Journal of Mines, Metals and Fuels, *71(10): 1764-1774; 2023. DOI: 10.18311/jmmf/2023/35062*

Print ISSN : 0022-2755

Journal of Mines, Metals and Fuels

Contents available at: *www.informaticsjournals.com/index.php/jmmf*

Metal-Infused Polyphenol-enriched Phyto-fabricated Nanoparticles: an In-depth Review of their Potent Prebiotic Properties

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Abstract

In light of its potential health benefits, including as improved gut health and management of the gut microbiota, herbal extracts have witnessed a major increase in demand as prebiotics in recent years. Many studies have demonstrated that polyphenol-rich herbal extracts can work as prebiotics by encouraging the growth of beneficial gut flora. Unfortunately, the limited solubility and stability of these herbal extracts, as well as their susceptibility to breakdown in the gastrointestinal system, can limited their bioavailability and efficiency. To address these limitations, the integration of metal nanoparticles has emerged as a promising strategy for the efficient delivery of herbal extracts, affording heightened bioavailability and precise targeting of the gut microbiota. In this paper, we present current breakthrough in metal infused nanoparticle-based assessment of herbal extracts as efficient prebiotics, with an emphasis on formulation, characterization, and biological activity. The integration of metal nanoparticles into polyphenol-rich herbal extracts represents a cutting-edge approach to enhancing the prebiotic properties of these compounds. Metal-infused polyphenol-enriched phyto-fabricated nanoparticles hold great promise for improving gut health and modulating the gut microbiota, offering innovative solutions to address the limitations associated with traditional polyphenol delivery. Furthermore, extracts of polyphenol-rich medicinal herbs such as rosehip flower, hibiscus flower, mango bark, bamboo stem, green tea, pomegranate, and dhataki flower have been investigated to assess the viability of employing these phyto generated metal infused nanoparticles as a potential prebiotic.

Keywords: *Bioavailability, Herbal Extract, Polyphenol, Prebiotics, Probiotics, Nanoparticles*

1.0 Introduction

The gut microbiota is essential for human health and has been related to a variety of disorders including inflammatory bowel disease, obesity, and diabetes[1]. Prebiotics are no digestible dietary substances that specifically stimulate the formation and activity of healthy gut bacteria[2,3]. Due to their capacity to alter the gut flora, herbal extracts, which include a range of bioactive compounds, have been studied as possible prebiotics[4]. However, the limited solubility and stability of these herbal extracts, together with their susceptibility to digestive system breakdown, might limit their bioavailability and efficiency[5]. Nanoparticles have been suggested as an efficient method of delivering herbal extracts to overcome these difficulties, enabling increased bioavailability and tailored administration to the gut flora[6,7].

This comprehensive review will provide a broad overview of how Phyto-fabricated nanoparticles made from herbal extracts high in polyphenols

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may be used as possible prebiotics to support gut health.

2.0 Gut Micro Biota and Its Importance

The human intestinal system has a complicated and diverse microbial ecology that is crucial to human health. According to estimations from Ley *et al.* and Qin et *al.*, our gut contains 100 times more genes and up to 1000 distinct bacterial species than the human genome[8,9]. Because of its considerable impact on human welfare, including host metabolism, physiology, nutrition, and immunological function, this community is sometimes referred to as our hidden metabolic organ[10]. It is well recognized that the intestinal Micro biota of healthy people offers a variety of health advantages such as pathogen defence, nourishment, homeostasis, and immunological regulation[11].

According to conventional wisdom, infants' intestines are either sterile or contain only a very small number of bacteria after birth[12]. But, after delivery, the infant's gastrointestinal tract quickly becomes colonized. Many factors, such as the mode of birth, the kind of feeding, or the use of antibiotics, prebiotics, or probiotics, can have a significant impact on the composition of the infant's gut[13]. There is emerging evidence that the gut microbiota has a significant impact on gut health and sickness. Modulating the gut microbiota as a therapeutic strategy to treat chronic illness should thus be researched. Prebiotics and probiotic supplements can modify gut flora to improve host health[10].

3.0 Prebiotics and their Advantages

Prebiotics are dietary ingredients that, in addition to boosting the immune system, promote the proliferation of probiotic bacteria in the human stomach[14]. The relationship between prebiotics and human health has drawn more attention in recent years. Prebiotics are a type of nutrition that the gut bacteria digest and use to nourish the intestinal flora. When they are broken down, they release short-chain fatty acids into the bloodstream, affecting not just the digestive system but also other organs[15].

Prebiotics are non-digestible food components that benefit the host by stimulating one or more types of bacteria in the colon to grow and operate in order to promote better human health[16]. According to a study conducted by Tzounis *et al.*, flavanols have been demonstrated to encourage the formation of lactic acid bacteria in both *in vitro* and *in vivo* screening[17]. Prebiotics give gut bacteria energy, enabling them to alter their makeup and activity. The ability of different bacterial species to ferment various prebiotics varies, and the chain length of the prebiotic also plays a role. Although certain by-products of prebiotic fermentation may be hostile, others can act as substrates for other bacteria. Prebiotics can also impact the gut environment by lowering pH levels, which can encourage Firmicutes to produce butyrate and alter the Micro biota in the gut[15].

4.0 Herbal Extracts as a Prebiotic

Herbal extracts have been studied as potential prebiotics, or chemicals that promote the growth and activity of beneficial bacteria in the stomach. Prebiotics are a type of dietary fibre that is resistant to digestion and is preferentially digested by the gut Microbiota, creating Short-chain Fatty Acids (SCFAs) that nourish the cells lining the colon and have other health benefits.

Polyphenols have aromatic rings with one or more hydroxyl groups in their chemical structure, which can range from a simple phenolic molecule to a complicated high-molecular mass polymer. Polyphenols are secondary plant metabolites[18]. These chemicals are more likely to interact with intestinal bacteria due to their extensive metabolism in the large intestine and restricted bioavailability. In reality, there is a bidirectional interaction between the gut microbiota and polyphenols, with bacteria influencing phenolic compound activity. By regulating their metabolism and absorption, this interaction can change polyphenols into metabolites that may have a variety of physiological impacts on the host[19].

5.0 Herbal Extracts High in Polyphenols as a Possible Prebiotic

Polyphenols are naturally occurring chemicals found in many fruits, vegetables, and herbs. They've been connected to a variety of health benefits, including anti-inflammatory, antioxidant, and prebiotic properties.

Several studies have found that polyphenol-rich herbal extracts including green tea, grape seed, and olive leaf can work as prebiotics by promoting the growth of beneficial gut bacteria like Bifidobacterium and Lactobacillus[20].

According to Alves-Santos *et al.,* applying a concentration of polyphenol enriched extracts from medicinal herbs can promote probiotic development while inhibiting pathogen antimicrobial action[19]. The precise mechanism by which polyphenols increase SCFA production is unknown. It is thought that an increase in anaerobic microbes, particularly butyrate-producing ones *like* Lactobacillus*, Lachnospiraceae,* and *Ruminococcaceae*, might encourage a spike in SCFA[21]. Another notion is that the polyphenols included in decaffeinated green and black tea decrease the activity of the enzymes-amylase and -glucosidase in saliva and the small intestine. As a result, certain carbs may linger in the large intestine and serve as a substrate for SCFA synthesis[22]. SCFA are the primary mediators linking disease, metabolism, intestinal microbiota, and dietary support[23]. Butyrate study has mostly focused on the existence of butyrate-producing bacteria, as well as butyrate itself, which is thought to have favourable effects on human health. This implies that it could be used as an indicator of prebiotic influence[24].

Because of their antioxidant, anti-inflammatory, and prebiotic qualities, polyphenol-rich medicinal herbal extracts such as rosehip flower, hibiscus flower, mango bark, bamboo stem, green tea leaves, pomegranate rind, and dhataki flower have been found to provide a variety of health advantages. Recently, researchers have been exploring the possibility of using polyphenol enriched herbal extracts as potent prebiotics.

The possible prebiotic effects of rose hip extract on the gut microbiota have been investigated. The fruit of the rose plant, or rose hips, is a good source of vitamin C, polyphenols, and other bioactive substances that may be beneficial for your health[25]. Rose hip extract may promote the growth of beneficial bacteria like Bifidobacteria and Lactobacilli while inhibiting the growth of harmful bacteria like *E. coli* and *Clostridium perfringens*, according to numerous *in vitro* and animal studies. Potential prebiotic effects on the gut microbiota of rose hip extract have been investigated. Rose hips, which are the fruit of the rose plant, are a great source of vitamin C, polyphenols, and other bioactive substances that may be beneficial for your health[25]. According to a number of in vitro and animal studies, rose hip extract may promote the growth of beneficial bacteria like Bifidobacteria and Lactobacilli while inhibiting the growth of harmful bacteria like *E. coli* and *Clostridium perfringens*.

Hibiscus flowers are high in bioactive substances like phenolic acids, flavonoids, anthocyanins, and polysaccharides. Several components have been investigated for possible health advantages, including prebiotic effects[26]. Hibiscus polysaccharides, which are found in the blooms of the plant, have been proven to have prebiotic characteristics by favourably promoting the growth of beneficial bacteria like Lactobacillus and Bifidobacterium. In addition to their prebiotic effects, hibiscus flowers also have anti-inflammatory, antioxidant, and hypoglycaemic effects[27]. These properties make hibiscus flowers a potential functional food ingredient for promoting gut health and overall wellbeing.

On the prebiotic benefits of mango bark, there is little study. The potential health advantages of numerous bioactive compounds found in mango bark, including tannins, flavonoids, and phenolic acids, have been researched[28]. While some research has suggested that certain components in mango bark, such as tannins, may have prebiotic effects, more research is needed to confirm these findings.

Bamboo stem may be a viable source of prebiotic fibre, according to the minimal study that has been done on its prebiotic benefits[29]. Bamboo stems have polysaccharides that cannot be broken down by human enzymes and, as a result, can specifically promote the development and activity of good bacteria in the gut Bamboo stem extract, according to Azmi *et al.*, can specifically encourage the growth of Bifidobacterium and Lactobacillus, which are known to have probiotic qualities[30]. Additionally, research on bamboo stem extract has revealed that it possesses anti-inflammatory and antioxidant qualities, which may aid in enhancing intestinal health and general wellbeing. To improve intestinal health, adding bamboo stems or bamboo shoot extract to your diet may be a helpful strategy.

Green tea leaves have been examined for their possible prebiotic effects on the gut flora. The catechins in green tea, especially epigallocatechin gallate (EGCG), have been proven to have prebiotic characteristics by specifically promoting the growth of beneficial bacteria in the stomach. Alves *et al.,* claim that the probiotic bacteria

Lactobacillus and Bifidobacterium can grow more readily when EGCG is present[19]. Green tea extract has also been seen to lessen the amount of potentially harmful bacteria in the gut, including Clostridium and Fusobacterium. Green tea leaves also contain a lot of fibre, which can encourage the development and activity of good bacteria in the stomach. Short-Chain Fatty Acids (SCFAs), which have been linked to a variety of health benefits, can be produced by gut bacteria using the fibre in green tea leaves as a substrate[31]. The polyphenols in decaffeinated green and black tea, which have been demonstrated to lessen the activity of the enzymes-amylase and -glucosidase in saliva and the small intestine, could be the basis of an alternative idea. Because of this, some carbs may persist in the large intestine and serve as a substrate for SCFA synthesis[22].

Punicalagin, a polyphenol found in high concentrations in the rind of pomegranates, has been studied for its potential prebiotic effects on gut flora. Prebiotics are indigestible food ingredients that specifically promote the growth and activity of beneficial bacteria in the digestive tract. Punicalagin from pomegranate rind, according to Li *et al.*, can limit the growth of harmful bacteria like *Escherichia coli* and *Clostridium perfringens* while promoting the development of good bacteria in the gut like Bifidobacterium and Lactobacillus[32]. Punicalagin has also been discovered to boost the production of Short-Chain Fatty Acids (SCFAs) in the gut, which have been associated to a number of health advantages, such as improved glucose management, reduced inflammation, and improved gut barrier function. Pomegranate peel has been reported to have prebiotic effects in addition to anti-inflammatory, antioxidant, and antibacterial qualities, which may contribute to its potential health benefits.[33]

Ayurveda has long prized the Dhataki flower, also known as *Woodfordia fruticosa*, as a medicinal plant because of the variety of health benefits it offers. The dried blooms of the Dhataki tree have been used as an astringent to treat ulcers, wounds, and diarrhoea in southern Asia[34,35]. Dhataki flower may affect the gut microbiome prebiotically, according to recent studies. Flavonoids, phenolic acids, and tannins are just a few of the bioactive substances found in dhataki flowers, and studies have shown that they have antioxidant, anti-inflammatory, and antibacterial activities[36-38]. In addition, it has been discovered that certain of these substances, particularly the tannins, have prebiotic effects on the gut microbiome by specifically promoting the growth of good bacteria like Bifidobacterium and Lactobacillus[39,40]. According to a study by Das *et al.,* a Dhataki flower extract greatly enhanced the development of Bifidobacterium and Lactobacillus *in vitro* while inhibiting the growth of harmful bacteria like *Escherichia coli* and *Staphylococcus aureus*[34]. According to the experts, the high concentration of tannins and other polyphenols in Dhataki flower is what causes its prebiotic benefits.

As a potential source of prebiotics, the current review largely focuses on botanical extracts rich in polyphenols. While these findings are promising, there is no conclusive evidence to support the prebiotic effects of aforementioned medicinal herbs. However, in detailed research is required to confirm their prebiotic effects and its potential benefits for human health.

6.0 Limitation of using Herbal Extracts as a Prebiotic

Prebiotics have been used with herbal extracts to promote the development of good gut flora. Despite numerous potential health advantages, there are a number of drawbacks to using plant extracts as prebiotics.

6.1 Lack of Standardization

One of the major limitations of herbal extracts as prebiotics is the lack of standardization. Different extraction methods can yield different chemical compositions, leading to inconsistent results in terms of their prebiotic effects[41,42].

6.2 Variable Composition

Herbal extracts may include a wide range of substances, some of which may be poisonous or hazardous to gut microbes. Additionally, different plant species, environmental circumstances, and processing techniques might affect the content of herbal extracts[43,44].

6.3 Limited Research

The prebiotic effects of certain plant extracts, notably in humans, have not gotten much attention. Despite some promising findings, more research is needed to determine the long-term efficacy and safety of using plant extracts as prebiotics[45].

6.4 Regulatory Issues

The regulation of herbal extracts can be a challenge, particularly in terms of ensuring quality and safety. In many cases, herbal extracts are marketed as dietary supplements rather than drugs, which means they are subject to less rigorous testing and oversight[46].

6.5 Interactions with Medications

Herbal extracts can interact with certain medications, potentially causing harmful side effects. This can be particularly problematic for individuals who are taking multiple medications or who have underlying health conditions[47].

6.6 Limited Drug Delivery

Herbal extracts have been used for centuries as traditional medicines. However, the use of herbal extracts in modern medicine has some limitations. One of the limitations is reduced drug delivery. The low solubility and permeability of herbal extracts, according to Kesarwani *et al.*, contribute to their low bioavailability[48]. This means that when herbal extracts are administered orally, they may not be absorbed efficiently into the bloodstream, leading to reduced drug delivery.

To address this issue, researchers have created revolutionary medication delivery devices based on nanotechnology. In a review article, it is discussed how nanotechnology-based medication delivery systems might increase the bioavailability and effectiveness of herbal remedies. According to Bonifacio and co-worker's, the solubility and permeability of herbal extracts can be increased by these methods, which will result in enhanced medication delivery[49].

Although there have been improvements, using herbal medicines still raises safety questions. Many studies talk about problems with toxicity that come up when using herbal medicines[45,50]. Additionally, pharmaceutical companies have reduced their focus on natural products due to several drawbacks such as inconsistent quality and quantity of active compounds in natural products[51,52].

Although plant extracts have been used for centuries as traditional medicines, their application in modern medicine is constrained by problems including decreased drug delivery brought on by poor solubility and permeability. Researchers developed brand-new drug delivery systems based on nanotechnology to overcome this issue. However, there are still issues with safety that need to be resolved when using herbal medicines.

7.0 Nanoparticle-based Delivery Systems

Nanoparticle-based delivery techniques have been developed to boost the bioavailability and bioactivity of herbal extracts enriched with polyphenols. By increasing phytochemical bioactivity and bioavailability, these delivery systems work as drug carriers that can overcome some of the disadvantages that herbal medicines have[53]. Nanotechnology is a potential method for boosting the efficacy of natural products[54].

Different types of nanoparticles, including polymeric nanoparticles (PNPs), nanocapsules, and nanospheres, have been used in drug delivery systems[55]. *Prunus avium* L. cherry extracts that are rich in polyphenols have been enclosed in PLGA (Poly Lactic-co-glycolic Acid), a biodegradable polymer[56]. Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) are other nanoparticle kinds that have been used in the creation of herbal medicines.[53]

A promising method for administering plant extracts that have been enhanced with polyphenols is nanoparticle-based delivery systems. These techniques can increase the bioavailability, site-specificity, and controlled release of nanoparticle medicines. To deliver natural substances like polyphenols, polymeric nanoparticles like nanospheres and nanocapsules are ideal drug delivery vehicles[57].

Phyto-fabricated nanoparticles have several advantages as prebiotics over traditional prebiotic compounds[58]. They are biocompatible, biodegradable, and can be easily synthesized from natural sources without the need for complex chemical reactions[59]. In addition to their prebiotic properties, phyto-fabricated nanoparticles have potential applications in the fields of drug delivery, wound healing, and cancer therapy due to their biocompatibility and ability to target specific cells and tissues[60,61].

It has been shown that nanoparticle-based delivery technologies improve the biological activity of herbal extracts as prebiotics[62]. For instance, by specifically encouraging the growth of advantageous gut bacteria, the encapsulating of ginger extract in chitosan nanoparticles improved its stability and increased its prebiotic effect[63]. Similar to this, resveratrol's solubility and stability were increased through its encapsulation in solid lipid nanoparticles, enabling targeted administration to the colon and regulation of the gut microbiota[64].

Nanoparticle-based delivery methods have emerged as a viable technique for increasing the bioavailability and efficacy of herbal extracts as prebiotics[5]. Nanoparticles can improve the stability and solubility of herbal extracts and enable targeted administration to the gut bacteria[65]. Further study is required to optimize the formulation and characterisation of nanoparticles for herbal extract administration, as well as to assess their safety and efficacy *in vivo*. Overall, the adoption of nanoparticle-based delivery methods has the potential to increase the potency of herbal extracts as prebiotics for improving gut health and avoiding illness.

Nanoparticles have been suggested as a successful delivery technique to get around the drawbacks of herbal extract as a prebiotic. By boosting their solubility and stability, nanoparticles can prevent the gastrointestinal tract from degrading herbal extracts and increase their bioavailability[66]. Additionally, nanoparticles can be created to target particular regions of the gastrointestinal system, enabling localised distribution of the herbal extracts to the gut Micro[67,68].

8.0 Preparation of Nanoparticles or Encapsulation of Extracts with Prebiotic Potential

The preparation of nanoparticles or encapsulation of extracts with prebiotic potential involves several steps, including selection of appropriate materials, formulation optimization, and characterization of the final product[69]. Here is an elaboration on each of these steps:

8.1 Selection of Materials

The choice of suitable materials is the first step in creating nanoparticles or encapsulating extracts. The material selection is based on the required characteristics of the finished product, including solubility, stability, and biocompatibility. Lipids, polymers, and metals are often employed materials in the creation of nanoparticles[70,71]. For instance, polymers like chitosan can be used to create polymeric nanoparticles, whereas lipids like phospholipids can be utilised to create liposomes[72,73]. Additionally, metallic nanoparticles can be created using metals like gold[74].

8.2 Formulation Optimization

The next step is the optimization of the formulation, which involves determining the optimal ratio of materials and the appropriate conditions for nanoparticle formation. The formulation can be optimized using various methods, such as statistical experimental design, response surface methodology, or artificial neural[75]. Particle size, surface charge, drug loading, and drug release kinetics are among the formulation variables that are frequently optimised. Based on desirable product characteristics including bioavailability, stability, and targeted distribution, formulation parameters are chosen[76].

8.3 Characterization

The finished product is characterised once the formulation has been optimised to make sure it adheres to the required standards[77]. Measurements of the nanoparticles' or extracts' physical and chemical characteristics, such as their size, shape, surface charge, drug loading, and drug release kinetics, are done during characterization[78]. Dynamic light scattering, transmission electron microscopy, and Fourier-transform infrared spectroscopy are examples of typical characterisation methods. These methods can help guarantee that the nanoparticles or encapsulated extracts fulfil the required standards by providing information on the physical and chemical characteristics of each[79,80]. The prebiotic action and safety of the encapsulated extracts can also be assessed *in vitro* and *in vivo*[81,82].

In conclusion, there are various phases involved in creating nanoparticles or encapsulating extracts with prebiotic potential, including choosing the right components, adjusting the formulation, and characterising the finished product. These procedures are essential for ensuring the manufacturing of prebiotic-potential nanoparticles or encapsulated extracts that are secure, efficient, and high-quality[83].

9.0 Conclusion

The potential of phyto-fabricated nanoparticles as a prebiotic has been addressed in this review. For polyphenol-enriched herbal extracts, nanoparticle-based delivery systems have been investigated, and nano-strategies have significantly increased the utilisation of polyphenols. High-molecular-weight phenolic compounds bioavailability has been shown to be improved by encapsulation, and polyphenols' bioavailability-related drug delivery systems have also been extensively used. The review highlights how these nanoparticles have the potential to improve gut health by encouraging the growth of helpful bacteria and reducing the activity of harmful bacteria. Additionally, it has been discovered that phyto-fabricated nanoparticles contain anti-inflammatory and antioxidant capabilities that may help to further improve general health. In conclusion, phyto-fabricated nanoparticles have a promising future as prebiotics because they can increase the stability and bioavailability of herbal extracts high in polyphenols. However, more investigation is required to completely comprehend the mechanisms underlying these effects and to establish the ideal dosages for secure and efficient use. Overall, this review suggests that phyto-fabricated nanoparticles have great potential as a prebiotic supplement for improving gut health and overall well-being.

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