaysia for financing this study (GP-IPS/2023/9772000).

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