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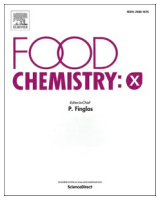

Effects of derivatization and probiotic transformation on the antioxidative activity of fruit polyphenols

Yixuan Wang [a,1], Chenxi Wang [a,1], Junling Shi [b,*], Yan Zhang [a,*]

[a] School of food science and technology, Shihezi University, Road Beisi, Shihezi, Xinjiang Province 832003, China.
[b] Key Laboratory for Space Bioscience and Biotechnology, School of Life Sciences, Northwestern Polytechnical University, Shaanxi, Xi'an Province 710072, People's Republic of China.

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ABSTRACT

Fruits contain numerous polyphenols in the form of conjugates, which exhibit low antioxidant activity. Probiotic fermentation is a strategy to improve the antioxidant activity of these conjugated polyphenols by modifying their structure. However, the mechanisms underlying the effects of functional groups and derivatizations on the antioxidative activities of polyphenols and the antioxidation enhancement by probiotic biotransformation haven't been comprehensively explored. This review aimed to explore the structure–antioxidant activity relationships of four functional groups and three derivatizations in flavonoids and phenolic acids. Further, the review elucidated the antioxidant mechanisms underlying the biotransformation of flavonoids and phenolic acids as glycoside, methylated, and ester conjugates by probiotic biotransformation. Deglycosylation, demethylation, and hydrolysis catalyzed by enzymes produced by *Bifidobacterium* and *Lactobacillus* facilitated the conversion of conjugated polyphenols into flavonoids and phenolic acids with hydrolyzed forms and highly active functional groups, thereby increasing hydrogen supply and electron transfer capacity to enhance the antioxidant activity.

1. Introduction

Polyphenols are secondary metabolites with diverse chemical structure and function and are widespread in fruits, which are more than 8000 phenolic structures currently known(Durazzo et al., 2019). They comprise a wide variety of molecules that contain a classic phenol ring structure (i.e. several hydroxyl groups in aromatic rings), which structure can vary from simple molecules to complex polymers with highly polymerized compounds (Câmara et al., 2020). These can be classified by origin, biological activities, and chemical structure, which is the most commonly used classification(Wojtunik-Kulesza et al., 2020).There are two key structural groups of polyphenols: flavonoids and phenolic acids (Fig. 1A). Both flavonoids (e.g. flavonols, flavones, chalcones, anthocyanins, flavanones and flavanols) and phenolic acids (e.g. hydroxybenzoic acids, hydroxycinnamic acids) generally accumulate in the vacuoles of fruits as glycoside, methoxy and ester conjugates or as hydrolyzed glycoside, methoxy and ester conjugates (Fig. 1B). Flavonoids are classified into different subclasses due to the oxidation state of the C-ring and the hydroxyl groups attached to different positions in the B-ring. Among which there are many substances represented by flavonols, such as kaempferol (e.g., kaempferol-3-O-rutinoside and kaempferol-3-O-glucoside), quercetin (e.g., quercetin-3-O-rutinoside and quercetin-3-O-glucoside), myricetin (e.g. myricetin-3-rutinoside and myricetin-3-glucoside) and isorhamnetin (e.g., isorhamnetin-3-rutinoside and isorhamnetin-3-glucoside), and some represented by flavones, such as apigenin (e.g., vitexin), luteolin (e.g., luteolin-7-O- glucoside), as well as others represented by isoflavones, such as daidzein, genistein, glycitein, and phlorizim which represented by chalcones are found in different fruits (e.g., tomato, sea buckthorn, *lycium chinense*, grapes, and jujube.) (Aparecida Plastina Cardoso et al., 2021; Fia, Bucalossi, Proserpio, & Vincenzi, 2021; Kumar et al., 2021; Neelam, Dey, Sim, Lee, & Au Eong, 2021).

Fruits also contain various flavonoid aglycones and polyhydroxy compounds, such as kaempferol, quercetin, gallocatechin, epicatechin, catechin, myricetin, apigenin, luteolin, naringenin, hesperetin, cyanidin and phloretin. Phenolic acids are the majority of the non-flavonoid class of polyphenols, and are characterized by a carboxyl group linked to the benzene ring. These compounds can be further subdivided into hydroxybenzoic acids (C1-C6 backbone) and hydroxycinnamic acids (C3-C6 backbone)(Durazzo et al., 2019). Phenolic acids also contain

* Corresponding authors.
E-mail addresses: sjlshi2004@nwpu.edu.cn (J. Shi), yanzhangzqgh@shzu.edu.cn (Y. Zhang).
[1] co-first author.

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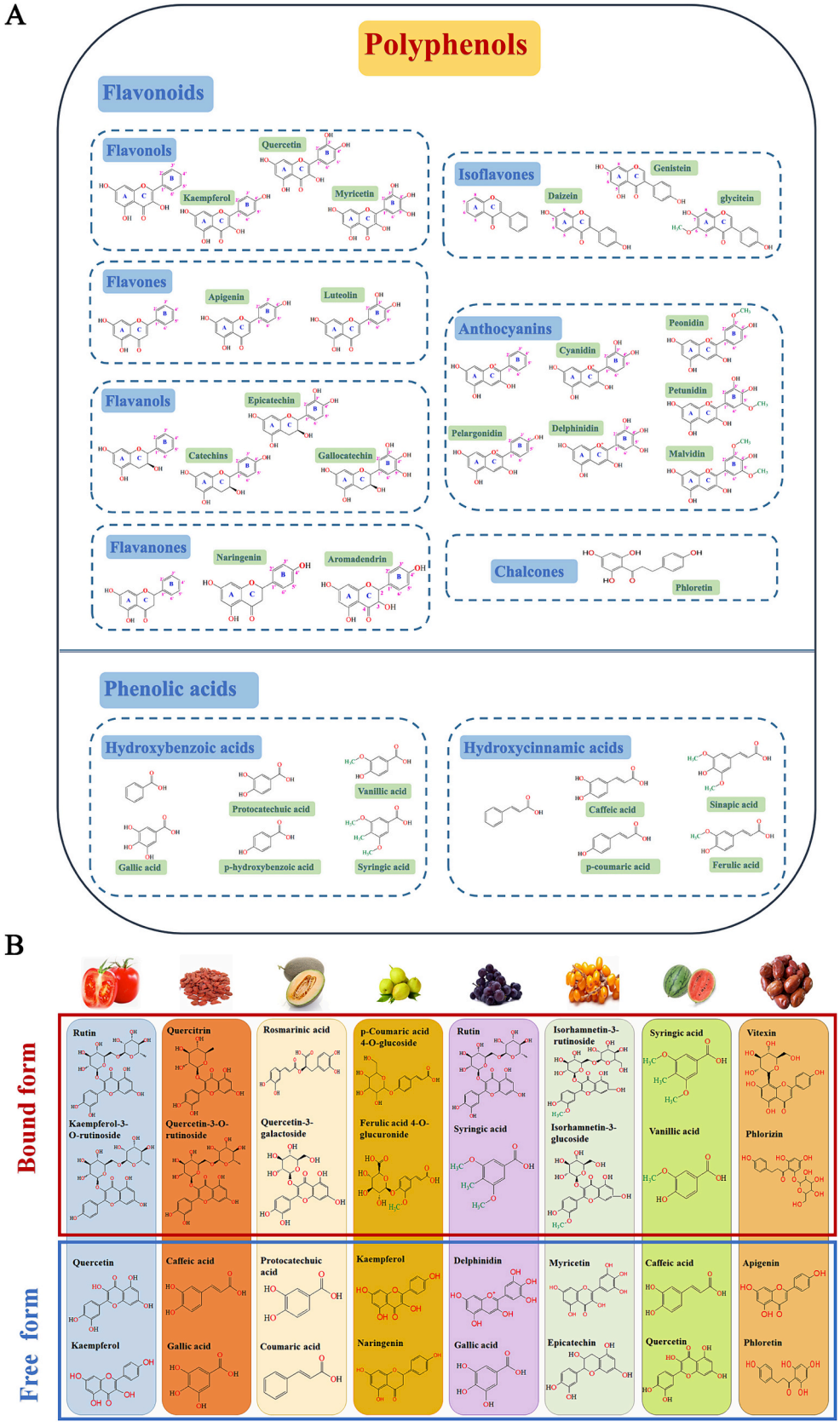

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Fig. 1. The structural characteristics and form of phytogenic polyphenols **(A):** Structural characteristics and representative substances of flavonoids and phenolic acids. The blue bond polyphenols was the types of polyphenols; The positions of the A, B and C rings are marked in blue in the structure of flavonoids; Oxygen represents red; methyl group represents green; **(B):** Glycoside, methylated, and ester conjugates and hydrolyzed conjugates in different classes of polyphenols in fruits. The polyphenols in the red circle was the form of glycoside, methylated, and ester conjugates (Bond form) in the different fruits; The polyphenols in the blue circle was the hydrolyzed glycoside, methoxy and ester conjugates form (free form) in the different fruits. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

glycoside, methoxy and ester conjugates, as well as methylated (e.g., vallic acid and syringic acid), esterified (e.g., rosmarinic acid) and glycoside forms (e.g., gallic acid 4-O-glucoside, protocatechuic acid 4-O-glucoside, and p-Coumaric acid 4-O-glucoside)(Domínguez et al., 2020; Gómez-García, Campos, Aguilar, Madureira, & Pintado, 2020; Tkacz et al., 2020). Gallic acid, protocatechuic acid and p-hydroxybenzoic acid are the main hydroxybenzoic acids in fruits, and caffeic, p-coumaric, and ferulic acids are examples of hydroxycinnamic derivatives present in fruits as glycoside, methoxy, and ester conjugates (Kuşçu & Bulantekin, 2020).

Multiple biological functions of polyphenols have been reported. Polyphenols can affect multiple diseases (e.g., cardiovascular disease, atherosclerosis, hypertension, diabetes, insulin resistance and obesity) and impact several bioactivities (e.g., anti-oxidative, anti-inflammatory, anti-aging, anti-mutagenic and anti-carcinogenic activities). Aglycones and hydrolyzed conjugates are bioavailable molecules with human health benefits. Septembre-Malaterre et al. summarized the effects of quercetin to decrease serum enzyme markers, resist virus cells (e.g., HCV, HBV, and MNoV) and inhibit the production of inflammatory factors (e.g., TNF-α, iNOS, and NO)(Septembre-Malaterre et al., 2022). Robert Kubina et al. reported that kaempferol can decrease inflammation, change disease activity, and alleviate resistance to antibiotics and chemotherapeutics(Kubina, Iriti, & Kabała-Dzik, 2021). Naringenin downregulates inflammation-mediated nitric oxide overproduction and potentiates endogenous antioxidant status during hyperglycemia (Rehman, Khan, Akash, Jabeen, & Haider, 2020). Yang, A.Y et al. reported that hesperetin has antioxidant, antiapoptotic, and anti-inflammatory effects in in a mouse model of lipopolysaccharide-induced cute kidney injury(A. Y. Yang, Choi, Kim, & Leem, 2023). Phloretin can suppress the NLRP3/Caspase-1/IL-1beta pathway to reverse structural and electrical remodeling after myocardial infarction to prevent the occurrence of ventricular arrhythmias and heart failure, and inhibited doxorubicin-induced oxidative stress and reduced nitric oxide levels in cardiac tissues of rats(B. Li, Xu, Liu, Zhou, & Jiang, 2023). Furthermore, apigenin, myricetin, epicatechin, cyanidin, gallic acid, and caffeic acid have antioxidant, cardio protective, anti-inflammatory, antibacterial, antiviral, and anticancer activities (Septembre-Malaterre et al., 2022).

Different compounds can vary in activity. Among flavonoids, gallocatechin, epicatechin and catechin, as typical representatives of flavanols, also have different activities due to their structural differences. Gallocatechin is the flavanol with has three hydroxyl groups in Ring B. Gallocatechin has high antioxidant activity and showed positive correlation with ABTS and DPPH free radical scavenging(Gris et al., 2011). Epicatechin has two hydroxyl groups in positions 3′ and 4′ and exhibits stable time-dependent antioxidant activity (IC50 value of 1.5 mug mL (−1)) and anticardioprotection activity(Jug, Naumoska, & Vovk, 2021). Catechin has a 4′-hydroxyl group, and has both antioxidant and anticholinesterase activities(Franca et al., 2023). Phloretin is a kind of chalcone and phlorizin is the glycoside form of phloretin, however, phlorizin has lower anti-inflammatory and antioxidant activities than phloretin(Chang, Huang, & Liou, 2012; Ongay, Granato, & Barreto, 2023). For phenolic acids, p-hydroxybenzoic and p-coumaric acid have a mono hydroxylation structure and lower antioxidant activity than protocatechuic acid and caffeic acid that have a di-hydroxylation structure. Caffeic acid has a higher antioxidant activity than that of protocatechuic acid, likely due to the different substituents and the position of substituents on the benzene ring(Gao, Li, Li, Zhang, & Liang, 2022). However, phenolic compounds substituted with a higher number of hydroxylic groups are reported to exhibit better antioxidant and anticancer properties compared with ones with no hydroxylic group substitution or –OCH3 derivatization. Vanillic acid and syringic acid are hydroxybenzoic acids with methoxy groups. These two phenolic acids both have anti-inflammatory properties(Grigalius & Petrikaite, 2017), but only vanillic acid showed positive correlation with DPPH free radical scavenging activity(Ashengroph, Nahvi, Zarkesh-Esfahani, & Momenbeik, 2011). And some flavonoids and phenolic acids with glycosides, methoxy and ester conjugates typically have lower activity, and few of these substances have been reported to have antioxidant and anti-inflammatory properties (Laoué, Fernandez, & Ormeño, 2022).

In general, flavonoids and phenolic acids almost all exist as glycosides, methoxy and ester conjugates in fruits, including as products of derivatization (e.g., glycosylation, methylation and esterification). These polyphenolic conjugates typically have lower activities than their hydrolyzed products, and different functional groups can affect the antioxidant activity of polyphenols that are not derivatised. This suggests that polyphenol structure is an important determinant of bioactivity.

Many studies have investigated the relationships between different structures and functional activities of polyphenols, especially for the antioxidant activity of flavonoids and phenolic acids(Gulcin, 2020; J. Yang, Chen, Hao, & Liu, 2021). For phenolic acids, the antioxidant activity is dependent on: (1) The number and position of the hydroxyl groups; (2) Glycosylation or methylation; (3) The distance between the -COOH and the aromatic ring; (4) The presence of a -CH=CH-COOH group. For flavonoids, the antioxidant activity is dependent on: (1) A-ring and B-ring with an ortho-dihydroxy (catechol) group; (2) the number and position of the hydroxyl groups in the A-ring and B-ring; (3) A-ring and C-ring with a 4-oxo group and a double bond between C-2 and C-3; (4) A-ring and C-ring with a 3- hydroxyl group and a double bond between C-2 and C-3; (5) A-ring and C-ring with 4-oxo groups and -OH groups near C-3 and C-5; and (6) Glycosylation or a methoxyl group at the C-3 position; both can reduce the high free radical scavenging ability.

The antioxidant activity of flavonoids and phenolic acids is also dependent upon the presence of hydroxyl groups at specific positions on the skeleton of flavonoids and phenolic acids. Various action mechanisms are involved in the quenching of free radicals by flavonoids and phenolic acids, with three considered primary antioxidant actions(Z. Xiao, Wang, Wang, Li, & Ma, 2019). First, hydrogen atom transfer (HAT), a one-step reaction governed by the O—H bond dissociation enthalpy. Second, single electron transfer followed by proton transfer (SET-PT), a first step that is governed by the ionization potential. Thirdly, sequential proton-loss electron transfer (SPLET), a first step governed by proton affinity.

However, there has been no systematical summarized of the antioxidant mechanisms of the different functional groups and flavonoids and phenolic acids with the structures of glycoside, methoxy and ester conjugates and non-derivatised. Overall, a better understanding of the differences in structure–antioxidant activity relationships and antioxidant mechanisms of flavonoids and phenolic acids in the form of glycoside, methoxy and ester conjugates and glycoside, methoxy and ester conjugates hydrolyzed would greatly help the determination of strategies to enhance antioxidant potential. Additionally, there is an ongoing demand to explore processing techniques to transform the polyphenolic compounds in the form of glycoside, methoxy and ester

conjugates with lower antioxidant activities to the polyphenolic compounds in the form of glycoside, methoxy and ester hydrolyzed conjugates with higher antioxidant activities.

In recent years, biotransformation has been explored as a strategy with immense potential to produce novel bioactive polyphenols. However, the bioavailability of bioactive polyphenols in the gastrointestinal (GI) tract is crucial to their health benefits. The polyphenolic compounds in the form of glycoside, methoxy, and ester conjugates improve the stability of bioactive polyphenols. However, these polyphenols have poor bioavailability due to factors such as solubility and complex chemical structure, which limit their metabolism (Câmara et al., 2020). Flavonoids in the form of rhamnoglucosides and polymeric tannins, such as rutin, hesperidin, naringin, and procyanidins, have low bioavailability in the GI tract (Amaretti, Raimondi, Leonardi, Quartieri, & Rossi, 2015; Mueller et al., 2017). Probiotics fermentation, especially with *Lactobacillus* and *Bifidobacterium* species, can modify the structure of plant-based polyphenols to improve their bioavailability and antioxidant potential (Cao, Chen, Jassbi, & Xiao, 2015). The transformation of the polyphenolic compounds from glycoside, methoxy, and ester conjugates with lower bioavailability into hydrolyzed conjugates with higher bioavailability through probiotics fermentation enhances the antioxidant potential of bioactive polyphenols in the human body. There have been several qualitative reviews on probiotics biotransformation of polyphenols have been published, with reports of changes in deglycosylation, demethylation, hydrolysis, decarboxylation, hydroxylation, dehydrogenation and oxidation(Braune & Blaut, 2016; Gaur & Gänzle, 2023). However, there has been no comprehensive review of the mechanisms of probiotics biotransformation, which transforms low antioxidant active polyphenols into high antioxidant active polyphenols. Therefore, in this review, we summarize recent research progress on fruit polyphenols including structural characteristics, form, and function. We also discuss the structure–antioxidant activity relationship and antioxidant mechanisms of flavonoids and phenolic acids in the form of glycoside, methoxy and ester conjugates and which in the form of glycoside, methoxy and ester hydrolyzed conjugates, and explore the mechanistic basis of enhanced antioxidant activity of the phenolics in the form of glycoside, methoxy and ester conjugates and partially phenolics in the form of glycoside, methoxy and ester hydrolyzed conjugates by probiotic biotransformation with reference to the structure–antioxidant activity relationships and antioxidant action mechanisms.

2. Effects of functional groups on the antioxidative activity of polyphenols

It has been widely found that the antioxidative activity of polyphenols varies greatly with their structure. The mechanisms for polyphenols to perform their antioxidative activity include: direct scavenging of radicals, inhibition of reactive oxygen species (ROS), activation of antioxidant enzymes, activation of metal-chelating activity, inhibition of oxidases (e.g., xanthine oxidase [XO], cyclooxygenase [COX], lipoxygenase, and phosphoinositide 3-kinase [PI3K]), and reduction of α-tocopheryl radicals. Of these mechanisms, study of the antioxidant mechanism has revealed that free radical scavenging is related to the overall polyphenol structure(Gulcin, 2020). Free radicals are highly active molecules produced during cellular respiration and normal metabolism, and reactive oxygen species (ROS) are closely related to physiological and pathological processes in animals. The species mainly include superoxide anion free radicals (O2-), hydroxyl free radicals (OH-), hydrogen peroxide (H2O2), and others. Numerous action mechanisms are involved in the quenching of free radicals by flavonoids and phenolic acids, with three considered primary antioxidant actions (Z. Xiao et al., 2019), which including hydrogen atom transfer (HAT), single electron transfer followed by proton transfer (SET-PT) and sequential proton-loss electron transfer (SPLET). The structure of flavonoids and phenolic acids affects the mechanism by which the moiety interacts with surrounding free radicals and therefore the antioxidant activity. There are two main findings of recent work in this area: 1) the key functional groups affect the antioxidant activity of polyphenols; 2) addition of glycoside, methoxy and ester conjugates after derivatization, can reduce antioxidant activity (as shown in Table S1).

2.1. Key functional groups for the antioxidative activities of flavonoids and phenolic acids

2.1.1. Hydroxyl groups

Hydroxylation is the process of introducing hydroxyl groups (OH) via substitution of functional groups or hydrogen atoms. This contributes to the formation of different classes of phenolic acids and flavonoids and increases the number of hydroxyl groups(Staniek et al., 2013). Panche et al. suggested that hydroxylation of flavonoids can improve their biological properties, including antioxidant and chelation activities(Panche, Diwan, & Chandra, 2016). Flavonoids with more than hydroxyl groups on the A-ring(Mierziak, Kostyn, & Kulma, 2014) and B-ring(L. Chen & Kang, 2013) exhibit higher antioxidant activity. For example, dihydroxy B-ring flavonoids, such as quercetin and lignans, are better scavengers of free radicals generated by UV irradiation than monohydroxy B-ketones, such as apigenin and kaempferol(Agati, Azzarello, Pollastri, & Tattini, 2012; Fini, Brunetti, Di Ferdinando, Ferrini, & Tattini, 2014). However, polyhydroxy phenolic acids including caffeic acid and gallic acid have higher antioxidant activities than mono-hydroxycinnamic acid (p-coumaric acid) and mono-hydroxybenzoic acid (protocatechuic acid)(Masek, Chrzescijanska, & Latos, 2016; Rzepecka-Stojko et al., 2015). Mono-hydroxy derivatives of phenolic acid have good antioxidant properties due to meta-hydroxylation, and dihydroxy derivatives of phenolic acids have high antioxidative activity by ortho- and meta-hydroxylation(J. Chen et al., 2020). The presence of polyhydroxyl groups provides more OH hydrogen bonding sites in ArOH, forming more unstable electrons for hydrogen supply and electron transfer, and ultimately scavenging free radicals (Gulcin, 2020)(Fig. 2A).

2.1.2. -CH=CH-COOH groups

Both hydroxycinnamic and hydroxybenzoic acids have antioxidant activity, with higher antioxidant activity for hydroxycinnamic acid compared to that of hydroxybenzoic acid. Caffeic acid, p-hydroxybenzoic acid, p-coumaric acid, gallic acid and protocatechuic acid have strong antioxidant activity(Castelluccio et al., 1995; RiceEvans, Miller, & Paganga, 1996; Singh, Kim, & Lee, 2022), with higher antioxidant activities of hydroxycinnamic acids (caffeic acid) than those of hydroxybenzoic acids (protocatechuic acid)(Masek et al., 2016). This is because hydroxybenzoic and hydroxycinnamic acid have -COOH groups, and -COOH can affect the ionic domains around ArOH to promote the formation of unstable electrons to facilitate the scavenging of free radicals. Similarly, -CH=CH also can affect the ionic domains around ArOH to increase the scavenging of free radicals (Gulcin, 2020). Hydroxycinnamic acid analogues with -CH=CH-COOH groups generate more ROOH through the efficacy superposition of the two groups, and the composite group can also generate ROO^{-} to stabilize free radicals. Therefore, hydroxycinnamic acids with -CH=CH-COOH exhibit higher antioxidant activities than the corresponding hydroxybenzoic acids (Balasundram, Sundram, & Samman, 2006; RiceEvans et al., 1996) (Fig. 2B).

2.1.3. A or B-ring with an ortho-dihydroxy(catechol) group

Ortho-dihydroxy(catechol) groups are widely present in phenolic acids and flavonoids. The importance of an A or B-ring with an ortho-dihydroxy(catechol) group in flavonoids and antioxidant activity has been studied. Gomes(Gomes et al., 2012) compared the antioxidant activity of trihydroxyflavones containing hydroxyl groups in different positions and found that the ortho-dihydroxy group is required for free

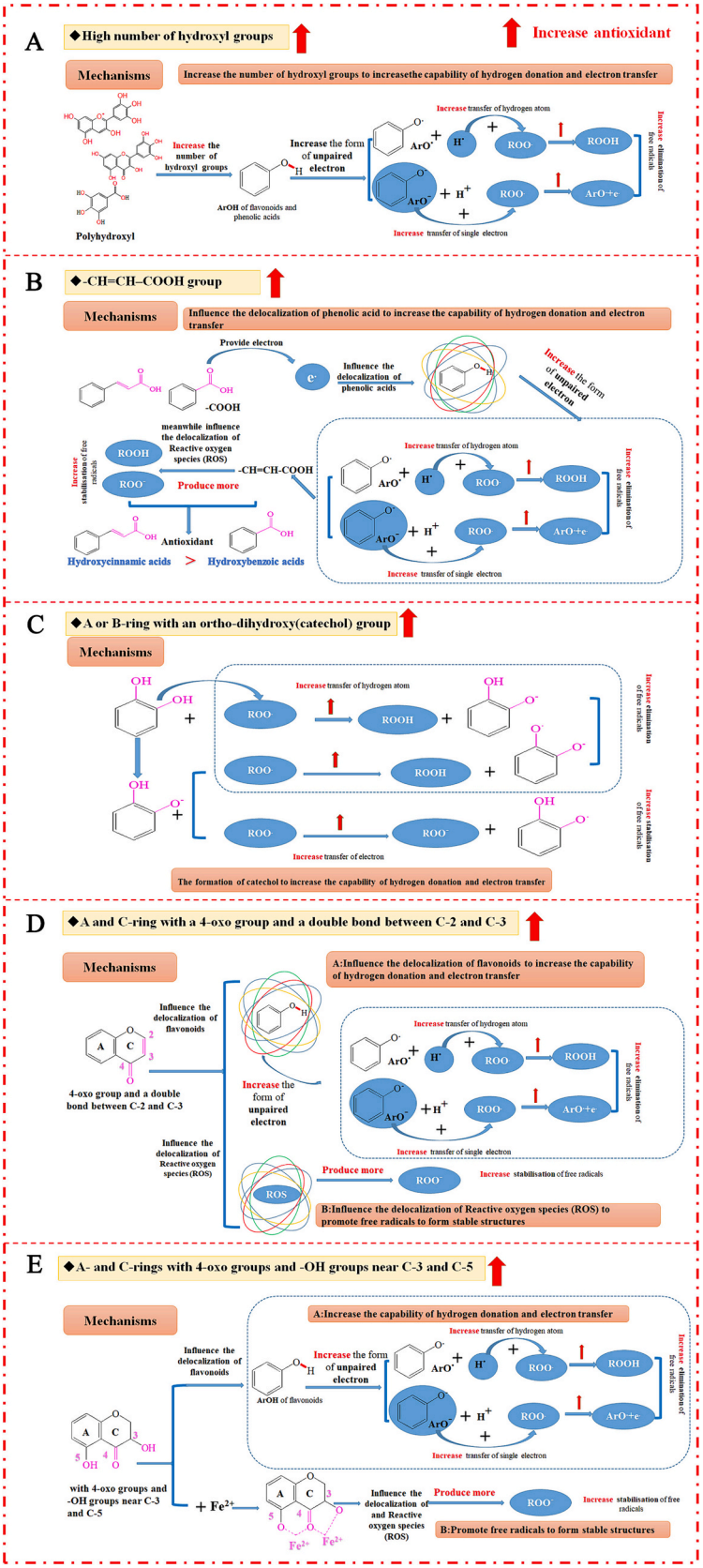

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Fig. 2. Constitutive mechanism for key functional groups for the antioxidative activities of flavonoids and phenolic acids. **(A):** Mechanisms of a high number of hydroxyl groups increases the antioxidant activity. **(B):** Mechanisms of -CH=CH and -COOH groups increases the antioxidant activity of phenolic acid. **(C):** Mechanism of A-ring or B-ring with an ortho-dihydroxy(catechol) group increases antioxidant activity of flavonoids. **(D):** Mechanism of A-ring and C-ring with a 4-oxo group and a double bond between C-2 and C-3 increases the antioxidant activity of flavonoids. **(E):** Mechanism of A-ring and C-ring with 4-oxo groups and -OH groups near C-3 and C-5 increase the antioxidant activity of flavonoids.ROO represents peroxyl Radical; ArOH represents benzene ring structure with hydroxyl groups in the side chain.

radical scavenging activity. Similarly, Ignas Grigalius reported that trihydroxyflavones have high DPPH free radical scavenging and anti-lung (A549), breast (MCF-7), and brain epithelial (U87) cancers due to the presence of the ortho-dihydroxy (catechol) group in B-ring, with higher antioxidant activity than apigenin which lacks this structure(Grigalius & Petrikaite, 2017). Other groups reported that hydroxybenzoic acid containing the ortho-dihydroxy(catechol) group had enhanced antioxidant activity. ŽIVANOVIĆ et al. investigated the effect of UV irradiation on polyphenol contents in tomatoes and found that hydroxycinnamic acids with ortho-dihydroxyl substitution on the B-ring (e.g. caffeic acid) are more efficient antioxidants than those with a single hydroxyl group (ŽivanoviĆ et al., 2017). Thus, the presence of an A-ring or B-ring with an ortho-dihydroxy(catechol) group increases the antioxidant activity of flavonoids. This is because one hydroxyl group in catechol can supply hydrogen to bind with ROO• to form ROOH. Catechol^{-} is formed when catechol loses one H^{+}, and this can supply hydrogen to bind to ROO• to form ROOH. Catechol^{-} can also bind to ROO• to form ROO^{-}. The formation of ROOH decreases free radicals, and the formation of ROO^{-} stabilizes free radicals. Thus, these two mechanisms explain why flavonoids containing the ortho-dihydroxy(catechol) group have higher antioxidant activities (Fig. 2C).

2.1.4. A-ring and C-ring with a 4-oxo group and a double bond between C-2 and C-3

Flavones and flavonols have an A-ring and C-ring with a 4-oxo group and a double bond between C-2 and C-3. Compared to flavones and flavonols, flavanones and flavanols lack these structures(Trigo, Alexandre, Saraiva, & Pintado, 2019). In studies of the antioxidant activities of these four groups of compounds, the flavones and flavonols exhibit stronger activities than those of flavanones and flavanols. Quercetin in flavonols and epicatechin in flavanols have the same number of hydroxyl groups, but the antioxidant activity of catechin is lower than that of quercetin(Chimi, Cillard, & Rahmani, 1991). Dome Barna et al. reported a stronger positive correlation between flavones such as apigenin and antioxidant activity than flavanones such as naringenin(Barna et al., 2022). Similarly, Cristina Arteaga et al. reported that apigenin could protect zebrafish embryos against oxidative stress while naringenin did not(Arteaga et al., 2021). Epicatechin does not have a double bond at the C2 and C3 and does not have a 4-oxo group, and naringenin also lacks the double bond at the C2 and C3. There are two main effects of these two groups. First, these two groups affect the ionic domains around ArOH in flavonoids, which further increases the formation of unpaired ArO• and ArO^{-} and promotes the scavenging of free radicals by hydrogen supply and electron transfer(Burda & Oleszek, 2001). Second, these two groups can affect the electrons around the radicals and promote the formation of ROO^{-} (Bors, Heller, Michel, & Saran, 1990; Gulcin, 2020)(Fig. 2D).

2.1.5. A- and C-rings with 4-oxo groups and -OH groups near C-3 and C-5

Among flavonoids, flavonols have been reported to have strong antioxidant activity and defend against oxidative stress-related diseases due to their A- and C-rings with 4-oxo groups and -OH groups near C-3 and C-5(Samsonowicz & Regulska, 2017). The most studied flavonols are kaempferol, quercetin, and myricetin with demonstrated antioxidative properties and a potential role in UV-defense, suggesting these compounds are critical for plant adaptation to climate change(Laoué et al., 2022). These three flavonols all have high antioxidant, anticancer, antiviral and anti-inflammatory activities(Septembre-Malaterre et al., 2022). Compared with flavonols, flavones lacking a 3-OH have lower antioxidant activity. As an example, in vegetable amaranth, there are higher levels of flavonols such as myricetin, leading to an increase in the ability to scavenge free radicals, while flavones such as apigenin do not have this ability(Sarker & Oba, 2020). This suggests that flavonoids with 4-oxo groups in both A- and C-rings and -OH groups near C-3 and C-5 have higher antioxidant activity. Studies of this correlation have determined that the structure can influence the ionic domains around ArOH to contribute to the formation of unstable free radicals. This increases hydrogen supply and electron transfer, to promote the scavenging of free radicals(Apak, Özyürek, Güçlü, & Çapanoğlu, 2016). Additionally, this structure can chelate with metal ions such as O on C-4, C-3 and C-5, which can combine with Fe for unstable forms. Electron transfer during metal chelation affects the ionic domains around the free radicals, which contributes to the formation of more ROO^{-} with stabilized forms(Ghosh et al., 2015; Gulcin, 2020) (Fig. 2E).

As described above, the presence of key functional groups increases the antioxidant activity of polyphenols, whereas during plant growth, polyphenols undergo derivatization to form more stable glycoside, methoxy and ester conjugates, and these structures lead to reduce antioxidant activity.

2.2. Decrease of antioxidative activity by derivatization

2.2.1. Glycosylation

Polyphenol structure can be modified by glycosylation (Subramanyam, Takahashi, Nagatoishi, Kuroda, & Tsumoto, 2018), such as replacing hydroxyl groups with O-glycosides or linking with C to form C-glycosides. Glycosylation affects the water solubility, transportability, and stability of plant polyphenols(Alseekh, Perez de Souza, Benina, & Fernie, 2020). João P. Trigo et al. reviewed studies of the effect of glycosylation on the functional activity of polyphenols and reported that substitution of hydroxyl groups by glycosylation generally decreases antioxidant activity(Trigo et al., 2019). Among isoflavonoids, soy isoflavone glycosides (e.g. daidzin, genistein, and glycitin) have significantly lower antioxidant activities than their aglycone counterparts (e.g. daidzein, genistein, and glycitein)(Cai, Mei, Jie, Luo, & Corke, 2006). Jianbo Xiao reported that flavonols and flavonol aglycones (quercetin, kaempferol, apigenin, baicalein, and luteolin) extracted from traditional Chinese medicines showed higher free radical scavenging rates than their corresponding glycosides, including quercetin 3-O-glucoside, quercetin 3-O-rutinoside, quercetin 3-O-rhamnoside, quercetin 3-O-glucoside-7-O-rhamnoside, kaempferol 3-O-glucoside, apigenin-7-O-glucoside, baicalin, and luetrolin-7-O-glycoside(J. Xiao, 2015). Overall, phenolic acids and flavonoids with glycosides have lower antioxidant activities than their aglycones. There are two main conclusions of recent investigations into the constitutive mechanism through which glycosides reduce antioxidant activity. First, glycosides reduce the formation of unpaired ArO• and ArO^{-} by affecting hydrogen bonding in ArOH in flavonoids and phenolic acids, which further reduces the binding of the H-atoms and ROO• and the transfer of single electrons to ultimately reduce the scavenging of free radicals by ArOH (Xu et al., 2020). Second, glycosides will directly reduce the ability of ArOH to bind directly to ROO• and then reduce the formation of the stable form of free radicals (ROO•)(Choi et al., 2002) to thus reduce the antioxidant activity (Fig. 3A).

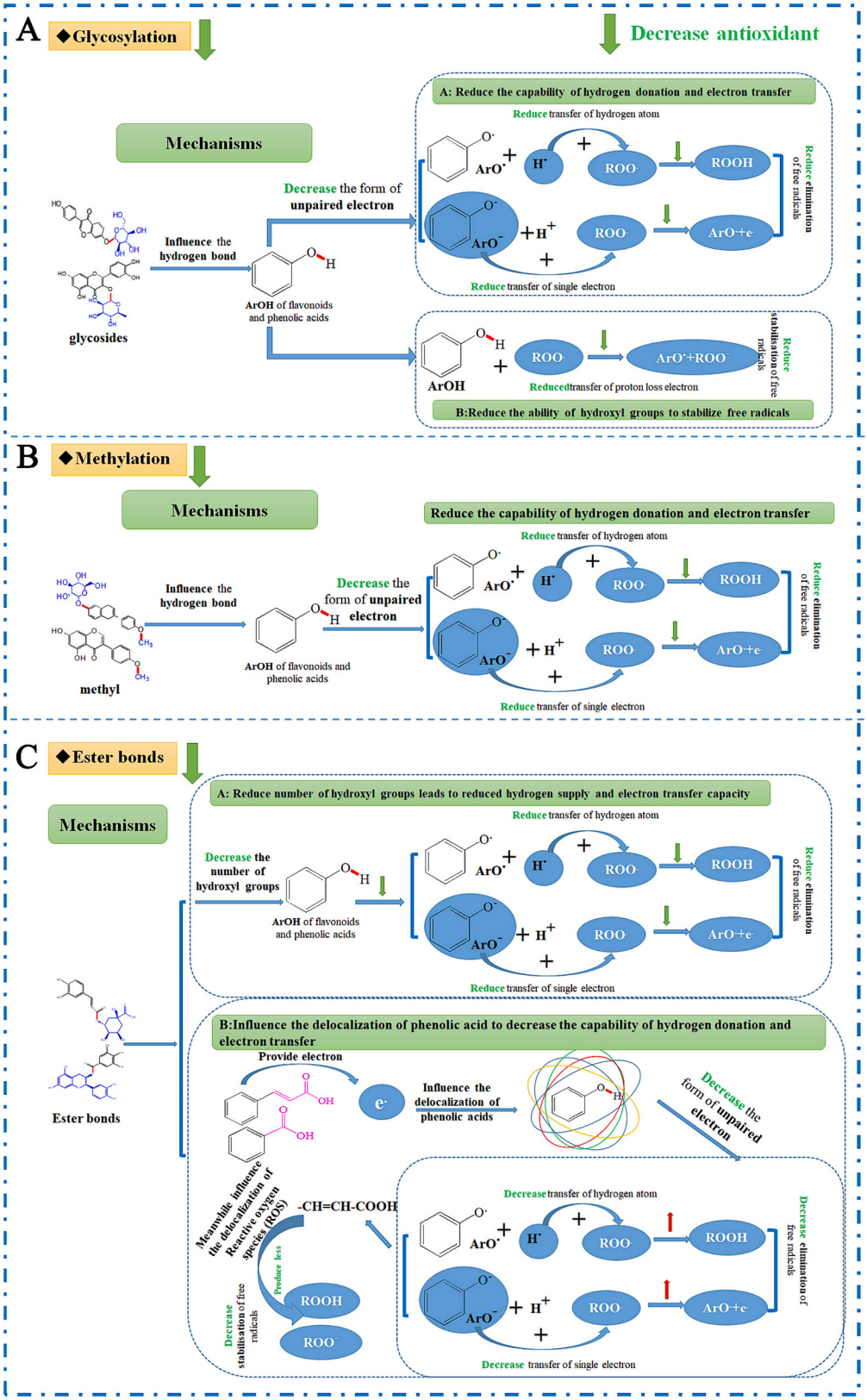

Fig. 3. Constitutive mechanism of decrease of antioxidative activity by derivatization. **(A):** Mechanisms of glycosylation decreases the antioxidant activity of phenolic acid and flavonoids. **(B):** Mechanisms of methylation decreases the antioxidant activities of phenolic acid and flavonoids. **(C):** Mechanisms of an ester bond decreases the antioxidant activity of some phenolic acids and flavonoids. ROO represents peroxyl Radical; ArOH represents benzene ring structure with hydroxyl groups in the side chain.

2.2.2. Methylation

In addition to glycosylation, methylation also affects the physicochemical properties of plant polyphenols including changes such as decreasing solubility, improving stability and transportability, and affecting color stability(Yang et al., 2011). However, Chen et al. investigated the effects of polyphenol methylation on polyphenol bioactivity in plants and found that methylation tends to reduce the antioxidant potential of some flavonoids and phenolics. For example, O-methoxy substances formononetin and biochanin A have low antioxidant activities(Curiel & Landete, 2022). In addition, 3′,4′-dimethoxyflavone and homoeriodictyol extracted from G. robertianummay may decrease antioxidant activity due to the presence of one or two methylated OH groups, respectively, on the orthocatechol group. Wang and others measured the IC50 of DPPH scavenging activity for quercetin and its methylated forms from *Halimodendron halodendron* and found that the activities were in the following order: quercetin (0. 024 mM) > 3,3′-di-*O*-methylquercetin (0.436 mM) > 3,3′ -di-*O*-methylquercetin 7-O-b-D-glucopyranoside (0.440 mM) > 3-O-b-D-rutinoside (0.842 mM)(J. Wang et al., 2012). Therefore, some phenolic acids and flavonoids with methyl groups have lower antioxidant activities than those of the unmethylated forms. Mechanistic studies have found that the hydrogen bonding of ArOH is affected by the methyl group, reducing the formation of unpaired electrons ($ArO^{\bullet}$ and ArO^{-}), which further reduces hydrogen donation and electron transfer to ultimately decrease the free radical scavenging power(Chen et al., 2017) (Fig. 3B).

2.2.3. Esterization

In nature, esterification can alter the physicochemical properties of polyphenols and phytosomes(Olszowy, 2019). For example, phenolic acids in the form of glycoside, methoxy and ester conjugates to arabinoxylans and other cell wall polysaccharides via ester bonds have enhanced stability(Vitaglione, Napolitano, & Fogliano, 2008), and phenolic acids and flavonoids linked to homogeneous or heterogeneous substances via ester bonds form macromolecular tannins to impart bitter and astringent flavors to phytosomes. Although intriguing, these findings does not directly reveal the effect of ester bonds on antioxidant activity, but a few studies suggested decreasing antioxidant activity of polyphenols in the ester conjugates form with the substitution of ester bonds for functional groups and functionalities. For instance, in Brazilian wines, ellagic acid and epicatechin gallate have diester bonds and corresponded to decreased DPPH and ABTS free radical scavenging ability, while their counterparts gallic acid and epicatechin were positively correlated with the above two indicators(Gris et al., 2011). Chlorogenic acid is a polyphenol and the ester of caffeic acid and quinic acid, and Sato, Y et al. found that caffeic acid had stronger antioxidant activity than that of chlorogenic acid(Sato et al., 2011). Substitution of functional groups by ester bonds reduces antioxidant activity mainly due to the substitution of functional hydroxyl groups by ester bonds. This substitution reduces the number of hydroxyl groups, and thus reduces the scavenging ability of functional hydroxyl groups for free radicals by limiting hydrogen supply and electron transfer(Gülçin, 2011). The substitution of functional groups by ester bonds mainly reduces the antioxidant activity because the -CH=CH-COOH functional groups in phenolic acids can influence the ionic domain of ArOH, which generates unstable electrons to scavenge free radicals by reacting with free radicals. When the two functional groups are present at the same time, they can further influence the nearby ionic domains to stabilize the free radicals(Chimi et al., 1991; Gulcin, 2020). Therefore, when -COOH is esterified, the effect of the functional groups disappears resulting in reduced free radical scavenging and stabilizing abilities, especially for hydroxycinnamic acids (Fig. 3C).

As described above, the structure of phenolic acids and flavonoids affects the antioxidant activity. Removal of derivatised glycosides, methyl and ester conjugates to form functional groups and functionally active sites with high antioxidant activity can enhance the antioxidant activity of polyphenols, suggesting strategies to transform low oxidative activity polyphenols into high antioxidant activity polyphenols.

3. Enhancement of the antioxidative activity of fruit polyphenols and flavonoids by probiotic fermentation

The modification of polyphenol structures can be performed using physical, chemical, enzymatic, and biological methods(Cao et al., 2015). Biological methods include the structural modification of polyphenols by conversion using microbial fermentation. This method has advantages of high efficiency and convenience, and it can increase the quality and functionality of plant polyphenol-derived foods (e.g., antioxidant, antibacterial, and anti-inflammatory activities)(Fouad, Sharaf, Abdelghany, & El Sayed, 2018) There is growing interest in the use of microbial fermentation and the production of probiotic-fermented foods (Lillo-Pérez, Guerra-Valle, Orellana-Palma, & Petzold, 2021). Most of the lactic acid bacteria (LAB) are autochthonous microbiota of raw vegetables and fruits. To get desirable properties on fermented plant-derived food products, LAB has to be adapted to the characteristics of the plant raw materials where phenolic compounds are abundant. In summary, as shown in Fig. 4 and Table S2, *Bifidobacterium* and *Lactobacillus* are commonly used in food fermentation and these bacteria can increase the antioxidant activities of the fermented foods. To dissect the mechanism by which antioxidant activity is enhanced by probiotic fermentation, many studies have explored the biotransformation of phytogenic functional active polyphenols by *Bifidobacterium* and *Lactobacillus*(Kowalski, Gustafson, Carroll, & Gonzalez de Mejia, 2020; Maisto et al., 2021). Conversion reactions that improve antioxidant activity can be classified into two types: 1) The process of removing derivatization that convert derivatization products into polyphenols with key functional groups, including processes of glycosylation, demethylation and hydrolysis that remove glycosides, methyl groups and hydrolyze ester bonds. These processes have been extensively studied in *Bifidobacterium* and *Lactobacillus* (Gaur & Gänzle, 2023); 2) Conversion of polyphenols with low activity to high activity through processes of hydroxylation, dehydrogenation and oxidation to generate highly antioxidant-active substances with multiple hydroxyl groups, double bond, and 4-oxo structure. However, little is known about the hydroxylation, dehydrogenation and oxidation of polyphenols by *Bifidobacterium* and *Lactobacillus.* The following section focuses on what is known about the process of removing derivatization that convert derivatization products into polyphenols with key functional groups, including processes of glycosylation, demethylation and hydrolysis that remove glycosides, methyl groups and hydrolyze ester bonds.

3.1. Deglycosylation

Depending on the site of conversion of glycoside polyphenols by the enzymes produced by probiotics and the substrates for conversion, the deglycosylation reactions of probiotics can be categorized into i) 7-O-glycoside flavonoids ii) 3-O- glycoside flavonoids iii) chalcone glycosides and iv) hydroxycinnamic acid glycoside deglycosylation, as shown in Fig. 5. Overall, deglycosylation improves the antioxidant activity of polyphenols by the removal of glycosides, increasing the number of functional hydroxyl groups, and promoting the formation of other functional groups.

3.1.1. Deglycosylation of 7-O- glycoside flavonoids

Bifidobacterium and *Lactobacillus* remove glycosides by generating glycosidase, which breaks the C—O bond at site 7. Polyphenols improve antioxidant activity by removing 7-O-glycosides from the A-ring of isoflavones and flavanones (Fig. 5A). Isoflavone glycosides (daidzin and genistin) can remove 7-O- monoglycosides to isoflavone aglycones (daidzein and genistein) in the form of glycoside hydrolyzed conjugates using the β-glucosidase produced by *Lacticaseibacillus rhamnosus*, *Lacticaseibacillus paracasei*, and *Lactiplantibacillus plantarum*(Tsangalis, Ashton, McGill, & Shah, 2002; Zhu, Wang, & Zhang, 2019).

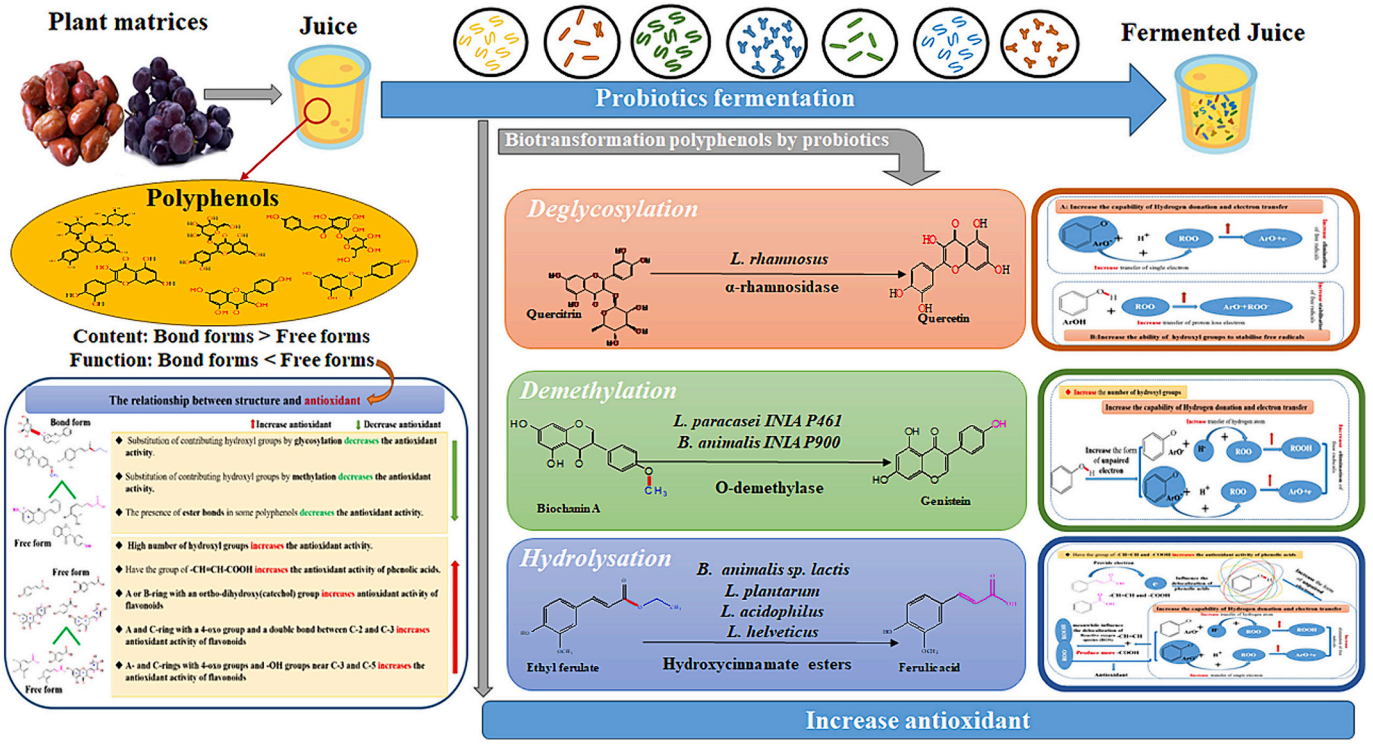

Fig. 4. Enhancement of antioxidant activity by the fermentation of plant-based food by *Bifidobacterium* and *Lactobacillus*. *L. rhamnosus: Lacticaseibacillus rhamnosus*; *L. paracasei: Lacticaseibacillus paracasei*; *B. animalis:Bifidobacterium animalis*; *B. animalis* sp. *lactis: Bifidobacterium animalis* subsp. *lactis*; *L. acidophilus:Lactobacillus acidophilus*; *L. plantarum:Lactiplantibacillus plantarum*; *L. helveticus: Lactobacillus helveticus*.

Bifidobacterium animalis sp. lactis BB12 or *Bifidobacterium breve* C0422 produce α-L-rhamnosidase that can remove the 7-O-diglycoside from hesperidin, flavanone with disaccharide glycosides, into hesperetin(Amaretti et al., 2015; Mueller et al., 2017). Another flavanone with disaccharide glycosides, eriocitrin, can similarly be converted into eriodictyol by *Bifidobacterium adolescentis* JCM 1275, *Bifidobacterium bifidum* IFO 14252, *L. plantarum* IAM 12477, *Lactobacillus acidophilus*, *Lactobacillus buchneri*, *Lacticaseibacillus casei,* or *Lactobacillus leichmanii*. However, the details of transformation and the enzymes released by the reactive strains have not been reported(Miyake, Yamamoto, & Osawa, 1997).

The improved antioxidant activity of the aglycones after the deglycosylation of the site 7 in the form of glycoside, methylated, and ester conjugates isoflavones and flavanones is sequential proton loss electron transfer (SPLET). The reaction enthalpy of the first step of this reaction corresponds to the proton affinity of the phenoxide anion (ArO^-) (Vianello & Maksić, 2006). In the second step, electron transfer from the phenoxide anion to ROO· occurs, and the phenoxy radical is formed. The reaction enthalpy of this step is denoted as electron transfer enthalpy. The 7-O-glycosides affect the hydrogen bonding of the ArOH of isoflavones and flavanones, which promotes the formation of unstable ArO^- that can combine with ROO^- to scavenge free radicals(Gocer et al., 2015). Additionally, 7-O-glycosides promote electron transfer from the ArOH of isoflavones and flavanones to ROO· to produce the stabilized form of ROO^-.

3.1.2. Deglycosylation of 3-O- glycoside flavonoids

Bifidobacterium and *Lactobacillus* produce glycosidase that acts on the C—O bond at site 3 to remove glycosides. The antioxidant activity of flavonols and anthocyanin glycosides can be enhanced by the removal of 3-O-glycosides from the middle C-ring by *Bifidobacterium* and *Lactobacillus* (Fig. 5B). The deglycosylation of 3-O-glycosides occurs with flavonols such as quercetin-3-O-glucoside, 3-O-rutinoside, and kaempferol-3-O-glucoside. The α-glucosidase produced by L. *rhamnosus* can remove the 3-O-glucoside from quercetin-3-O-glucoside to yield quercetin(Lin et al., 2014). Kaempferol-3-O-glucoside can be deglycosylated to kaempferol by the β-glucosidase produced by *Bifidobacterium. longum* subsp. infantis B7875 or *Bifidobacterium breve* B7824(Marotti, Bonetti, Biavati, Catizone, & Dinelli, 2007). Isorhamnetin-3-glucoside can be deglycosylated to isorhamnetin by the β-glucosidase produced by *Bifidobacterium animalis* subsp. lactis AD011(Ahn et al., 2020). Rutin with rhamnoside (disaccharide glycoside) can be deglycosylated to quercetin by the α-rhamnosidase produced by L. *rhamnosus* or L. *acidophilus* (Francesca et al., 2016).

There are two main explanations of the higher antioxidant activity of the aglyconees after removal of 3-O-glucosides. First, the removal of 3-O glucosides can increase the number of hydroxyl groups on the benzene ring. When polyphenols encounter free radicals, there are more ArOH to generate unstable electrons, which further promotes hyrdogen donation and electron transfer to scavenge free radicals(Gulcin, 2020; Lespade & Bercion, 2012). Second, for flavonols, the structure with 4-oxo groups and -OH groups near C-3 and C-5 will be formed after the removal of the glycoside at 3 site to supplement H. This structure can promote ArOH to generate unstable electrons to scavenge free radicals by affecting the ionic domains around flavonols(Bors et al., 1990; Ghosh et al., 2015). Additionally, it can chelate with metal ions, which affects the electron domains around the free radicals promoting a more stable form.

3.1.3. Deglycosylation of chalcones glycosides

In addition to 7-O-glycosides and 3-O -glycosides, there are 5-O-glycosides. The 5-O-glycosides of chalcones can be removed by *Bifidobacterium* and *Lactobacillus* for improved antioxidant activity (Fig. 5C). Phlorizin is a chalcone glycoside and phloretin is the corresponding chalcone algycone. Liu et al. found that β-glucosidase produced by *L. rhamnosus* L08(Liu et al., 2021) can remove glycosides from the glycoside precursor phlorizin to get phloretin with higher antioxidant activity than phlorizin.

The enhanced antioxidant activity that results from the

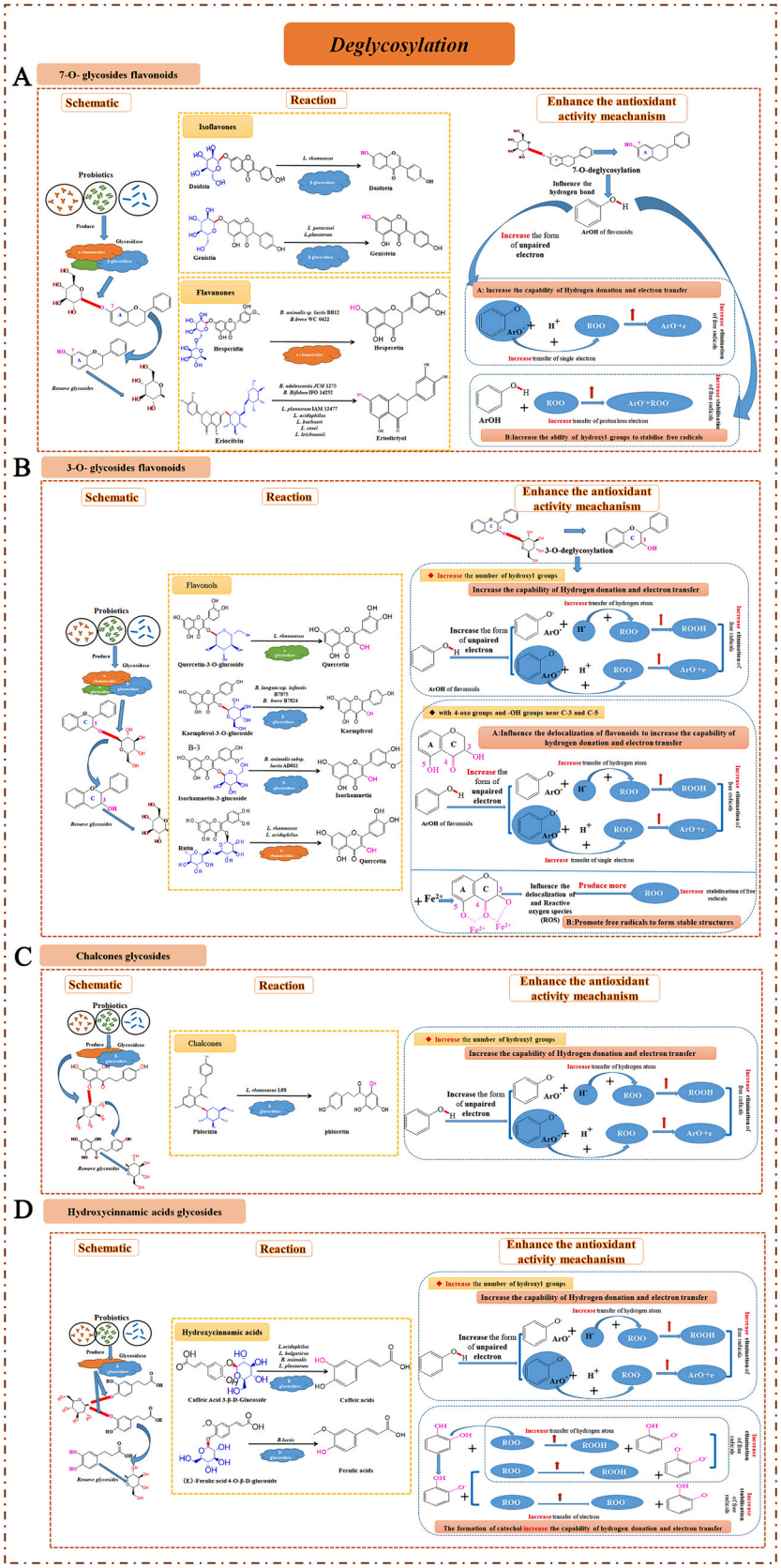

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Fig. 5. Principles of polyphenol deglycosylation and mechanisms of enhancing antioxidant activity by probiotics. **(A):** The schematic and reactions and mechanisms of 7-O- glycoside increases the antioxidant activity of flavonoids. **(B):** The schematic and reactions and mechanisms of 3-O- glycoside increases the antioxidant activity of flavonoids. **(C):** The schematic and reactions and mechanisms of chalcone glycosides increases the antioxidant activity of flavonoids. **(D):** The schematic and reactions and mechanisms of hydroxycinnamic acid glycosides increases the antioxidant activity of phenolic acid. *L. rhamnosus: Lacticaseibacillus rhamnosus*; *L. paracasei: Lacticaseibacillus paracasei*; *L. plantarum:Lactiplantibacillus plantarum*; *B. animalis* sp. *lactis: Bifidobacterium animalis* subsp. *lactis*; *B. longum: Bifidobacterium longum*; *L. acidophilus:Lactobacillus acidophilus*; *B. longum* subsp. *Infantis*:*Bifidobacterium longum* subsp. *infantis*; *B. breve: Bifidobacterium breve*; *L. bulgaricus:Lactobacillus bulgaricus*; *B. lactis: Bifidobacterium animalis* subsp. *lactis*; *B. adolescentis: Bifidobacterium adolescentis*; *B. bifidum:Bifidobacterium. bifidum*; *L. buchneri: Lactobacillusbuchner; L. leichmanii: Lactobacillus leichmanii*.

deglycosylation of phlorizin is due to the formation of phloretin after the removal of glycosides, with addition of a hydroxyl group at the 5 site. Compared to phlorizin, phloretin has more ArOH to generate unstable electrons, which further promotes hyrdogen donation and electron transfer to scavenge free radicals for higher antioxidant activity(Gulcin, 2020; Shahidi & Ambigaipalan, 2015; Wright, Johnson, & DiLabio, 2001).

3.1.4. Deglycosylation of hydroxycinnamic acid glycosides

The glycoside form hydroxycinnamic acid can be deglycosylated by enzymes produced by *Lactobacillus* and *Bifidobacterium* to increase antioxidant activity, with compounds such as caffeic Acid 3-β-D-Glucoside and (*E*)-Ferulic acid 4-O-β-D- glucoside (Fig. 5D). Caffeic Acid 3-β-D-Glucoside can be deglycosylated to form caffeic acid by the β-glucosidases produced by L. *acidophilus*, *Lactobacillus bulgaricus, Bifidobacterium animalis* or L. *plantarum*(do Carmo, Pressete, Marques,

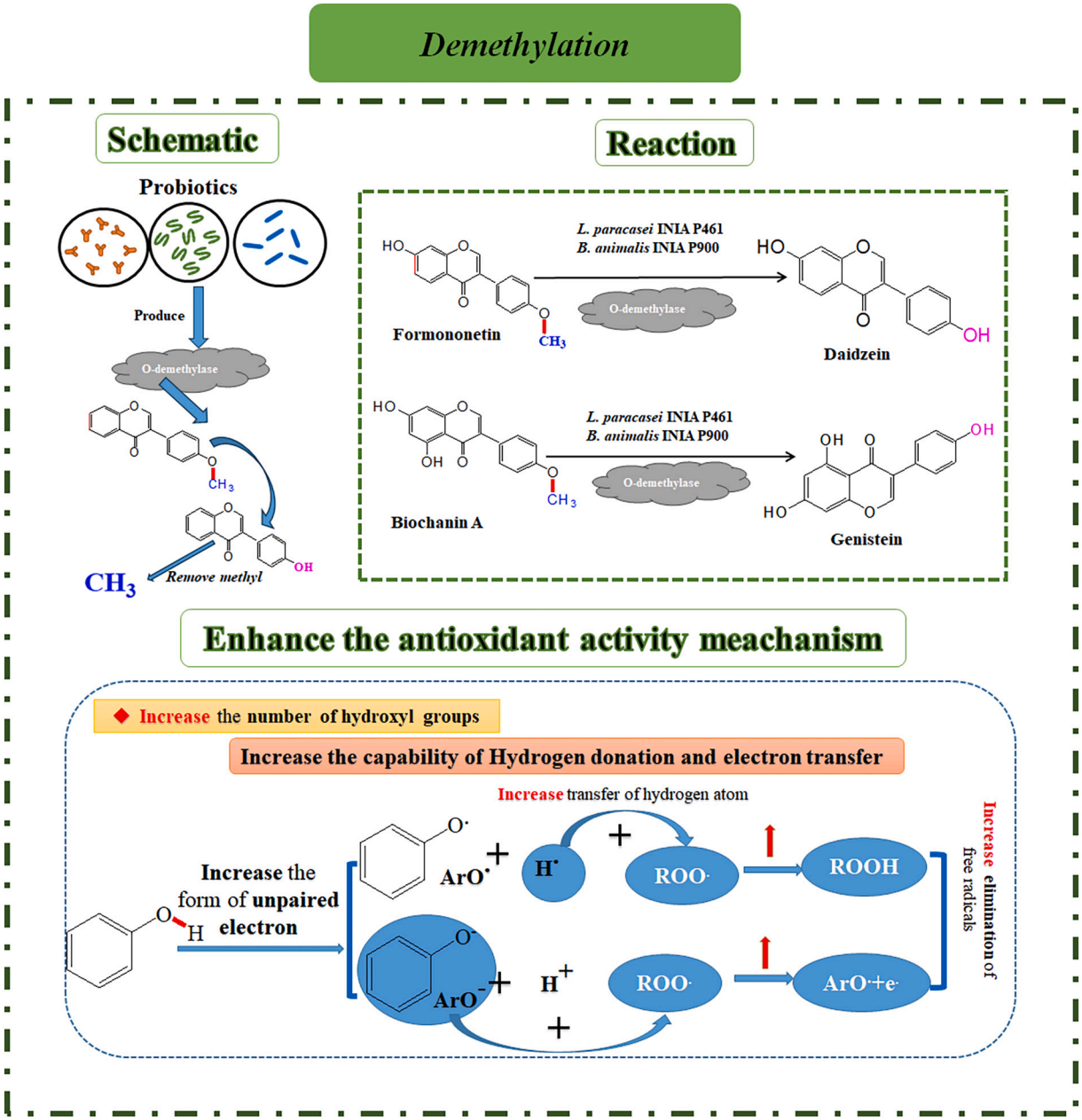

Fig. 6. Principles of polyphenol demethylation and mechanisms of enhancing antioxidant activity by probiotics.*L. paracasei: Lacticaseibacillus paracasei*; *B. animalis: Bifidobacterium animalis*.

Granato, & Azevedo, 2018). (E)-Ferulic acid 4-O-β-D-glucoside can be deglycosylated to form ferulic acid by enzymes produced by *Bifidobacterium animalis* subsp. lactis(Nyambe-Silavwe et al., 2015).

After transforming, the antioxidant activity of caffeic acids and ferulic acids was higher than the glycoside forms of caffeic acid 3-β-D-glucoside and (E)-Ferulic acid 4-O-β-D-glucoside. The removal of the glycoside can increase the number of hydroxyl groups on the benzene ring, and these hydroxyl groups can scavenge free radicals through hydrogen donation and electron transfer. At the same time, the formed catechol can either directly supply hydrogen to scavenge free radicals or lose an H^+ to form catechol,$^-$ which combines with ROO• to form ROO^- to stabilize free radicals(Gomes et al., 2012; Gulcin, 2020; ŽivanoviĆ et al., 2017).

3.2. Demethylation

Polyphenols in the methoxy form are mainly phenolic acids and some flavonoids, as shown in Fig. 6. There have been few studies of the demethylation of polyphenols by probiotics, with only the demethylation reaction of *Bifidobacterium* to methoxylated isoflavonoids reported. Pilar Gaya et al. found that formononetin and biohcanin A can be converted in daidzein and genistein through an O- Demethylation reaction of L. *paracasei* INIA P461, *B. animalis* INIA P900, and *B. breve* INIA P734 (Gaya, Peirotén, & Landete, 2017). Jos'e Antonio Curiel et al. first reported the *O*-demethylase gene from *B. breve* INIA P734, and verified that this strain can produce *O*-demethylase to transform formononetin and biohcanin A(Curiel & Landete, 2022). The demethylated products (daidzein and genistein) showed higher antioxidant activity than the methylated precursors (formononetin and biohcanin A).

Demethylation can enhance the antioxidant activity of polyphenols by the removal of methyl groups, which increases the number of functional hydroxyl groups. The methyl group occupies the site of the functional hydroxyl group, and when the methyl group is removed in formononetin and biohcanin A, a new hydroxyl group is formed on the benzene ring, and the hydroxyl group at this site can further produce new unpaired electron (O• and O^-) and scavenge free radicals by hydrogen donation and electron transfer. However, the conformational change due to the demethylation reaction of flavonoids by probiotics and the corresponding antioxidant activity needs to be further explored.

3.3. Hydrolysis

Lactobacillus and *Bifidobacterium* act on ester bonds using hydrolysis and esterase enzymes to form functional -COOH and -OH. Ester polyphenols, such as ester phenolic acids and tannins(Gaur & Gänzle, 2023) have improved antioxidant activity through hydrolysis by *Lactobacillus* and *Bifidobacterium*. As shown in Fig. 7, the penta-O-galloyl-β-D-glucose, a gallotannin, was hydrolyzed to gallic acid by tannin acyl hydrolase produced by L. *plantarum* and L. *rhamnosus*(Rodríguez, Landete, Rivas, & Muñoz, 2008; Serrano, Puupponen-Pimiä, Dauer, Aura, & Saura-Calixto, 2009). Chlorogenic acid, an ester phenolic acid, can be hydrolyzed to caffeic acid by feruloyl esterase produced by L. *rhamnosus*(Gaur & Gänzle, 2023). Another ester phenolic acid, ethyl ferulate, can be hydrolyzed to ferulic acid by hydroxycinnamate esters produced by *Bifidobacterium. animalis* sp. Lactis, *L. plantarum*, *L. acidophilus*, or *Lactobacillus helveticus*(Rodríguez-Daza et al., 2021; Wu et al., 2020). There are similarities in the conformational changes of the above three hydrolysis reactions to improve antioxidant activity. After the breaking of the ester bond in the penta-O-galloyl-β-D-glucose, chlorogenic acid, and ethyl ferulate, the hydrolysis products have -COOH and -CH=CH-COOH groups. These groups can influence the ionic domains around phenolic acids and free radicals to facilitate the scavenging of unstable electrons to free radicals by hydrogen donation and electron transfer. Additionally, the formation of ROO^- can stabilize the free radicals (Gulcin, 2020; J. Yang et al., 2021).

Bora, Li, Zhu, and Du reported that (−)-epicatechin-3-O-gallate, an ester polyphenol formed by polymerization of a flavanol and hydroxybenzoic acid, can be hydrolyzed to form the corresponding flavanol monomer (−)-epicatechin and the monomer hydroxybenzoic acid gallic acid by L. *plantarum* IFPL935(Sánchez-Patán et al., 2012). However, the specific enzyme was not identified. In this reaction, the hydrolysis of (−)-epicatechin-3-O-gallate gives the monomeric flavanol a hydroxyl group at C-3, and the increased number of hydroxyl groups increases the instabilities (ArO• and ArO^-) in the flavanol that can provide hydrogen atoms and electron transfer for an increase in the scavenging of free radicals (Gulcin, 2020; Shahidi & Ambigaipalan, 2015). Additionally, the formation of carboxyl groups in hydroxybenzoic acid affects the ionic domains of phenolic acids, which further promote the scavenging of free radicals by unstable electrons through hydrogen donation and electron transfer(J. Yang et al., 2021). Although both *Lactobacillus* and *Bifidobacterium* can hydrolyze polyphenols, less is known about the hydrolytic capacity of *Bifidobacterium*, so further studies on ester hydrolysis in this species are warranted.

Besides the aforementioned forms of biotransformations, other forms include hydroxylation, hydrogenation, dehydrogenation, oxidation, isomerization, and multi-step synthesis of polyphenols through the fermentation of *Bifidobacterium* and *Lactobacillus* (Cao et al., 2015; Gaur & Gänzle, 2023). For example, after *Bifidobacterium* fermentation, dihydroartemisinin is produced through hydrogenation, vanillin is converted into vanillic acid through oxidation, and pelargonidin is the product of a multi-step synthesis from naringenin (Wang et al., 2022). However, the structure–antioxidant relationships for hydroxylation, dehydrogenation, and oxidation of polyphenols by *Bifidobacterium* and *Lactobacillus* are less explored. Overall, the antioxidant activities of fruit polyphenols and flavonoids generally increase during fermentation due to the biotransformation of flavonoids and phenolic acids in the form of glycoside, methoxy, and ester conjugates. This process increases the content of free-form polyphenols and flavonoids in the system and produces new chemical compounds. Nevertheless, given the complexity of the fermentation system, three additional sources can enhance the antioxidant activity of the system: (1) the transformation of polyphenol precursors, (2) the transformation of non-polyphenol antioxidant compounds, and (3) the metabolism of antioxidant compounds by *Bifidobacterium* and *Lactobacillus*. In the first case, phenylpropanoid synthesis is a precursor pathway for the formation of polyphenols and flavonoids. It is the main pathway in metabolomics-based enrichment of metabolic pathways after probiotic plant-based fermentation, and phenylpropanoids are directly or indirectly transformed with flavonoids and phenolic acids (Shen et al., 2022; Y. Wang et al., 2024). In the second case, the structures of converted non-polyphenol products, such as amino acids with multiple sulfhydryl or hydroxyl groups, carbohydrates with reactive oxygen on benzene rings, and fatty acids with unsaturated bonds, short chains, and glycosides, have higher antioxidant activity in reducing free radicals compared with their precursors after *Bifidobacterium* fermentation(Y. Wang, Wang, Lan, et al., 2024). Meanwhile, these non-polyphenol products form polyphenols with antioxidant activity through the multi-step biosynthesis of secondary metabolites. In the third case, metabolites such as carboxylic acids, pyrimidines, purines, fatty acids, and amino acids are isolated from *Lactobacillus.* Wang et al. reported that uridine diphosphate (UDP) was the central metabolite of purines, which exhibited an indirect translational relationship with upregulated orotic acid. Further, orotic acid was detected only in *Lacticaseibacillus paracasei* YL-29–fermented juice and exhibited anti-inflammatory properties (C. Wang, Wang, Teng, & Zhang, 2024). Similarly, acetyl-CoA served as a key metabolite in lipid metabolism and was indirectly converted into citraconic acid and cortisone. Cortisone with high antioxidant activity was specifically detected in L. *paracasei* YL-29–fermented juice (C. Wang, Wang, Teng, & Zhang, 2024). Therefore, new free-form polyphenols and flavonoids were generated during probiotics fermentation, the conjugated fruit polyphenols and flavonoids were released through biotransformation, and other new antioxidant profiles were formed. However, further studies are needed to

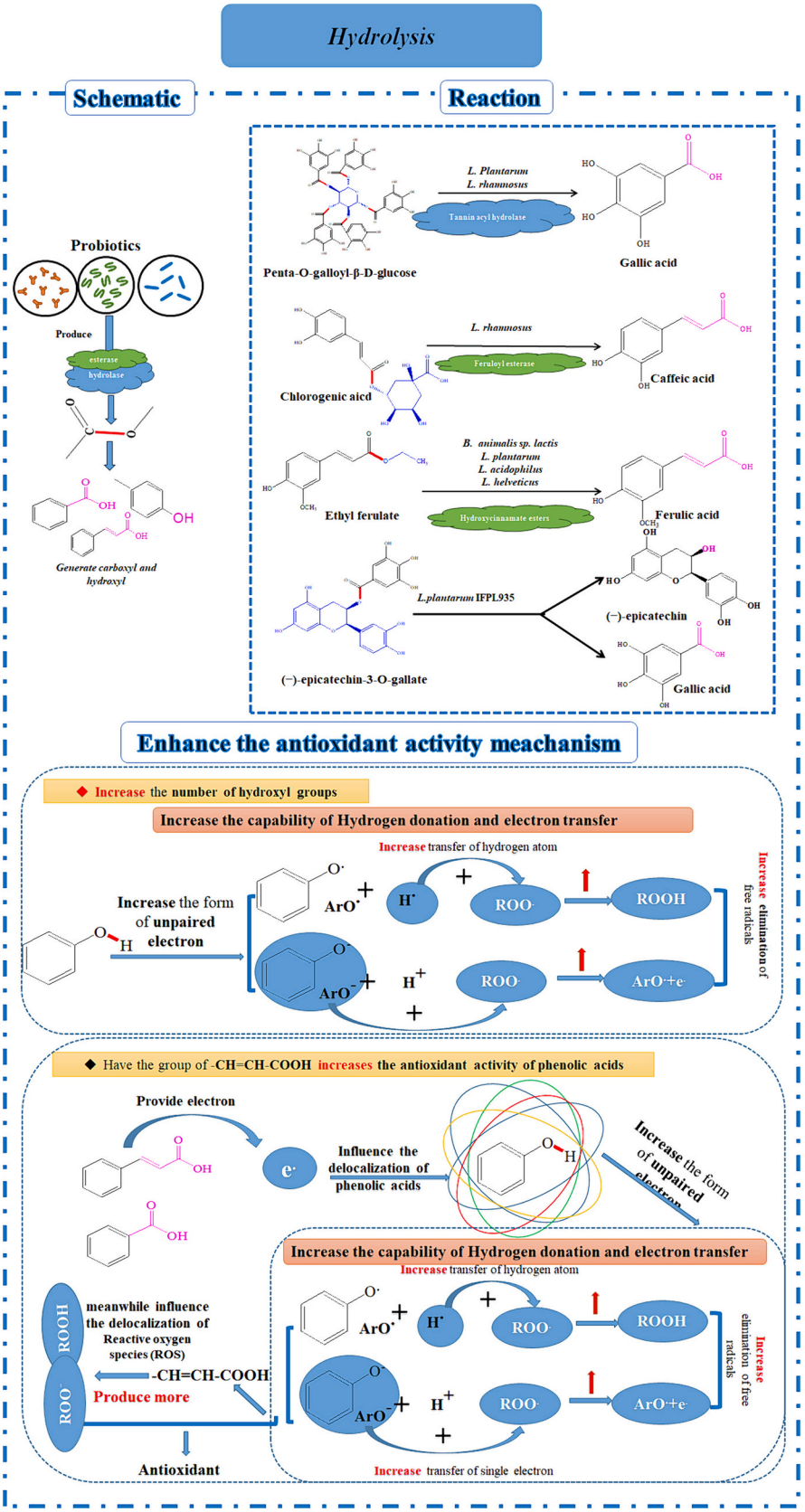

Fig. 7. Principles of hydrolysis of ester polyphenols and mechanisms of enhancing antioxidant activity by probiotics. *L. plantarum:Lactiplantibacillus plantarum*; *L. rhamnosus:Lacticaseibacillus rhamnosus*; *B. animalis sp. lactis: Bifidobacterium animalis* subsp. *lactis*; *L. acidophilus:Lactobacillus acidophilus*; *L. helveticus: Lactobacillus helveticus*.

investigate the structure–antioxidant relationship between the aforementioned three additional sources and the polyphenolic compounds in terms of their conversion and the mechanisms underlying the enhancement of antioxidant activity.

4. Key factors for the enhancement of antioxidant activity by probiotic fermentation

Many studies have explored the transformation of plant-derived functional polyphenols by probiotics, providing insights into the enzymes, metabolic pathways, transformation mechanisms, and product functionality of the bacterial strains involved in transformation.

4.1. Microbial enzymes

The bacterial transformation of polyphenols depends on the action of bacterial enzymes produced by the strain on specific sites of the polyphenol structure.

Bifidobacterium and *Lactobacillus* can release glycosidases, hydrolases, decarboxylases, demethylases, reductases, and esterases that can act on flavonoids and phenolic acids. However, identification of specific bacterial enzymes providing esterase and glycosidase activities in food fermentation remains incomplete. Most studies rely on quantification of a decrease in concentration of specific compounds with a corresponding increase in expected metabolites. Few studies used isogenic mutants to confirm the activity of specific enzymes in fermentation(Gaur & Gänzle, 2023) and there are little data on the expression of genes in complex food substrates. The recent identification of several genes related to the metabolism of phenolic compounds provides the necessary tools to address this limitation. To explore transforming enzymes, Kin Kwan Lai et al. selected esterases from *Lactobacillus johnsonii*(Lai, Lorca, & Gonzalez, 2009) by using genomic analysis coupled to protein purification and catalytic screening. Gaya et al. cloned β-glucosidase genes from *Lactobacillus mucosae* INIA P508 and verified that the produced synthetase resulted in the transformation of the glycoside daidzin into the correspondent aglyconee daidzein by HPLC(Gaya, Peirotén, & Landete, 2020).

In addition, datasets from 16S rDNA analysis and transcriptomics measurements have expanded understanding of the genomes of probiotics and suggested enzymes whose metabolic functions contribute to the bioavailability and bioactivity of unabsorbed (poly)phenols. Putative transforming enzymes can be verified by analyzing genes with significant differences in expression before and after fermentation, using database information to annotate the enzyme genes, and performing real-time quantitative analysis of functional enzyme gene expression. To date, the polyphenol metabolism of L. *plantarum* is one of the best-studied among probiotic bacteria. The genes encoding enzymes of intracellular tannase (tanBLP), gallate decarboxylase (lpdB, lpdC), aryl glycosidase(Landete, Curiel, Rodríguez, de Las Rivas, & Muñoz, 2014), rhamnosidases (rhaB1, rhaB2)(Reverón, de Las Rivas, Matesanz, Muñoz, & López de Felipe, 2015), phenolic acid decarboxylase (hcrB, lp_3665), and vinylphenol reductase (lp_3125) in L. *plantarum* have been identified, and future work is required to assay the roles of these genes in the transformation of functional polyphenols(Ávila et al., 2009).

4.2. Transformation pathway

The transformation of polyphenols by probiotics can differ for different phenolic species. In previous studies, qualitative and quantitative analysis of polyphenols in the fermentation matrix was performing using total phenolic content measurement, liquid chromatography–mass spectrometry, and HPLC or HPLC-MS(High Performance Liquid Chromatography-tandem Mass Spectrometry). The types of substances transformed by probiotics were tentatively identified based on changes of species and content. Ratchadaporn Kaprasob et al. predicted the transformation of tannins by *Lactobacillus plantarum*, L. *casei* and *L. acidophilus* by determining the total phenolic contents, the condensed tannin contents and the hydrolysable tannin contents (Kaprasob, Kerdchoechuen, Laohakunjit, Sarkar, & Shetty, 2017). Similarly, Tianlin Li et al. predicted that L. *acidophilus*, *L. casei*, *L. helveticus* and L. *plantarum* have the ability to transform flavonoid polyphenols based on total polyphenol contents, flavonoid contents, and HPLC assay results. However, these results can only suggest the type of polyphenol transformation by probiotics, and cannot locate the specific profiles and transformation types. Thus, this approach has only demonstrated the transformation of a few polyphenols by probiotics.

With the development of localization and omics techniques, single-omic or multi-omics analysis by isotope tracer technology can further localize metabolic pathways in the fermentation process, facilitating the identification of functional transforming enzymes. Gallardo-Fernandez et al. elucidated biosynthesis pathways in *Saccharomyces cerevisiae* for hydroxytyrosol formation by isotope tracer technology(Gallardo-Fernández et al., 2022). In whole crop corn ensiling systems with homofermentative *Lactobacillus plantarum* or heterofermentative *Lactobacillus buchneri*., metabolomic analysis revealed changes in many metabolites with biofunctional activities like bacteriostatic (naringin and 3,4-dihydroxybenzoic acid), antioxidant (ferulic acid and catechol), central nervous system inhibitory (4-aminobutyric acid), and anti-inflammatory (salicin) compounds(Xu et al., 2020). The expression of genes for anthocyanin synthesis were up-regulated in red wine based on metabolomics and transcriptomics analysis.

Interestingly, the anthocyanin glycoside concentrations in red wine were low or even not detected(Yue, Xu, Xiang, Yu, & Yao, 2018). Overall, the mining of metabolic pathways and substance transformations can facilitate biosynthesis and engineering functional production. To improve the medicinal value of the caffeic acid titer, Lian Wang et al. enhanced caffeic acid production in *Escherichia coli* by engineering the biosynthesis pathway and transporter. The overexpression of ycjP, as a sugar ABC transporter permease, improved the caffeic acid titer to 775.7 mg/L, and was further improved to 7922.0 mg/L in a 5-L fermenter, the highest titer achieved by microbial fermentation(L. Wang, Li, Yu, & Zhou, 2023). Clearly, the specific transformation reactions (corresponding reaction precursors and transformation products) and detailed metabolic pathways in the conversion of polyphenols by probiotics should be the focus of future work. Wang et al. used metabolomics analysis to reveal flavonoid, isoflavonoids, flavone and flavonol biosynthetic pathways involved in the transformation of polyphenols by *Bifidobacterium animalis* subsp. lactis HN-3, predicted the enzymes in the deglycosylation and hydroxylation reactions of the strain, and verified the deglycosylation of coniferin by *Bifidobacterium animalis* subsp. *Lactis* HN-3(Y. Wang et al., 2022).

4.3. Validation evaluation

4.3.1. In vitro assays

There is significant interest in the food industry in identifying new functions of food. In particular, probiotic fermented plant-based products are a developmental focus of functional food development. Fermentation of food by probiotics can significantly improve the content of functional components in fruit juices, especially polyphenols with antioxidant activity. The antioxidant activity of probiotic-fermented foods can be measured using in vitro antioxidant indexes. These analyses are widely used because they are inexpensive and can be performed quickly. As in vitro indicators of antioxidant compound activity, 2,2-diphenyl-1-picrylhydrazyl radical (DPPH) inhibition, Ferric Reducing Antioxidant Power (FRAP), Oxygen Radical Absorbance Capacity (ORAC), 2,2′-azinobis-3-ethylbenzothiazoline-6-sulfonic acid (ABTS), and Cupric Reducing Antioxidant Power (CUPRAC) are measured(Mota, Almeida, Freitas, Stockler-Pinto, & Guimarães, 2023). In vitro antioxidant index changes and polyphenol content changes demonstrated that probiotics can be used to improve the functional activity of fermented juice (Kowalski et al., 2020; Wu et al., 2020).

4.3.2. In vivo validation

However, in vitro antioxidant index assays cannot fully characterize the antioxidant activity of polyphenol products after transforming by probiotics and in vivo experiments are necessary to validate the functional activity of the transformed polyphenol products of probiotics. In previous studies, researchers extracted functional polyphenols from food products and verified animal models. Xiaoyue Gong et al. established an intestinal inflammation model in the model organism zebrafish and extracted polyphenols from *Dendrobium candidum* to study anti-inflammatory mechanisms. The results showed that fermented *D. candidum* polyphenols may protect intestinal cells from oxidative damage by up-regulating the activities of SOD and GSH-Px, enhance the antioxidant defense mechanism of intestinal cells, and delay the cell damage caused by intestinal inflammation(Gong, Jiang, Tian, Xiang, & Zhang, 2020). Additionally, the ability of polyphenols like genistein, hesperidin, and phlorizin to modulate glucose metabolism while inhibiting the expression of fatty liver factors was validated by mice models (Li et al., 2022; Zhang et al., 2022).

4.4. Future studies

According to the previous description, it is important to investigate the enzymes, reactions, metabolic pathways and functional activity validation of probiotics conversion to polyphenols for the development of probiotic-fermented functional foods and polyphenol applications. Therefore, future studies should elucidate the types of polyphenols that can be transformed by a given strain, the mode of transformation, the transforming enzymes, and the sites of action.

In the future, strains producing transforming enzymes that act on specific sites can be modified to produce products with better functional activity or applied for the batch production of potential drugs or functional fermented beverages. For the products with better functional substances, the precursors that are abundant in nature and convenient to extract are screened, and the synthesis rate and yield of the functional substances are increased by cloning the expressed enzymes.

And then, it is necessary to explore the corresponding transformation reactions and metabolic pathways of transforming polyphenols by probiotics to provide a theoretical basis for the further production of duplibiotic/symbiotic efficacy products and to improve the production of medicinal polyphenols. In addition, for the functional studies of probiotic transformed polyphenols, it can be proved more comprehensively that probiotics are used as a means of transforming polyphenols to improve the functional activity and be more conducive to the development of functional fermented foods by extracting and purifying the transformed products with high functional activity and combining with the in vitro and in vivo experiments for the verification of the functional activity.

5. Concluding remarks

In recent years, there has been increased attention to the relationship between polyphenol structure and function. Phenolic acids and flavonoids as glycoside, methoxy and ester hydrolyzed onjugates with functional groups (e.g., polyhydroxyl groups, phenolic acids with -CH=CH-COOH, flavonoids with 4-oxo groups and a double bond between C-2 and C-3) or with functional groups in characteristic sites (e.g., flavonoids in A- and C-rings with a 4-oxo group and a double bond between C-2 and C-3 or flavonoids at A- and C-rings with 4-oxo groups and -OH groups near C-3 and C-5) show elevated antioxidant activity. After derivatision, functional groups can decrease the antioxidant activity of flavonoids and phenolic acids because these groups reduce the formation of unstable ions with their own functional hydroxyl groups and also affect the ionic domains of the free radicals. These changes reduce the scavenging ability of unstable ions on the free radicals and the overall stability of the free radicals. Free radical scavenging capacity can be enhanced by increasing electron transfer and the functional capacity of hydroxyl groups with destabilizing functions and by enhancing the stability of free radicals by directly affecting the ionic domain around the radicals after metal chelation. Overall, probiotic fermentation is a powerful approach to modify the structures of bioactive polyphenols for enhanced activity.

In this review, we summarized the types and mechanisms of the reactions of probiotic fermentation that enhance the antioxidant activity of glycoside, methoxy, and ester conjugate polyphenols. In the presence of enzymes produced by probiotics, glycoside, methoxy and ester conjugates can be transformed into hydrolyzed forms through deglycosylation, demethylation, and hydrolysis reactions. With decreased antioxidant active groups, conjugates can increase antioxidant activity by increasing scavenging capacity and stability against free radicals.

Although few studies have been conducted on the probiotic transformation of polyphenols, future work should focus on optimizing the transformation of glycoside, methoxy and ester conjugates into compounds with high antioxidant activity. Strains producing transforming enzymes that act on specific sites can be modified to produce products with better functional activity or applied for the batch production of potential drugs or functional fermented beverages.

CRediT authorship contribution statement

Yixuan Wang: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Chenxi Wang:** Writing – review & editing, Writing – original draft, Validation, Supervision, Formal analysis, Conceptualization. **Junling Shi:** Resources, Project administration. **Yan Zhang:** Writing – review & editing, Writing – original draft, Resources, Project administration, Investigation, Funding acquisition.

Declaration of competing interest

The author(s) declared no potential conflicts of interest with respect to the research, author- ship, and/or publication of this article.

The authors declared that they have no conflict of interest.

Data availability

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

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Appendix A. Supplementary data

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