



Review

Unique roles in health promotion of dietary flavonoids through gut microbiota regulation: Current understanding and future perspectives

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ABSTRACT

Advances in understanding the biological effects of dietary flavonoids and flavonoid-rich foods have been reported. Improving knowledge about their beneficial effects, and mechanisms of action, is crucial for better utilization. However, mechanisms responsible for their health benefits are still unclear. Previous research considered has suggested that gut microbiota might be linked to the metabolism of dietary flavonoids. To understand the bioactivities of dietary flavonoids/flavonoid-rich foods better, and the role of microbiota, we explored systematically 1) types of dietary flavonoids and associated health benefits, 2) low bioaccessibilities and metabolic characteristics, 3) gut microbiota role in regulation, and 4) crosstalk between regulation mechanisms. Current challenges and future perspectives were also considered, offering new research directions and identifying trends in the development of flavonoid-rich food products.

1. Introduction

Flavonoids, as important phenolic compounds, are widely distributed in fruits and vegetables, and their health benefits have been studied intensively (Battino et al., 2021; Yang et al., 2021; Xiao, 2022). Flavonoids ingested with food enter the circulatory system through the intestinal tract to exert their beneficial effects (Wang, Zhao, Wen, Ho, & Li, 2021). Numerous studies suggest that dietary flavonoid-rich foods and flavonoid compounds present a diverse range of biological activities (Barreca et al., 2021; Zhang et al., 2022). However, the large-scale application of flavonoids as food dietary supplements are still limited due to their poor bioavailability, instability in gastrointestinal digestion, and lack of targeted bioaffinity (Teng, Zheng, Cao, Huang, Xiao, & Chen, 2021).

Generally, the substances absorbed are not in the original format but become metabolites (Joardder, Kumar, & Karim, 2018). Moreover, many studies did not focus on investigating their metabolites at a physiological concentration (Chen, Cao, Huang, Xiao, & Teng, 2021).

Recently, gut microbiota has been applied in the studies of the metabolism of dietary flavonoids (Duan et al., 2021; Pei, Liu, & Bolling, 2020). It has been demonstrated that dietary flavonoids and gut microbiota can together contribute to the production of catabolites and metabolites (Chen & Yang, 2020). The microbial populations could act as an indicator of the individual responses to food ingredients (Qu et al., 2018). The fermentation of different dietary flavonoids and other substances in the intestine produce different metabolites that affect the intestinal environment and regulate gut microbiota (Rowland et al., 2018; Yang, Zhu, Sun, Ai, Edirisuriya, & Zhou, 2020).

During the past decade, reports on flavonoid activities and regulatory mechanisms proliferated (Ferraz et al., 2020; Maaliki, Shaito, Pintus, El-Yazbi, & Eid, 2019; Maleki, Crespo, & Cabanillas, 2019; Yu, Pei, & Li, 2022). However, the mechanisms involved in the health benefits of dietary flavonoids are still unclear. Moreover, flavonoids and their metabolites may exert their unique activities through multiple biological pathways (Daveri et al., 2018). The investigation of crosstalk among the signal pathways is highly demanded to evaluate the bioactivities of

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dietary flavonoids.

In the current perspective, the main types of dietary flavonoids, their bioaccessibility properties, and the health benefits of dietary flavonoids or flavonoid-rich foods are overviewed. More importantly, the effects of dietary flavonoids on regulating gut microbiota are summarized to highlight their roles in health promotion. In addition, the challenges and further perspectives for clarifying the health benefits of dietary flavonoids are highlighted, and new research opportunities for precision nutrition based on dietary flavonoids are provided.

2. Health benefits of dietary flavonoids

2.1. Flavonoid bioaccessibility

Flavonoids are divided into different classes based on heterocycle types, and shown in Fig. S1 are the six major classes, namely flavanols, flavanones, flavones, anthocyanins, flavonols, and isoflavones (Dias, Pinto, & Silva, 2021). As the main phenolic compounds in nature, flavonoids are the most studied phenolic compounds due to their potential benefits (Williamson, Kay, & Crozier, 2018). The exertion of dietary flavonoids' health benefits is confronted with obstacles, especially the low bioaccessibility, which is attributed to the compounds' low stability and non-targeted release (Toro-Uribe et al., 2019). Therefore, improving the bioaccessibility of dietary flavonoids is crucial in promoting their health benefits (Ravisankar, Agah, Kim, Talcott, Wu, & Awika, 2019; Song et al., 2022).

Recent studies on the performance of flavonoid bioaccessibility *in vitro* digestion are summarized in Table 1. In fact, flavonoid bioaccessibility is associated with many factors, among which food matrix effects are important for the bioactivities of dietary flavonoids (Alashi, Taiwo, Oyedele, Adebooye, & Aluko, 2019). The absorption and excretion of flavonoids and metabolites are both associated with their ability to bind with macronutrients in foods (Kamiloglu, Tomas, Ozdal, & Capanoglu, 2021). The non-covalent interactions of flavonoids and proteins, carbohydrates, or lipids have attracted intensive attention. For instance, the interaction with macronutrients via van der Waals interactions could affect the flavonoids' properties, including bioaccessibility and radical scavenging activity (Meng et al., 2021). Generally, proteins, carbohydrates, lipids, and other components in the food matrix are all influential in dietary flavonoid digestion (Kamiloglu, Tomas, Ozdal, & Capanoglu, 2021).

To overcome poor bioaccessibility, delivery systems have been developed for the targeted release of flavonoids to retain their bioactivities, thereby solving the problem of low oral bioavailability and poor intestinal absorption for some flavonoids (Zhang, Zhu, Yang, Huang, & Ho, 2021). Liposomal encapsulation, and micro- and nano-encapsulation studies have been performed to determine the beneficial effects of flavonoids (Zhao et al., 2018). Nano-encapsulation is a promising technique to deliver various hydrophobic flavonoids *in vivo* (Ayala-Fuentes & Chavez-Santoscoy, 2021). Importantly, novel scientific reports are crucial to support future opportunities to reveal food-body interactions and to develop delivery systems with edible materials for dietary flavonoids, as well as other functional food products (McClements, 2020).

2.2. Dietary flavonoid metabolism

Flavonoids, flavonoid-rich foods, and their derivatives, should present their bioactivities as human dietary supplements to exert their health benefits (Wang, Zhao, Wen, Ho, & Li, 2021). Foods containing flavonoids can reach the gut lumen and then enter the bloodstream following further absorption and metabolism (Ribas-Agustí, Martín-Belloso, Soliva-Fortuny, & Elez-Martínez, 2018). For example, the catabolism of anthocyanins and flavanones produces many derivative compounds, including 4-protocatechuic acid, gallic acid, and vanillic acid (Kay, Pereira-Caro, Ludwig, Clifford, & Crozier, 2017). The

Table 1
In vitro changes in the bioaccessibility of flavonoids.

Flavonoid source	Processing	Bioaccessibility performance	Reference
Rutin in Meghalayan cherry pomace	Microwave-assisted extraction and <i>In vitro</i> SGD	More than 50 %	(Kashyap, Riar, & Jindal, 2022)
Flavonoids from <i>Diospyros kaki</i>	<i>In vitro</i> SGD	100 % higher than in aqueous leaf extract	(Martínez-Las Heras, Pinazo, Heredia, & Andrés, 2017)
Galloylated flavonoids from grape seeds extract	Sodium caseinate binding interaction	Increase in both foam and emulsion	(Elegbede, Li, Jones, Campanella, & Ferruzzi, 2018)
Naringenin from tomato sauce	Industrial processing	Overall positive effect	(Tomas, Beekwilder, Hall, Sagdic, Boyacioglu, & Capanoglu, 2017)
Proanthocyanidin in baobab fruit shell	<i>In vitro</i> SGD	Increase	(Ismail et al., 2021)
Flavonoids from six quinoa seeds	<i>In vitro</i> SGD	12.64 %	(Pellegrini et al., 2017)
Anthocyanins from <i>Carissa macrocarpa</i>	Freeze drying and <i>in vitro</i> SGD	Increase	(Seke, Manhivi, Shoko, Slabbert, Sultanbawa, & Sivakumar, 2021)
Yoghurt fortified with rutin-casein coprecipitate	<i>In vitro</i> SGD	Increase	(Acevedo-Fani, Ochoa-Grimaldo, Loveday, & Singh, 2021)
Flavonoids-enriched juice mixture	Processing of pulsed electric technologies	Increase	(Buniowska, Carbonell-Capella, Frigola, & Esteve, 2017)
Fruit juices	<i>In vitro</i> SGD	24.25 %–67.00 %	(Mihaylova, Desseva, Stoyanova, Petkova, Terzyiska, & Lante, 2021)
Flavonoids in finger millet	Roast with lime juice added	25 % increase	(Hithamani & Srinivasan, 2017)

Note: SGD-simulated gastrointestinal digestion.

absorption of flavonoids requires the removal of glycosides via hydrolysis. In addition, cytosolic β -glucosidase and lactase phlorizin hydrolyase, are employed for glucoside hydrolyzation (Kulkarni et al., 2017; Yang, Liu, Yang, Gupta, & Jiang, 2018). After hydrolysis, many transporters and metabolizing enzymes contribute to flavonoid metabolism. Taking (–)-epicatechin metabolism as an example, the ingested (–)-epicatechin-3'-O- β -D-glucuronide is hydrolyzed for further conversion (Fig. 1). Different metabolites with varying abundances, including structurally related metabolites, 5-carbon rings, and carbon-side chain ring fission metabolites, were shown at different times (0–36 h) in systemic circulation and urine (Ottaviani et al., 2016).

Besides, dietary flavonoids can interact with glucuronic acid, methyl, and sulfate in intestinal phase II metabolism, and the related metabolites interfere with many biochemical processes (Chalet, Hollebrands, Jansen, Augustijns, & Duchateau, 2018). Fifteen metabolites of bioactive flavonoids from *Scutellaria baicalensis* Georgi (Lamiaceae) have been identified as sulfate/glucuronide conjugates, acetylated, deoxygenated, hydroxylated, and methylated products (Du et al., 2015). Moreover, the major metabolites of quercetin are phloroglucinol, dihydrocaffeic acid, 2-(3,4-dihydroxyphenyl)acetic acid, and 3,4-dihydroxybenzoic acid (Di Pede et al., 2020; Tang et al., 2016). Importantly, low-molecular-weight phenolics can be transformed from flavonoids by colonic microbiota, and the absorption sites and forms of flavonoids are key factors in determining their metabolism and bioactivities (Catalkaya et al., 2020). Gallic acid, 3,4-dihydroxybenzoic acid, and 3-hydroxybenzoic acid

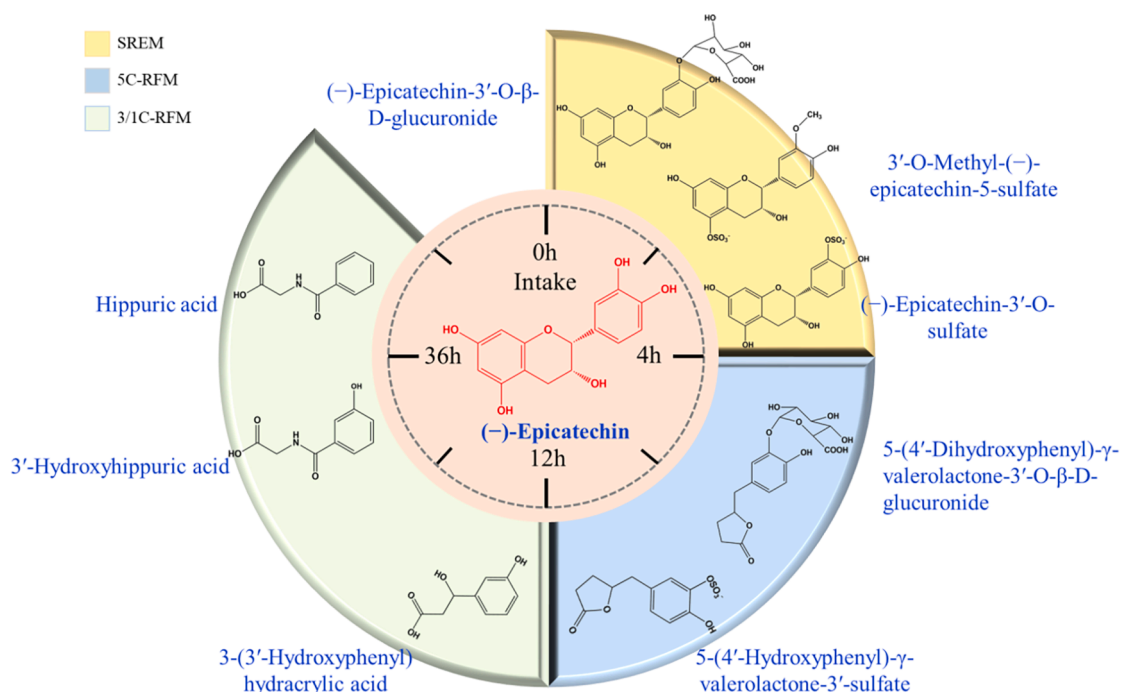


Fig. 1. (-)-Epicatechin metabolites with the most abundance in human after dietary intake (0–36 h). SREM: structurally related (-)-epicatechin metabolites. 5C-RFM: 5-C ring fission metabolites. 3/1C-RFM: 3-C-side and 1-C-side chain ring fission metabolites. Adapted from reference (Ottaviani et al., 2016) with permission.

derived from theaflavin-3-ogallate catabolism can be determined by microbiota-mediated steps as shown in Fig. S2 (Pereira-Caro et al., 2017). Moreover, the phase II metabolism and colonic microbiota metabolism of dietary flavonoids are different in the catabolism of dietary flavonoids (Baky, Elshahed, Wessjohann, & Farag, 2021; Williamson et al., 2018).

Moreover, the bioactivities of flavonoids may synergize or weaken the bioactivities of their parent flavonoids. The combination of natural extracts and apigenin–quercetin synergistically can inactivate ATP

binding cassette transporter expression and inhibits P-glycoprotein activity for enhancing their bioavailability (Ravisankar et al., 2019). Recently, a systematical review has been highlighted to summarize some potential pathways for the metabolism of representative flavonoids from a historical perspective, as an attractive work to enrich our knowledge of flavonoid metabolism (Williamson et al., 2018).

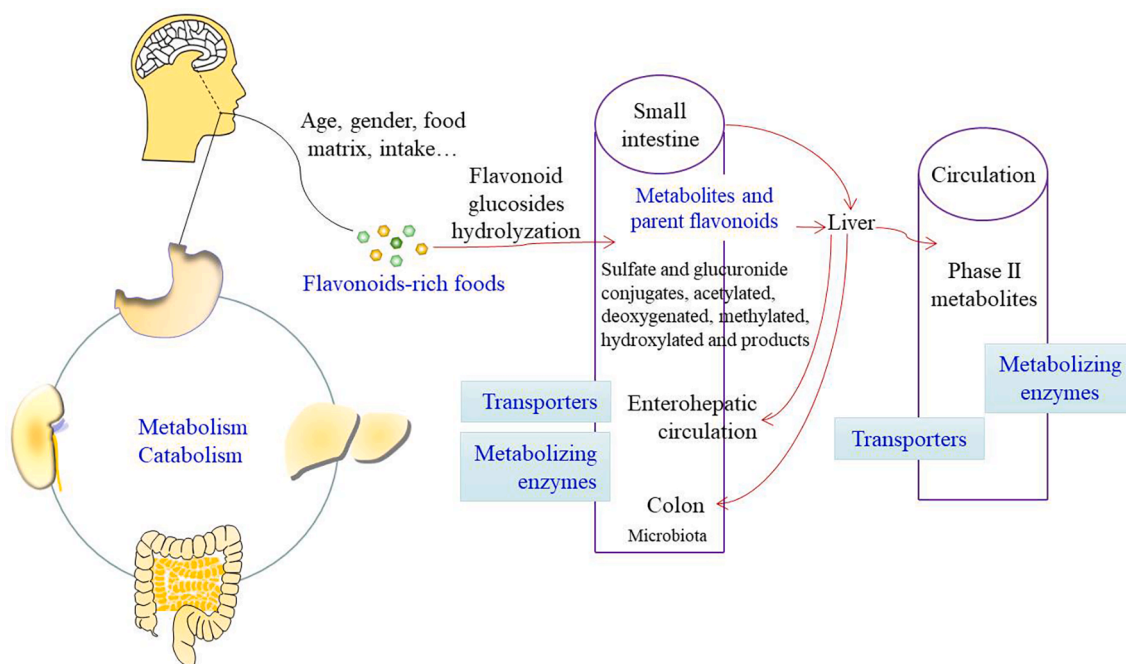


Fig. 2. Scheme for the metabolism of ingested flavonoid-rich foods. All the parameters were cited from (Kalt, McDonald, Liu, & Fillmore, 2017; Murota et al., 2018; Pei et al., 2020; Pereira-Caro et al., 2017; Williamson et al., 2018).

2.3. Health benefits of dietary flavonoids

Many factors influence the ability of dietary flavonoids to exert health benefits, including age, sex, food matrix, digestive enzymes, and intestinal transporters (Fig. 2) (Murota, Nakamura, & Uehara, 2018; Murphy, Walker, Dyer, & Bryan, 2019). Notably, the investigations of the metabolite profiles in different sites are remarkable to elucidate the mechanisms on the health promotion of dietary flavonoids and their derivatives. The appearance of radiolabeled compound profiles in urine, plasma, and other organs can provide information relevant to dietary flavonoid metabolism, their absorption sites, and forms. Fundamental data can be acquired using the isotopic label to describe the absorption and distribution of dietary flavonoids, as well as metabolism and excretion. The specie-dependent differences in metabolites are also valuable for revealing the mechanisms of the health benefits, as well as strengthening the health-promotion investigations and safety assessments of dietary flavonoid intake (Nie et al., 2021; Ottaviani et al., 2016; Zeng et al., 2019).

Dietary flavonoid-rich foods are associated with the improvement of health status (Brewis, SturtzSreetharan, & Wutich, 2018; Wu & Bal-lantyne, 2020; Zhou et al., 2022). The health benefits of dietary flavonoids are involved in the amelioration of bone mineral density (Sarmadi, Ismail, Yusof, & Yunoh, 2020), acute lung injury (Tang et al., 2018), UV-induced skin damage (Liu et al., 2018), and depression (Khan, Perviz, Sureda, Nabavi, & Tejada, 2018).

Moreover, dietary flavonoid consumption produces substantial

health status improvement in risk populations (Rees, Dodd, & Spencer, 2018). Long-term dietary flavonoid intake is considerably involved in lower odds of subjective cognitive decline, as health-promotion effects, reported in a 16-year investigation in the US with the participation of 49,493 women and 27,842 men (Yeh, Yuan, Ascherio, Rosner, Willett, & Blacker, 2021). However, the conclusive direct evidence regarding flavonoid-induced health benefits is also limited. Clarifying the potential health benefits of long-term dietary flavonoid intake is still clearly urgent.

2.4. Crosstalk of signaling pathway regulation

The primary actions of flavonoids are due to their redox and physical binding activities. Flavonoids have been employed to regulate the NFE2-related factor 2/heme-oxygenase-1 (Nrf2/HO-1) pathway of HepG2 Cells *in vitro* and inhibit reactive oxygen species production (Yu, Li, Cao, Huang, & Yang, 2019). The effects of flavonoids on inflammatory response in cells are mediated by regulating the mitogen-activated kinase/nuclear factor kappa B (MAPK/NF- κ B) pathway in cells. Consequently, dietary flavonoids are used to potentiate the inhibition of IFN- α on cancer cell viability by activating the JAK2/STAT3 signaling pathways (Li et al., 2016). In addition, flavonoids have elevated the P38/PPAR- α pathway to inhibit cell apoptosis and autophagy in mice (Lu et al., 2018).

As shown in Fig. 3A, dietary flavonoids modulate other crosstalk points associated with NF- κ B and Nrf2 pathways (Williamson et al.,

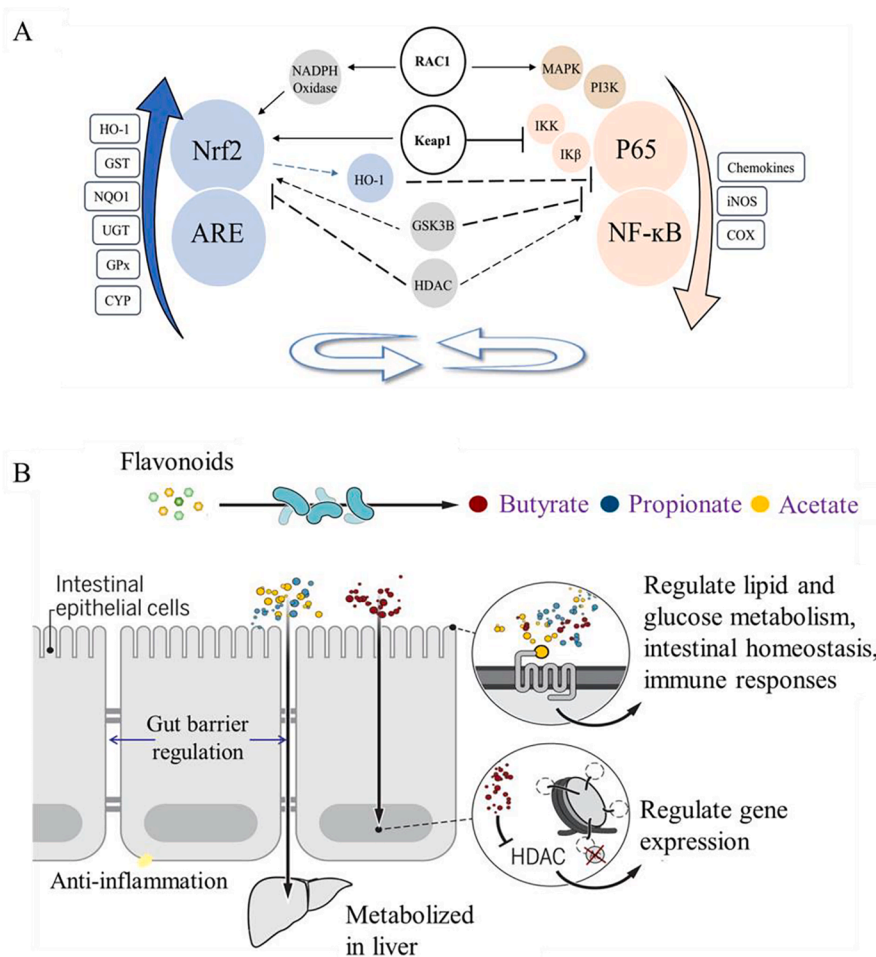


Fig. 3. (A) Regulation of chemokines, enzymes, and crosstalk proteins by flavonoids via Nrf2 and NF- κ B pathways. Reprinted from the reference (Williamson et al., 2018) with permission. (B) Dietary flavonoid fermentation produces short-chain fatty acids to regulate lipid and glucose metabolism, immune responses, and mediate related gene expression. Reprinted from the reference (Gentile and Weir, 2018) with permission.

2018). NF- κ B, Nrf2, MAPK, P13K, and Akt-mTOR signaling pathways, as well as multiple signaling pathways, have been revealed as important candidates for the modulation of flavonoid bioactivity (Chu et al., 2019; Jian et al., 2020; Kim, Cheong, Lee, Sok, & Kim, 2020; Yuan, Che, Zhang, & Ruan, 2021). The evidence of crosstalk between NF- κ B and Nrf2 pathways comprises the association of Rac Family Small GTPase 1 (RAC1) with the Kelch-like ECH associated protein 1 (KEAP1)-NF- κ B and Nrf2 pathways, attenuating inflammation and oxidative stress (Blaser, Dostert, Mak, & Brenner, 2016; Taniguchi & Karin, 2018). Certainly, flavonoid-rich foods and their metabolites may likely share common crosstalk among protein/enzymes and receptors to regulate multiple transcription factors and signaling pathways for exerting their mechanism of action (Ciumărnean et al., 2020; Williamson et al., 2018).

3. Roles of dietary flavonoids in gut microbiota regulation

Recently, the relationship between gut microbiota and health promotion has been a research focus (Soderborg et al., 2018; Wan et al., 2019). It has been considered that gut microbiota are involved in health status modulation (Forbes-Hernandez et al., 2016; Agus, Planchais, & Sokol, 2018; Fan & Pedersen, 2021). In this section, the roles of gut microbiota regulation by dietary flavonoid intake are highlighted to evaluate the health benefits, as well as short-chain fatty acids (SCFAs) regulation and bile acid metabolism. In addition, the crosstalk of signaling pathways is summarized to exhibit the regulation mechanism of dietary flavonoids for health promotion.

3.1. Gut microbiota reconstruction

The regulation of dietary flavonoids reshaping gut microbiota for health benefits is the frontier of food nutrition research (Annunziata et al., 2021; Zmora, Suez, & Elinav, 2019). Gut microbiota regulation mediated by dietary flavonoid intake is associated with health benefits, contributing to the regulation of host immunity, inflammatory status, and the alteration of microbiota diversity (Li, Christman, Li, & Gu, 2020). During the past decades, studies focused on increasing beneficial bacteria, inhibiting deleterious species, and exploring interactions between dietary flavonoids and gut microbiota (Ma et al., 2019).

The majority of gut microbiota associated with flavonoid

transformation contribute to the O-deglycosylation of flavonoids in flavonoid transformation, such as *Bifidobacteriaceae*, *Lactobacillaceae*, *Lachnospiraceae*, and *Enterococcaceae* (Kim et al., 2020; Yan & Zhang, 2022; Barber, Houghton, & Williamson, 2021), whereas others are involved in the cleaving of flavonoid-C-glucosides or the degradation of aglycones (Braune & Blaut, 2016).

Flavonoids can improve health status by reconstructing the gut microbiota. Bilberry anthocyanin extract intake promotes the intestinal barrier function by reshaping the gut microbiota (Li, Wu, Li, Wang, Chen, & Lyu, 2019). The fermentation in the intestine of different dietary structures produces different metabolites that affect the intestinal environment and regulate gut microbiota (Makki, Deehan, Walter, & Bäckhed, 2018). Diets with high flavonoid contents might contribute to the alteration of gut microbiota composition and function within weeks (Maier et al., 2017). Table 2 shows recent studies on the roles of flavonoids in gut microbiota regulation. In general, flavonoids are subject to catabolism by gut microbiota, and the mechanism is likely via the regulation of gut microbiota, although the regulatory mechanisms of certain flavonoids and extracts require further exploration.

The different roles of gut microbiota have been explored recently, and the host circadian rhythm can be regulated through the gut-brain axis and the improvement of gut microecology, supporting new clues to clarify the health benefits of dietary flavonoids (Guo et al., 2019). However, the gut microbiota-dietary flavonoid interactions associated with the circadian rhythm remain complex and unclear (Song, Yang, Zhang, & Wang, 2021). The framework is proposed to provide new insights to discover the roles of dietary flavonoids and gut microbiota (Fig. S3) for circadian rhythm regulation. More efforts should be performed to reveal the complex relationships between circadian rhythm, gut microbiota, and dietary flavonoids, especially from the perspective of the gut-liver axis and gut-brain axis.

3.2. Short-chain fatty acids and bile acid metabolism

Flavonoids usually play a similar role as gut prebiotics in regulating the metabolism of SCFAs (Qi et al., 2021). SCFAs are the metabolites of carbohydrates fermented by gut microbiota, such as acetic acid, propionic acid, butyric acid, isobutyric acid, valeric acid, and isovaleric acid (Sanna et al., 2019). Diet structures have reshaped the gut microbiota to

Table 2
Performance of dietary flavonoids in gut microbiota regulation.

Flavonoid	Model	Mechanism	Reference
Aglycone quercetin	Germ-free mice with non-alcoholic fatty liver	Decrease of <i>Akkermansia</i> abundance and increase of NLRP3 expression	(Porras et al., 2019)
Anthocyanin	Colorectal cancer animal model	Substantial reduction of pro-inflammatory <i>Bilophila wadsworthia</i>	(Fernández, García, Monte, Villar, & Lombó, 2018)
Isoorientin	BALB/c mice	Inhibited growth of inflammation-related bacteria	(Yuan, Li, He, Gao, Wang, & Shao, 2018)
Myricetin	Nonalcoholic fatty liver disease in rats	Modulations in fecal butyric-acid-related bacteria and improvement of gut barrier function	(Sun et al., 2021)
Baicalein	Rats with high-fat diet-induced diabetes	Increase of SCFA-producing bacteria and decrease of pathogens, Positive effects produced by <i>Bacteroidales</i> S24-7	(Zhang et al., 2018)
Flavonoids from whole-grain oat	High fat fed C57BL/6N mice	Decrease of <i>Colidextribacter</i> , <i>Desulfovibrio</i> , and <i>Lachnoclostridium</i>	(Duan et al., 2021)
Grape seed proanthocyanidins	Female Wistar rats	Increase of <i>Bacteroidetes</i> and <i>Proteobacteria</i> , reduction of <i>Firmicutes</i>	(Casanova-Martí et al., 2018)
Flavonoids from <i>Cyclocarya paliurus</i>	High-fat diet-induced obesity mouse model	Decrease in the ratio of <i>Firmicutes</i> / <i>Bacteroidetes</i>	(Cheng et al., 2019)
Ougan juice	C57BL/6J mice with high-fat diet	Decrease of phylum <i>Erysipelatoclostridiaceae</i> and genus <i>Erysipelatoclostridium</i> , and remarkable increase of SCFA-producing bacteria	(Guo et al., 2021)
Flavonoid-rich extract from <i>Grifola frondosa</i>	Rats with high-fat diet	Increased abundance of <i>Butyricimonas</i> genus	(Pan et al., 2018)
Naringin	ApoE ^{-/-} mice with high-fat diet	Regulation of bile salt hydrolase- and 7 α -dehydroxylase-producing bacteria levels	(Wang et al., 2020)
Cranberry extract	High fat/high sucrose-fed C57BL/6J mice	Increase of the population of <i>Akkermansia</i>	(Anhê et al., 2015)
Mulberry leaves	Obese mice with high-fat diet	Increase of <i>Akkermansia</i> level and <i>Bacteroidetes</i> / <i>Firmicutes</i> ratio	(Sheng et al., 2019)
Flavonoid-rich extract from Green Seaweed	Mice with Type 2 diabetes	Higher abundance of <i>Lachnospiraceae</i> and <i>Alistis</i>	(Yan et al., 2019)

change the composition of SCFAs (Zhu, Han, Ding, Zhu, Song, & Xiao, 2021). Moreover, a high-fat diet causes a decrease in SCFAs compared with a low-fat diet (Wan et al., 2019). SCFAs are associated with many biochemical processes, playing an important role in health benefits. SCFAs have been used as an energy source for intestinal epithelial cells and signaling molecules for the peripheral organs of the intestine. They are also employed to promote the stable state of the gut microbiota (Gentile & Weir, 2018). Fig. 3B shows that SCFAs can regulate lipid metabolism, glucose metabolism, and immune responses, and mediate related gene expression.

Enterohepatic circulation is involved in the metabolism of dietary flavonoids. As an immune organ comprising immune cells, the liver is exposed to gut microbiota through the portal vein. The intimate cross-talk between the liver and the gut is associated with the metabolism of nutrients and the clearance of bacterial metabolites (Gentile and Weir, 2018; Koudoufio, Desjardins, Feldman, Spahis, Delvin, & Levy, 2020; Moorthy, Chaiyakunapruk, Jacob, & Palanisamy, 2020). Bile acid metabolism is a complex process, and the metabolites of microbial regulation contribute to the diversity of the hydrophobic bile acid pool. The regulation of gut microbiota might be associated with both bile acid synthesis and uptake. Moreover, dietary flavonoids can be used to promote bile acid homeostasis (Duan et al., 2021; Wang, Xia, Yang, & Tang, 2019).

4. Current challenges and future perspectives

Although much progress has been achieved to strengthen and clarify the metabolism, bioavailability, and health promotion of dietary flavonoids, it is difficult to verify the full potential of dietary flavonoids due to the numerous challenges and barriers to clarifying their roles. As the most susceptible property, the low bioavailability of dietary flavonoids contributes to the limitations of health benefits. The smart, flexible design of delivery systems or encapsulation with edible materials is urgently needed to address the low stability and non-targeted release of

dietary flavonoids.

Lifespan-essential dietary flavonoids are consistently associated with health promotion, and the lack of flavonoids leads to an increased risk of developing chronic diseases. Current studies are mainly performed using animal models or *in vitro* experiments, and medium- and long-term health promotion investigations should be strengthened for understanding the mechanisms of health regulation of dietary flavonoids or flavonoid-rich food intake.

As one of the frontiers of food nutrition, the reshaping of gut microbiota by dietary flavonoids for health promotion has attracted numerous interests. Engagingly, future food design should be performed according to gut microbiota feeding for achieving health benefits (Ercolini & Fogliano, 2018). Although much progress has been made on gut microbiota regulation by dietary flavonoids, achieving the goal of health benefits and precision nutrition is still an urgent task. Challenges remain for the identification of gut microbiota in complex matrices, particularly at low concentrations with insufficient resolution, as well as uncultured microbes. Although considerable efforts are underway currently by multi-omic analysis, advanced techniques should be further developed to evaluate the regulatory mechanisms of dietary flavonoids for gut microbiota.

Although numerous studies have indicated that different dietary flavonoids or metabolites and catabolites of flavonoids achieve health promotion through gut microbiota regulation, systematic research is still urgent to clarify the mechanism of action. Therefore, in the current perspective, a research framework (Fig. 4) is proposed, contributing to further research and understanding of the benefits of dietary flavonoids through gut microbiota regulation. It may also help perform innovative novel research toward precision nutrition.

Given the insufficient reports on the change of gut microbiota by dietary flavonoid intake among populations in different areas, achieving a distinct conclusion on the differences in gut microbes that contribute to flavonoid metabolism among populations in different areas is difficult. Gut microbiota among populations in different areas may vary due

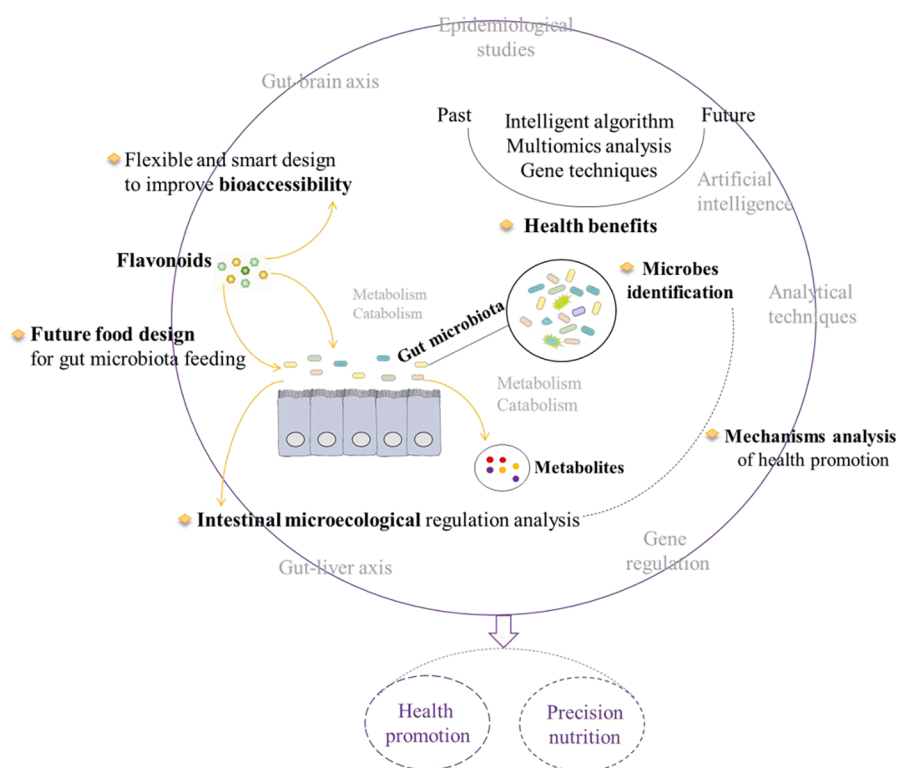


Fig. 4. Research framework for the analysis of the health promotion mechanisms of dietary flavonoids through gut microbiota regulation, as well as the systematic research toward precision nutrition.

to their diet structures, causing dissimilar behaviors of flavonoid metabolism (Kawabata, Yoshioka, & Terao, 2019). Precision nutrition among populations in different areas may be developed by the clarification of gut microbiota that contributes to flavonoid metabolism (O'Grady & Shanahan, 2021).

Importantly, more valuable results can be achieved by performing research to (i) clarify the molecular mechanism of dietary flavonoids for gut microbiota regulation accurately, (ii) evaluate the metabolic changes of digestion under the modulation of food matrix–flavonoid interactions by using simulated digestion system, (iii) understand the mechanisms of dietary flavonoids under metabolic environments comprehensively rather than simply reflecting the output of health effects in human beings, (iv) reveal the theoretical molecular mechanisms of dietary flavonoids for gut microbiota regulation by multi-omic analysis and intelligent algorithms, (v) determine the individual response to dietary flavonoids in different intestinal microecological backgrounds, and (vi) develop precision nutrition based on dietary flavonoids–gut microbiota interactions.

Overall, the current perspectives provide new insights into how dietary flavonoids regulate gut microbiota and how gut microbiota improves health status, offering new prospects for future research trends and opportunities to boost functional food product development toward precision nutrition.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.foodchem.2022.133959>.

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