Journal of
Materials in Life Sciences

Vol. 2 No. 1 (2023)

Full Paper

Potential Use of Phytochemical Extract as Prebiotic Compounds – A Brief Review

Anis Athirah Kharuddin[a], Rosnani Hasham[a,*], Fathilah Ali[b], Nadia Adrus[a], Jamarosliza Jamaluddin[a], Roshanida Abdul Rahman[a], Mariani Abdul Hamid[a], Harisun Yaakob[a]

[a] Department of Bioprocess and Polymer Engineering, Faculty of Chemical and Energy Engineering, Universiti Teknologi Malaysia, 81310 Johor Bahru, Malaysia
[b] Department of Chemical Engineering and Sustainability, Kulliyyah of Engineering, International Islamic University Malaysia (IIUM), Jalan Gombak, 53100 Kuala Lumpur, Malaysia

Article history
Received
25 January 2023
Revised
5 April 2023
Accepted
6 April 2023
Published online
25 May 2023

*Corresponding author
r-rosnani@utm.my

Abstract

Our gastrointestinal tract's (GI) functioning is influenced by a diverse collection of bacteria. Prebiotics are one of the most promising strategies for changing the composition of the gut microbiota and the metabolic process. Prebiotics can be thought of as a 'food' for probiotics in general. Prebiotics in the diet have been shown in numerous studies to be an effective way to manipulate the intestinal microbiota through diet. This topic has attracted widespread attention and is being managed for the benefit of human health. Because of the rising demand for prebiotics, a new source of prebiotics is needed such as plants, one that is reasonably inexpensive when compared to commercially available prebiotics. Turmeric and *Garcinia atroviridis* are common and cheap cooking ingredients used in Malaysia that are rich in dietary polyphenols and able to modulate gut and intestinal microbiota. Therefore, the purpose of this review is to emphasize the prebiotic potential of naturally occurring non-digestible carbohydrates in various plants.

Keywords Prebiotic, turmeric, *Garcinia atroviridis*

1.0 INTRODUCTION

Today's consumers are more conscious of the choice of food they consume and gradually look for food with beneficial effects on their health. In recent years, the production of functional foods containing prebiotic ingredients is an area with a very promising market in the food industry due to the scientific evidence of its nutritional value. Hence, a wide variety of beverages and foods that includes dairy products, cereals, bread, and dietary supplements have been incorporated with prebiotics such as inulin and fructooligosaccharide [1]. In the meeting of the International Scientific Association of Probiotics and Prebiotics (ISAPP) of 2016 [2], "prebiotics" was outlined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit".

2.0 PREBIOTICS

Prebiotics are components of food which are used selectively by the gut bacteria, giving a health benefit, especially in stimulating the bifidobacteria growth [3]. Similarly, Alves-Santos et al. [4] described prebiotics as substrates that are utilized selectively by the host of microorganisms offering health benefits on metabolic health, gastrointestinal system, mental health and bone health. In another study, Aquino et al. [5] stated that the rising interest in the study of the prebiotic effect of foods is due to how the intake of these foods affects the gut microbiota and the way its metabolic activity influences the health and well-being of the host. The current ever-increasing demand for prebiotics has resulted in the development of prebiotic production from new novel sources and food industrial wastes [6]. Therefore, it is essential to find novel sources of prebiotics which are relatively cost-effective [7].

3.0 NATURAL SOURCES OF PREBIOTICS

Compounds with prebiotic activity occur naturally in many whole foods. Plants with possible prebiotic properties have been reported as good sources of indigestible carbohydrates. Carbohydrate components in plants with prebiotic potential include polysaccharides in plant cell walls, for example, xylans and pectin.

The plant cell walls component that is made of main polysaccharides, oligosaccharides cellulose and hemicellulose are known as fibers. Fibers are well-recognized for their health benefit. According to Barber et al. [8], it is reported that an increase in dietary fiber intake may aid healthier bowel function, prevent diabetes, and also reduce obesity risk and certain cancer diseases. In another study, it is found that dietary fiber has the potential to be used as prebiotics in the human diet to promote the growth, survival, and metabolic functions of beneficial gut microflora such as *Lactobacillus spp*. and *Bifidobacterium spp*. which are recognized as the most abundant and broadly studied probiotic lactic acid bacteria [9].

Established prebiotics at present are the dietary fiber types especially resistant oligosaccharides including fructooligosaccharides, galactooligosaccharides and inulin which are well-recognized in the studies [3,10]. Oligosaccharides are small molecular carbohydrates comprising up to twenty monosaccharides with degrees of polymerization (DP) between 3 and 10 linked by glycosidic bonds [11]. Since the late 1990s, the beneficial properties of non-digestible oligosaccharides as prebiotic compounds have garnered scientists' interest [12]. According to Wang [13], the inability to digest oligosaccharides by human enzymes represents the ability to resist gastric pH, breakdown by mammalian enzymes and absorption. Furthermore, the prebiotic properties of galactooligosaccharides (GOS), fructooligosaccharides (FOS), and chitooligosaccharides (COS) have been studied extensively whereas the potential prebiotic activity of novel oligosaccharides is presently under investigation [11]. Similarly, Kaur et al. [14] reflected that presently non-digestible carbohydrates, such as FOS, GOS, inulin, and lactulose are the well-known prebiotics whereas IMO, XOS, soybean oligosaccharides, Xylo-polysaccharide, beta-glucans, polydextrose and arabinoxylan have shown prebiotic potential based on clinical evidence.

Interest in oligosaccharides has been rising globally since its prebiotic status and prebiotic potential. In addition, Patel and Goyal [15] also described that oligosaccharides extracted from natural sources might lead to the discovery of novel prebiotics. However, prebiotics validation studies are limited and only include commercial inulin, GOSs, FOSs, and XOSs.

4.0 POTENTIAL OF MALAYSIAN PLANTS AS PREBIOTIC

Extensive studies are now focused on the prebiotic potential of polysaccharides extracted from natural sources such as mushrooms (*Pleurotusostreatus ostreatus*), dragon fruit flesh, coconut kernel cake, bamboo shoots and oil palm empty fruit bunch fibers as summarised in **Table 1**. Now, this review will cover some plants such as turmeric and *Garcinia atroviridis* as prebiotics in the form of polyphenols.

Recently, turmeric has gained interest as a potential prebiotic compound. *Curcuma longa L*. or commonly known as turmeric and locally as kunyit is a valuable herb used as a herbal remedy, dietary spice, food colouring and in the beverage industries [23,24]. The major biologically active compound of turmeric is curcumin. Curcumin is a naturally occurring polyphenolic compound that has at least one aromatic ring structure with at least one hydroxyl group, which is attributed to several properties, mainly particular antioxidant, anti-inflammatory, antimicrobial, anti-angiogenic, and antimutagenic [23,25].

A previous study reported that polyphenols from turmeric such as curcumin, demethoxycurcumin and bisdemethoxycurcumin reduced the gut cardiometabolic risk through inhibition of glucose uptake and appetite modulation by increasing the gut hormone peptide tyrosine-tyrosine postprandial levels [26]. In addition, curcumin is potentially useful in the treatment of irritable bowel syndrome (IBS) due to its ability to modulate the gut microbiota [23,25]. Similarly, curcumin may provide health benefits as various study has suggested that curcumin modulate the intestinal barrier, influence the function of the intestinal barrier, sustain high concentrations in the intestinal mucosa and reduce decreasing high concentrations of bacterial lipopolysaccharide (LPS) levels [23]. In addition, curcuminoids are metabolized by colonic microbiota, modulating bacterial populations and their metabolic activity [27].

G. atroviridis or better known as asam gelugor or asam keeping locally is common endemic fruit tree species in Peninsular Malaysia [28,29]. Ripen fruit of *G. atroviridis* are usually sliced, dried and used as ingredients in numerous local food for their sour taste. In addition, the dried fruit and various plant parts of *G. atroviridis* are also used in Asian folk medicine to treat coughs, to improve improving blood circulation, also as an expectorant and laxative and also for pre and postpartum medication [29,30].

In addition, numerous compounds have been determined from the fruit extract of *G. atroviridis* that includes flavonoids such as quercetin and luteolin, sesquiterpenoids including (-)-β-caryophyllene, β-caryophyllene alcohol and α-humulene and also organic acids such as hydroxycitric acid, ascorbic acid, citric acid, tartaric acid, malic acid, dodecanoic acid, nonadecanoic acid and pentadecanoic acid [31]. According to Abdullah et al. [28] and Taher et al. [30], hydroxycitric acid or HCA is the main fruiting acid in the fruit and rind of Garcinia fruits that are commercialized as weight management products which help to burn fat and utilise spares carbohydrates at rest and during exercise. In addition, sesquiterpenoids such as (-)-β-caryophyllene, β-caryophyllene alcohol and α-humulene are the predominant volatile constituents of *G. atroviridis* fruits and have shown antimicrobial properties by destroying microbial cell membranes and other membranous organelles [30]. However, studies on the antioxidant of *G. atroviridis* fruit extract and its chemical constituents and bioactivities are limited [30,31].

Table 1 List of Malaysian plants as prebiotics and their prebiotic compounds

Plant	Prebiotic compounds	Potential benefit	References
Turmeric	● Curcumin	● Antioxidant and anti-inflammatory ● Enhance proliferation of *Lactobacillus rhamnosus* GG and *Bifidobacterium animalis*	[16]
G. atroviridis	● Flavonoids (quercetin and luteolin) ● Organic acids such as hydroxycitric acid, ascorbic acid and citric acid	Enhance bifidobacteria and lactobacilli, and significantly decreased the number of harmful bacteria (Clostridia)	[17]
Pleurotusostreatus ostreatus	B-glucans	Immunosuppressive activity	[18]
Dragon fruit flesh (*Hylocereus undatus*)	● Oligosaccharides ● β-carotene ● Lycopene ● Vitamin E	Stimulate the growth of lactobacilli and bifidobacteria	[19]
Coconut kernel cake	Soluble polysaccharide	Enhance *L. plantarum* and *L. rhamnosus* proliferation	[20]
Bamboo shoots (*Chimonobambusa quadrangularis*)	Polysaccharide	Enhance proliferation and stimulated higher short chain fatty acid (SCFA) of *B. adolescentis, B. infantis, B. bifidum*, and *L. acidophilus*	[21]
Oil palm empty fruit bunch fibers	Hemicellulose (convert into xylooligosaccharide)	Enhance *B. bifidum* and *L. plantarum*	[22]

4.0 PHYTOCHEMICAL COMPOUND ENHANCED PROBIOTIC FUNCTION

Phytochemicals include prebiotics and probiotics, as well as several chemical compounds such as polyphenols and derivatives, carotenoids, and thiosulfates [32]. The largest group comprises polyphenols. Polyphenols are plants' secondary metabolites that are characterized by having at least one aromatic ring bearing one or more hydroxyl groups attached to their chemical structure [33]. Polyphenols can be found in a broad range of fruits and vegetables such as berries and grapes and food items including cereals, wine, tea, coffee, dark chocolate and cocoa powder [34,35]. According to Singh et al. [35], the major groups of dietary polyphenols include phenolic acids, flavonoids, tannins, stilbenes and diferuloylmethane. Polyphenols can be obtained through the extraction of plant materials. It was reported that different part of the plant produces different phytochemical content due to the plant matrices; thus, the suitability of an extraction process depends on the desired compound [36]. The beneficial phytochemicals can be extracted using a variety of procedures, ranging from basic maceration to the most advanced supercritical fluid extraction technology [37].

Polyphenols and other phenolic compounds can be further grouped into different classes based on the number of phenolic rings and the bonds that join the rings. The basic flavonoid molecule consists of 15 carbon atoms forming two benzene rings with a three-carbon structure in the shape of a heterocyclic ring of pyran or Pyron in between [38] as shown in Fig. 1. On the other hand, the structure of phenolic acids contains a carboxyl group linked to a benzene ring whereas the basic structural unit of anthocyanins is the flavylium ion (2-phenylchromenylium). However, the chemical structure largely influenced the absorption and metabolism in which about 90–95% of dietary polyphenols are not being absorbed in the small intestine thus reaching the colon. Similarly, Dueñas et al. [34] reported that most flavonoids are poorly absorbed in the small intestine while highly metabolized in the large intestine. The low bioavailability and extensive metabolism in the large intestine of these compounds favoured interactions with intestinal microorganisms [4]. The undigested polyphenols accumulate in the large intestine along with the bile conjugates released into the lumen and are exposed to the enzymatic activities of gut microbial [35].

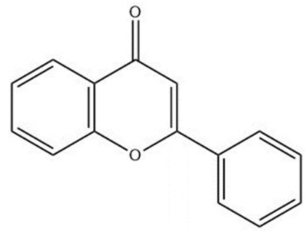

Figure 1 Flavone is a basic structure of a flavonoid molecule.

Even though recently accepted prebiotics is carbohydrate-based, however polyphenols and polyunsaturated fatty acids converted to respective conjugated fatty acids may fit the criteria in time as evidence gathers [10]. According to Dueñas et al. [34] and Plamada and Vodnar [39], polyphenols exert their prebiotic-like effects by stimulating the growth of beneficial probiotic bacteria of the families Lactobacillaceae and Bifidobacteriaceae and lowering the number of pathogenic bacteria such as *Escherichia coli*, *Helicobacter pylori* and *Clostridium perfringens*. In addition, studies evidence that dietary polyphenols exert prebiotic-like effects through the stimulation of the growth of beneficial bacteria such as lactobacilli and bifidobacteria and the inhibition of pathogenic bacteria thus preserving the gut microbial balance and contribute to the maintenance of intestinal health [34].

Despite the limitations of studies in the prebiotic effect of dietary polyphenols, it is evident that polyphenols especially catechins, anthocyanins, and proanthocyanidins, can stimulate the growth of microorganisms recognized as prebiotic targets including *Lactobacillus* spp., *Bifidobacterium* spp., *Akkermansia* spp., *Roseburia* spp., and *Faecalibacterium* spp. [4]. Although the roles of polyphenols in modulating the composition of the gut microbiota are recently recognized, further clarification on its mechanisms and research focusing on the polyphenols' effects in clinical trials are necessary to clearly defined their prebiotic effect as conclusive evidence is not available for it to be used therapeutically [4,35,39].

5.0 CONCLUSION

The metabolic activity of the gut microbiota and its influence on the health and well-being of the host is attracting interest in studying the prebiotic effect of foods. The current ever-increasing demand for prebiotics has resulted in the development of prebiotic production from new novel sources and food industrial wastes with unique health benefits, increase added value to the foods, and reduce waste generation. Compounds beyond the common prebiotic carbohydrates, such as polyphenols, may also provide the next generation of prebiotics. In Malaysia, there are limited studies on the extraction of prebiotics from agro-industrial waste. Recently, turmeric has gained interest as a potential prebiotic compound. On the other hand, studies on the antioxidant of asam gelugor fruit extract and its chemical constituents and bioactivities are limited.

Acknowledgement

The authors would like to acknowledge the Ministry of Higher Education Malaysia for financial support under Fundamental Research Grant Scheme (R.J130000.7851.5F344, FRGS/1/2020/TK0/UTM/02/4).

References

[1] Rolim, P. M. 2015. Development of prebiotic food products and health benefits. Food Science and Technology, 35: 3-10. http://dx.doi.org/10.1590/1678-457X.6546

[2] Gibson, G. R., Hutkins, R., Sanders, M. E., Prescott, S. L., Reimer, R. A., Salminen, S. J., Scott, K., Stanton, C., Swanson K. S., Cani, P. D., Verbeke, K. and Reid, G. 2017. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nature Reviews Gastroenterology & Hepatology, 14: 491-502. https://doi.org/10.1038/nrgastro.2017.75

[3] Lockyer, S. and Stanner, S. 2019. Prebiotics–an added benefit of some fibre types. Nutrition Bulletin, 44(1): 74-91. https://doi.org/10.1111/nbu.12366

[4] Alves-Santos, A. M., Sugizaki, C. S. A., Lima, G. C. and Naves, M. M. V. 2020. Prebiotic effect of dietary polyphenols: A systematic review. Journal of Functional Foods, 74: 104169. https://doi.org/10.1016/j.jff.2020.104169

[5] de Souza Aquino, J., Batista, K. S., Menezes, F. N. D. D., Lins, P. P., de Sousa Gomes, J. A. and da Silva, L. A. 2017. Models to evaluate the prebiotic potential of foods. In: Hueda, M. C. (Eds) Functional Food: Improve Health Through Adequate Food.

[6] Patel, S. and Goyal, A. 2012. The current trends and future perspectives of prebiotics research: a review. 3 Biotech, 2(2): 115-125. https://doi.org/10.5772/intechopen.69174

[7] Thakur, K., Xu, G. Y., Zhang, J. G., Zhang, F., Hu, F. and Wei, Z. J. 2018. In vitro prebiotic effects of bamboo shoots and potato peel extracts on the proliferation of lactic acid bacteria under simulated GIT conditions. Frontiers in Microbiology, 9: 2114. https://doi.org/10.3389%2Ffmicb.2018.02114

[8] Barber, T. M., Kabisch, S., Pfeiffer, A. F. and Weickert, M. O. 2020. The health benefits of dietary fibre. Nutrients, 12(10): 3209. https://doi.org/10.3390%2Fnu12103209

[9] Silva, J. K., Cazarin, C. B. B., Junior, S. B., Augusto, F. and Junior, M. R. M. 2014. Passion fruit (*Passiflora edulis*) peel increases colonic production of short-chain fatty acids in Wistar rats. LWT-Food Science and Technology, 59(2): 1252-1257. https://doi.org/10.1016/j.lwt.2014.05.030

[10] Gibson, G. R., Hutkins, R., Sanders, M. E., Prescott, S. L., Reimer, R. A., Salminen, S. J., Scott, K., Stanton, C., Swanson, K. S., Cani, P. D. and Verbeke, K. 2017. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nature reviews Gastroenterology & Hepatology, 14(8): 491-502. https://doi.org/10.1038/nrgastro.2017.75

[11] Meyer, T. S., Miguel, A. S., Fernández, D. E., and Ortiz, G. M. 2015. Biotechnological production of oligosaccharides — applications in the food industry. Food Production and Industry, 2: 25-78. https://doi.org/10.5772/60934

[12] Jovanovic-Malinovska, R., Kuzmanova, S. and Winkelhausen, E. 2014. Oligosaccharide profile in fruits and vegetables as sources of prebiotics and functional foods. International Journal of Food Properties, 17(5): 949-965. https://doi.org/10.1080/10942912.2012.680221

[13] Wang, Y. 2009. Prebiotics: Present and future in food science and technology. Food Research International, 42(1): 8-12. https://doi.org/10.1016/j.foodres.2008.09.001

[14] Kaur, A. P., Bhardwaj, S., Dhanjal, D. S., Nepovimova, E., Cruz-Martins, N., Kuča, K., Chopra, C., Singh, R., Kumar, H., Șen, F. and Kumar, V. 2021. Plant prebiotics and their role in the amelioration of diseases. Biomolecules, 11(3): 440. https://doi.org/10.3390%2Fbiom11030440

[15] Patel, S. and Goyal, A. 2011. Functional oligosaccharides: production, properties and applications. World Journal of Microbiology and Biotechnology, 27(5): 1119-1128. https://doi.org/10.1007/s11274-010-0558-5

[16] Yazdi, F. G., Soleimanian-Zad, S., van den Worm, E. and Folkerts, G. 2019. Turmeric extract: Potential use as a prebiotic and anti-inflammatory compound? Plant Foods for Human Nutrition, 74: 293–299. https://doi.org/10.1007/s11130-019-00733-x

[17] Promjiam, P., Siripongvutikorn, S. and Wichienchot, S. 2017. Functional properties of curry paste in relation to digestibility and fermentation by gut microbiota. International Journal of Food Properties, 20(12): 3204-3214. https://doi.org/10.1080/10942912.2017.1282515

[18] Synytsya, A., Mickova, K., Synytsya, A., Jablonsky, I., Spevacek, J., Erban, V., Kovarikova, E. and Copikova, J. 2008. Glucans from fruit bodies of cultivated mushrooms *Pleurotus ostreatus* and *Pleurotus eryngii*: Structure and potential prebiotic activity. Carbohydrate Polymers, 76(4): 548-556. https://doi.org/10.1016/j.carbpol.2008.11.021

[19] Wichienchot, S., Jatupornpipat, M. and Rastall, R. A. 2010. Oligosaccharides of pitaya (dragon fruit) flesh and their prebiotic properties. Food Chemistry, 120(3): 850-857. https://doi.org/10.1016/j.foodchem.2009.11.026

[20] Abbasiliasi, S., Joo, S. T., Bello, B., Ibrahim, T. A. T., Yew, J. T., Ariff, A. and Mustafa, S. 2019. Prebiotic efficacy of coconut kernel cake's soluble crude polysaccharides on growth rates and acidifying property of probiotic lactic acid bacteria in vitro. Biotechnology & Biotechnological Equipment, 33(1): 1216-1227. http://dx.doi.org/10.1080/13102818.2019.1649603

[21] Chen, G., Chen, X., Yang, B., Yu, Q., Wei, X., Ding, Y. and Kan, J. 2019. New insight into bamboo shoot (*Chimonobambusa quadrangularis*) polysaccharides: Impact of extraction processes on its prebiotic activity. Food Hydrocolloids, 95: 367-377. https://doi.org/10.1016/j.foodhyd.2019.04.046

[22] Rathamat, Z., Choorit, W., Chisti, Y. and Prasertsan, P. 2021. Two-step isolation of hemicellulose from oil palm empty fruit bunch fibers and its use in production of xylooligosaccharide prebiotic. Industrial Crops and Products, 160: 113124. https://doi.org/10.1016/j.indcrop.2020.113124

[23] Jabczyk, M., Nowak, J. and Hudzik, B., Zubelewicz-Szkodzinska, B. 2021. Curcumin and its potential impact on microbiota. Nutrients, 13; 2004. https://doi.org/10.3390%2Fnu13062004

[24] Ali, A., Wu, H., Ponnampalam, E. N., Cottrell, J. J., Dunshea, F. R. and Suleria, H. A. 2021. Comprehensive profiling of most widely used spices for their phenolic compounds through LC-ESI-QTOF-MS^2 and their antioxidant potential. Antioxidants, 10(5): 721. https://doi.org/10.3390/antiox10050721

[25] Zam, W. 2018. Gut microbiota as a prospective therapeutic target for curcumin: A review of mutual influence. Journal of Nutrition and Metabolism, 2018: 1367984. https://doi.org/10.1155/2018/1367984

[26] Zanzer, Y. C., Plaza, M., Dougkas, A., Turner, C., Björck, I. and Östman, E. 2017. Polyphenol-rich spice-based beverages modulated postprandial early glycaemia, appetite and PYY after breakfast challenge in healthy subjects: A randomized, single blind, crossover study. Journal of Functional Foods, 35: 574-583. https://doi.org/10.1016/j.jff.2017.06.016

[27] Lu, Q. Y., Summanen, P. H., Lee, R. P., Huang, J., Henning, S. M., Heber, D., Finegold, S. M. and Li, Z. 2017. Prebiotic potential and chemical composition of seven culinary spice extracts. Journal of Food Science, 82(8): 1807-1813. https://doi.org/10.1111/1750-3841.13792

[28] Abdullah, A. R., Bakhari, N. A. and Osman, H. 2013. Study on the relationship of the phenolic, flavonoid and tannin content to the antioxidant activity of Garcinia atroviridis. Universal Journal of Applied Science, 1(3): 95-100. http://dx.doi.org/10.13189/ujas.2013.010304

[29] Nursakinah, I., Zulkhairi, H. A., Norhafizah, M., Hasnah, B. and Razif, D. 2012. Nutritional content and in vitro antioxidant potential of *Garcinia atroviridis* (Asam gelugor) leaves and fruits. Malaysian Journal of Nutrition, 18(3): 363-371.

[30] Taher, M., Hamidon, H., Susanti, D., and Zakaria, Z. A., 2016. Garcinia atroviridis – A review on phytochemicals and pharmacological properties. Marmara Pharmaceutical Journal, 21: 38-47. http://dx.doi.org/10.12991/marupj.259879

[31] Thongkham, E., Aiemsaard, J. and Kaenjampa, P., 2021. Antioxidant and Antimicrobial Properties of Ethanolic Extract of Asam Gelugor Fruit (Garcinia atroviridis). Burapha Science Journal, 26(2): 1293-1307.

[32] Carrera-Quintanar, L., Lopez Roa, R. I., Quintero-Fabián, S., Sánchez-Sánchez, M. A., Vizmanos, B. and Ortuño-Sahagún, D. 2018. Phytochemicals that influence gut microbiota as prophylactics and for the treatment of obesity and inflammatory diseases. Mediators of Inflammation, 2018: 9734845. https://doi.org/10.1155/2018/9734845

[33] Cueva, C., Silva, M., Pinillos, I., Bartolomé, B. and Moreno-Arribas, M. V. 2020. Interplay between dietary polyphenols and oral and gut microbiota in the development of colorectal cancer. Nutrients, 12(3): 625. https://doi.org/10.3390/nu12030625

[34] Dueñas, M., Muñoz-González, I., Cueva, C., Jiménez-Girón, A., Sánchez-Patán, F., Santos-Buelga, C., Moreno-Arribas, M. and Bartolomé, B. 2015. A survey of modulation of gut microbiota by dietary polyphenols. BioMed Research International, 2015: 850902. https://doi.org/10.1155/2015/850902

[35] Singh, A. K., Cabral, C., Kumar, R., Ganguly, R., Kumar Rana, H., Gupta, A., Rosaria Lauro, M., Carbone, C., Reis, F., and Pandey, A. K. 2019. Beneficial effects of dietary polyphenols on gut microbiota and strategies to improve delivery efficiency. Nutrients, 11(9): 2216. https://doi.org/10.3390/nu11092216

[36] Abd Aziz, N. A., Hasham, R., Sarmidi, M. R., Suhaimi, S. H. and Idris, M. K. H. 2021. A review on extraction techniques and therapeutic value of polar bioactives from Asian medicinal herbs: Case study on *Orthosiphon aristatus*, *Eurycoma longifolia* and *Andrographis paniculata*. Saudi Pharmaceutical Journal, 29(2): 143-165. https://doi.org/10.1016/j.jsps.2020.12.016

[37] Suhaimi, S. H., Hasham, R., Hafiz Idris, M. K. H., Ismail, H. F., Mohd Ariffin, N. H. and Abdul Majid, F. A. 2019. Optimization of ultrasound-assisted extraction conditions followed by solid phase extraction fractionation from *Orthosiphon stamineus* Benth (Lamiace) leaves for antiproliferative effect on prostate cancer cells. Molecules, 24(22): 4183. https://doi.org/10.3390/molecules24224183

[38] Kasprzak-Drozd, K., Oniszczuk, T., Stasiak, M. and Oniszczuk, A. 2021. Beneficial effects of phenolic compounds on gut microbiota and metabolic syndrome. International Journal of Molecular Sciences, 22(7): 3715. https://doi.org/10.3390%2Fijms22073715

[39] Plamada, D. and Vodnar, D. C. 2021. Polyphenols—Gut Microbiota Interrelationship: A Transition to a New Generation of Prebiotics. Nutrients, 14(1): 137. https://doi.org/10.3390/nu14010137