Inhibitors of $\alpha$-amylase and $\alpha$-glucosidase: Potential linkage for whole cereal foods on prevention of hyperglycemia

Lingxiao Gong | Danning Feng | Tianxi Wang | Yuqing Ren | Yingli Liu | Jing Wang

China-Canada Joint Lab of Food Nutrition and Health (Beijing), Beijing Engineering and Technology Research Center of Food Additives, Beijing Technology & Business University (BTBU), Beijing, China

Correspondence
Jing Wang, China-Canada Joint Lab of Food Nutrition and Health (Beijing), Beijing Engineering and Technology Research Center of Food Additives, Beijing Technology & Business University (BTBU), Beijing 100048, China.
Email: wangjing@th.btbu.edu.cn

Funding information
Natural Science Foundation of Beijing Municipality, Grant/Award Number: KZ201810011014; First-Class Disciplines Fund, Grant/Award Number: PXM2019_014213_000010; Support Project of High-level Teacher in Beijing Municipal Universities, Grant/Award Number: IDHT 20180506

Abstract
The strategy of reducing carbohydrate digestibility by controlling the activity of two hydrolyzing enzymes ($\alpha$-amylase and $\alpha$-glucosidase) to control postprandial hyperglycemia is considered as a viable prophylactic treatment of type 2 diabetes mellitus (T2DM). Thus, the consumption of foods rich in hydrolyzing enzyme inhibitors is recommended for diet therapy of diabetes. Whole cereal products have gained increasing interests for plasma glucose-reducing effects. However, the mechanisms for whole cereal benefits in relation to T2DM are not yet fully understood, but most likely involve bioactive components. Cereal-derived phenolic compounds, peptides, nonstarch polysaccharides, and lipids have been shown to inhibit $\alpha$-amylase and $\alpha$-glucosidase activities. These hydrolyzing enzyme inhibitors seem to make whole cereals become nutritional strategies in managing postmeal glucose for T2DM. This review presents an updated overview on the effects provided by cereal-derived ingredients on carbohydrate digestibility. It suggests that there is some evidence for whole cereal intake to be beneficial in amelioration of T2DM through inhibiting $\alpha$-glucosidase and $\alpha$-amylase activities.

KEYWORDS
enzyme inhibitor, hyperglycemia, peptides, polyphenols, polysaccharides

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is commonly featured by postmeal or postprandial hyperglycemia. Nutritional strategies that designed to improve postprandial glycemia by reducing the glucose intake from the digestible carbohydrates were advised to the early-stage diabetes patients before they were administered on pharmacologic treatment (Ch’ng et al., 2019). $\alpha$-Amylase (1,4-$\alpha$-D-glucan-glucanohydrolase, EC 3.2. 1.1) and $\alpha$-glucosidase (EC 3.2.1.20) are the two key enzymes involved in the carbohydrate digestion process (Dona et al., 2010). Inhibitors of $\alpha$-amylase and $\alpha$-glucosidase, which slow the final stages of carbohydrate digestion and consequently preventing the entry of glucose into the circulation, are considered as a viable prophylactic treatment of hyperglycemia. However, synthetic and chemical $\alpha$-amylase and $\alpha$-glucosidase inhibitors have certain adverse effects such as causing gastrointestinal symptoms such as bloating, diarrhea, and abdominal pain (Chiasson et al., 2002). Natural glucosidase inhibitors from plants have become more important for the treatment of diabetes because of their less side effects and effectiveness.
Whole cereals are generally recommended for diabetic patients to control their blood glucose level. There have been many clinical and animal studies focused on the use of cereals and its components for the prevention of diabetes, especially based on glycemic Index values and hypoglycemic effects (Berglund et al., 1982; Brand-Miller et al., 2003; Halfbrisch et al., 2003; Lundin et al., 2004). Although these beneficial effects are thought to be associated with dietary fiber intake, the actual underlying mechanism remains unclear. Besides dietary fiber, cereals are abundant in nutrients and bioactive ingredients for prevention and treatment of diabetes, such as polyphenol, anthocyanins, triterpenoids, saponins, polysaccharides, and peptides. It has been found that polysaccharides (Kim et al., 2015), phenols (Mcdougall & Stewart, 2005; Nyambe-Silavve et al., 2015; Tan & Chang, 2017), and proteins (Svensson et al., 2004) present in plants have an inhibitory effect on carbohydrate digestion enzymes. This paper presents a modern perspective on the inhibition of digestive enzymes by cereal constituent to encourage the design and development of whole cereal products for preventing T2DM.

2 | α-AMYLASE AND α-GLUCOSIDASE INHIBITORS

Carbohydrate digestibility has been reported to relate to elevated postprandial blood glucose. One of the strategies to reduce postprandial hyperglycemia is to limit the activity of carbohydrate digestive enzymes in intestinal tract. α-Amylase is the key enzyme that degrades the polymeric substrate into shorter oligomers by catalyzing the hydrolysis of α-1,4-glucan linkages present in starch, maltodextrins, and other related carbohydrates (Truscheit et al., 2010). α-Glucosidase has been found on the brush border of human intestinal mucosal cells (including maltase, α-dextrinase, and sucrase). This enzyme participates in the body’s carbohydrate metabolism and cuts glucose from the nonreducing end of the polysaccharide by hydrolyzing the α-1,4-glycosidic bond. The dietary starch and other related carbohydrates are digested by α-amylase to large number of maltose, which is further digested by α-glucosidase to glucose to be absorbed in human intestine (Vocadlo & Davies, 2008). Therefore, strict control of postprandial blood glucose by inhibiting α-glucosidase and α-amylase is significant for the development of diabetes and the prevention and treatment of diabetic patients (Elbein, 1991; Tundis et al., 2010). α-Amylase inhibitors (AIs) can act as carbohydrate blockers, limiting the digestibility and absorption of carbohydrate in the gastrointestinal tract (Horii et al., 1986). Clinically, AIs can be used to prevent diseases such as diabetes, hyperglycemia, hyperlipemia, and obesity. Moreover, in most cases, the inhibitory mechanism of protein to α-amylase occurs by directly blocking the active centers of several subsites of the enzyme (Francoise, 2004). To determine the inhibition of α-amylase, the most widely used method is the dinitrosalicylic acid (DNSA) assay, which is not selective for the reduction in oligosaccharide ends formed during hydrolysis (Bernfeld, 1955). The α-glucosidase inhibitor (GI) inhibits α-glucosidase activity by reversibly occupying α-glucosidase and sugar-binding sites, thereby reducing polysaccharide degradation, delaying intestinal absorption of carbohydrates, and achieving hypoglycemic effects. The most prominent feature of GIs is the inhibition of α-glucosidase on the rate of intestinal carbohydrate decomposition (Larr, 2008; Seifarth et al., 1998), and it does not stimulate insulin secretion to lower blood sugar, thus not increasing the islet β-cell burden. For α-glucosidase, synthetic chromogenic molecular probes such as p-nitrophenyl-glucoside (pNPG) are widely used assays because of the ease of measurement. Natural GIs include iminosugars, thiosugars, flavonoids, alkaloids, and terpenes (Ghani, 2015).

3 | WHOLE CEREAL PRODUCTS WITH LOWERING EFFECTS ON PLASMA GLUCOSE

The results of an umbrella review of meta-analyses suggest that daily whole cereal intakes of 2 or 3 servings (30–45 g/day) can significantly reduce the incidence of developing T2DM and 1.5 servings of whole cereal per day significantly reduced both serum glucose and insulin concentrations (Mcrae, 2017). A meta-analysis of randomized controlled trials including 17 studies and 212 subjects reported that the consumption of barley and barley products lowered postprandial glycemic response (Abumweis et al., 2016).

A series of experiments demonstrated that postprandial glucose response was improved when whole cereal products were consumed versus when refined cereals were consumed. For example, the consumption of breakfast meals with whole rye or whole wheat in healthy volunteers had lower early glucose responses (0–60 min) and incremental glucose peaks in comparison with white wheat bread. The whole rye and wheat products displayed a lower rate of starch hydrolysis (Rosén & Björck, 2011). Shukla and Srivastava (2014) reported that the glycemic index of refined wheat noodles incorporated with 30% finger millet was significantly lower (45.1) than refined wheat noodles (62.6) in ten normal female subjects aged 24–26 years. Several other studies also indicated the lowering effects of whole cereals and whole cereal products on plasma glucose (Berglund et al., 1982; Brand-Miller et al., 2003; Lundin et al., 2004).

4 | CEREAL ORIGINATED INHIBITORS AND INHIBITOR MECHANISMS

Cereals are rich in polysaccharides, protein, and phenolic compounds, and are valuable resources for inhibitors of amylase and glucosidase (Figure 1). AIs have been found in cereals such as wheat, barley, sorghum, rye, and rice (Elbein, 1991; Mishra et al., 2017; Pradeep & Sreerama, 2015; Premakumara et al., 2013). The wheat AI isolated by Maeda et al. (1985) is the most studied inhibitors in cereals. It has been reported that taking a wheat amylase inhibitor for 9 weeks after meals can reduce postprandial amylase levels, delay carbohydrate digestion and absorption, and lower blood glucose levels without altering pancreas growth (Bernfeld, 1955). In this part, the recent advances made in discovery of starch hydrolase inhibitors from cereals are summarized.
4.1 | Phenolic compounds

Starch hydrolase inhibitors from cereals have been reported for phenolic acids, tannins, anthocyanins, and flavonoids (Table 1). Most of the reported studies used crude phenolic extracts, including soluble and bound forms. The phenolic compounds from corn, rice, barley, sorghum, millet, and quinoa (Pradeep & Sreerama, 2015; Rosén & Björck, 2011; Shukla & Srivastava, 2014) were reported to be potent inhibitors of α-amylase and α-glucosidase. The soluble and bound phenolic extracts of whole cereals and their milled fraction inhibited the activities of α-amylase and α-glucosidase in a dose-dependent manner (Qin et al., 2013). The enzyme inhibitory activities of cereal phenolic extracts depend on the cereal types and processing methods. For example, the phenolic extracts of little millet cultivars had superior inhibition of both α-amylase and α-glucosidase than those of foxtail millet cultivars. Among the evaluated cultivars, the soluble and bound fractions of foxtail millet cultivar CO7 (IC$_{50}$ 22.37 and 57.26 μg/ml) and the little millet cultivar CO4 of (IC$_{50}$ 18.97 and 55.69 μg/ml) showed strong inhibition of α-glucosidase (Pradeep et al., 2018). HPLC analysis of phenolic extracts revealed variations in individual phenolic acid composition among the evaluated samples. Naringenin, kaempferol, luteolin glycoside, apigenin, (+)-catechin/(−)-epicatechin, daidzein, caffeic acid, ferulic acid, and syringic acid from cereals are considered as the enzyme inhibitors (Shobana et al., 2009). Caffeic, ferulic, and sinapic acids were found as the predominant phenolic acids in soluble fractions, while ferulic and p-coumaric acids were abundant in bound fractions. Quercetin was the most abundant flavonoid presented in all the fractions. Quercetin, and ferulic and p-coumaric acids are reported to have high α-glucosidase inhibitory activity by mixed noncompetitive inhibition (Adisakwattana et al., 2009; Li et al., 2009). The results of Mishra et al. (2017) had shown that organic rye varieties have higher ferulic acid content and α-amylase inhibitory activity, while traditional rye varieties have higher catechin content and α-glucosidase inhibitory activity.

The enzyme inhibition potency of individual phenolic compounds through mixed, uncompetitive, and competitive type is highly correlated with their structures (Di Stefano et al., 2018; Kim et al., 2019; Malunga et al., 2018; Tadera et al., 2006). Hydroxycinnamic acids are reported to be more potent on inhibition of α-glucosidase compared with their corresponding hydroxybenzoic acid derivatives. The structure–activity relationship suggests that the number of hydroxyl and methoxy groups present in the aromatic ring phenolic acids decides the inhibitory activity (Malunga et al., 2018). Furthermore, flavonoids appeared to have a better α-glucosidase inhibitory activity than phenolic acids due to the additional hydroxyl groups in flavone skeleton, which is most likely responsible for the more pronounced inhibitory activity (Di Stefano et al., 2018; Tadera et al., 2006). Additionally, proper glucoside substitutions may boost the enzyme inhibition activities and types due to increased number of total aromatic hydroxyl groups (Şöhretoğlu et al., 2018). For example, the hydroxy (–OH) groups at C-3 position of ring C, C-3’ and C-4’ position of ring B, and the glucose substitutions at the C-3 position of ring C were crucial for the enzyme inhibition activities of flavonols. Molecular docking studies revealed that phenolic compounds bind at both the active sites and allosteric sites, resulting in structural changes and activity inhibitors (Kim et al., 2019; Martinez-Gonzalez et al., 2019). Hydrogen bonds, hydrophobic interactions, and van der Waals interactions are the predominant force involved in the complexation of the phenolic compounds with enzymes (Di Stefano et al., 2018; Martinez-Gonzalez et al., 2019).

Polyphenols with higher polymerization also have inhibition effects on the enzymes. Pigmented cereals always gained attention due to their health benefits associated with anthocyanins (Pei-Ni et al., 2006). Premakumara et al. (2013) screened the most resistant varieties of α-amylase in 70% ethanol extracts from 35 varieties of rice (red and white) in Sri Lankan. The results showed that the anti-amylase activity of the red wheat bran extract was significantly higher than the white wheat bran extract. The traditional red rice varieties Masuran, Sudu Heenati, etc., all showed significant anti-amylase activity in a dose-dependent manner. Yao et al. (2010) studied Chinese colored cereals, including red, purple, black rice, purple corn, black barley, and black soybeans. Among the Chinese colored cereals studied, black rice (IC$_{50}$ = 13.56 ± 1.2 mg/ml) has the highest total anthocyanin content, total phenolic content, and α-glucosidase inhibitory activity. Anthocyanin in purple rice (IC$_{50}$ = 475.14 ± 25.46 mg/ml) has stronger inhibitory activity against α-glucosidase than proanthocyanidins in red rice (IC$_{50}$ > 1,000 mg/ml). On the other hand,
| No. | Variety               | Part used | Active compounds                        | Inhibited enzyme | Enzyme origin       | Method                        | IC$_{50}$ (μg/ml) | Reference                        |
|-----|-----------------------|-----------|-----------------------------------------|------------------|---------------------|------------------------------|--------------------|----------------------------------|
| 1   | Buckwheat             | Bran      | Flavonoids                              | α-Glucosidase    | Saccharomyces        | pNPG                         | 16.9               | Li et al. (2009)                  |
|     |                       |           |                                         |                  | cerevisiae          |                              |                    |                                  |
| 2   | Millet                | Seed coat | Phenolic extracts                       | α-Amylase        | Porcine pancreatic   | DNSA                         | 16.9               | Shobana et al. (2009)             |
|     |                       |           |                                         | α-Glucosidase    | Rats' intestine      | pNPG                         | 23.5               |                                  |
| 3   | Black rice            | Kernels   | Anthocyanin                             | α-Glucosidase    | Rat intestine        | p-Nitrophenyl-α-D-glucopyranoside | 13.56 ± 1.2  | Yao et al. (2010)                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
|     | Purple rice           | Kernels   | Anthocyanin                             | α-Glucosidase    | Rat intestine        | p-Nitrophenyl-α-D-glucopyranoside | 475.14 ± 25.46 |                                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
|     | Purple corn           | Kernels   | Anthocyanin                             | α-Glucosidase    | Rat intestine        | p-Nitrophenyl-α-D-glucopyranoside | 833.33 ± 56.31 |                                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
|     | Black barley          | Kernels   | Anthocyanin                             | α-Glucosidase    | Rat intestine        | p-Nitrophenyl-α-D-glucopyranoside | >1,000            |                                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
|     | Red rice              | Kernels   | Anthocyanin                             | α-Glucosidase    | Rat intestine        | p-Nitrophenyl-α-D-glucopyranoside | >1,000            |                                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
| 4   | Proanthocyanidin-rich | Bran      | Simple flavonoids and proanthocyanidins | α-Glucosidase    | Porcine pancreas    | EnzChek Ultra Amylase Assay Kit | 1.4                | Hargrove et al. (2011)            |
|     | sumac sorghum         |           |                                         |                  |                     |                              |                    |                                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
|     | Proanthocyanidin-free | Bran      | Simple flavonoids and proanthocyanidins | α-Glucosidase    | Porcine pancreas    | EnzChek Ultra Amylase Assay Kit | 11.4               |                                  |
|     | black sorghum         |           |                                         |                  |                     |                              |                    |                                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
|     | Sumac sorghum         | Bran      | Simple flavonoids and proanthocyanidins | α-Glucosidase    | Porcine pancreas    | EnzChek Ultra Amylase Assay Kit | 12.1               |                                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
|     | Black sorghum         | Bran      | Simple flavonoids and proanthocyanidins | α-Glucosidase    | Porcine pancreas    | EnzChek Ultra Amylase Assay Kit | 18.8               |                                  |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
| 5   | Buckwheat             | Seed      | Total phenols                           | α-Glucosidase    | Rat intestine        | p-Nitrophenyl-α-D-glucopyranoside |                 | Qin et al. (2013)                 |
|     |                       |           |                                         |                  |                     |                              |                    |                                  |
| 6   | Rice of Sri Lankan    | Bran      | Ethanol extracts                        | α-Amylase        | Bacillus amyloliquefaciens | DNSA                     |                    | Premakumara et al. (2013)         |
|     |                       |           |                                         | α-Glucosidase    | Rice                 | pNPG                         |                    |                                  |

(Continues)
| No. | Variety       | Part used   | Active compounds       | Inhibited enzyme | Enzyme origin | Method  | IC$_{50}$          | Reference                           |
|-----|---------------|-------------|------------------------|------------------|---------------|---------|------------------|-------------------------------------|
| 7   | Sorghum       | Bran        | Condensed tannins      | α-Amylase        | Porcine       | DNSA    | 554.5 μg/ml (IC$_{50}$ of acarbose = 3.1 μg/ml) | Links et al. (2015)                  |
|     | Sorghum       | Bran        |                        | α-Glucosidase    | Yeast         | pNPG    | 0.4 μg/ml (IC$_{50}$ of acarbose = 8,464.0 μg/ml) |                                     |
| 8   | Barnyard millet | Raw grains  | Phenolic extracts      | α-Amylase        | Porcine pancreatic | DNSA    | 32.59 ± 0.04 µg/ml | Pradeep and Sreerama (2015)          |
|     | Barnyard millet | Germinated grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 18.60 ± 0.83 µg/ml |                                     |
|     | Barnyard millet | Steamed grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 17.26 µg/ml |                                     |
|     | Barnyard millet | Steamed grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 7.46 µg/ml |                                     |
|     | Barnyard millet | Microwave grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 59.21 µg/ml |                                     |
|     | Barnyard millet | Microwave grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 42.71 µg/ml |                                     |
|     | Barnyard millet | Microwave grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 49.7 µg/ml |                                     |
|     | Foxtail millet  | Raw grains  | Phenolic extracts      | α-Amylase        | Porcine pancreatic | DNSA    | 67.38 ± 3.5 µg/ml |                                     |
|     | Foxtail millet  | Germinated grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 19.21 ± 1.42 µg/ml |                                     |
|     | Foxtail millet  | Steamed grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 41.81 µg/ml |                                     |
|     | Foxtail millet  | Steamed grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 8.61 µg/ml |                                     |
|     | Foxtail millet  | Microwave grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 108.64 µg/ml |                                     |
|     | Foxtail millet  | Microwave grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 51.26 µg/ml |                                     |
|     | Proso millet   | Raw grains  | Phenolic extracts      | α-Amylase        | Porcine pancreatic | DNSA    | 98.62 µg/ml |                                     |
|     | Proso millet   | Germinated grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 61.43 µg/ml |                                     |
|     | Proso millet   | Germinated grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 34.15 ± 1.87 µg/ml |                                     |
|     | Proso millet   | Germinated grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 29.47 ± 1.47 µg/ml |                                     |
|     | Proso millet   | Steamed grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 20.04 µg/ml |                                     |
|     | Proso millet   | Steamed grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 16.09 µg/ml |                                     |
|     | Proso millet   | Microwave grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 94.37 µg/ml |                                     |
|     | Proso millet   | Microwave grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 66.19 µg/ml |                                     |
|     | Proso millet   | Microwave grains | Phenolic extracts | α-Amylase      | Rats’ intestine | pNPG    | 84.14 µg/ml |                                     |
|     | Proso millet   | Microwave grains | Phenolic extracts | α-Glucosidase    | Rats’ intestine | pNPG    | 84.62 µg/ml |                                     |
| No. | Variety | Part used | Active compounds | Inhibited enzyme | Enzyme origin | Method | IC\textsubscript{50} | Reference |
|-----|---------|-----------|------------------|-----------------|---------------|--------|----------------|-----------|
| 9   | Quinoa  | Whole grains | Phenolic extracts | α-Amylase | Porcine pancreatic | DNSA | 163.52 ± 2.5 μg/ml (IC\textsubscript{50} of acarbose = 7.21 ± 0.4 μg/ml) | Hemalatha et al. (2016) |
|     |         |           |                  | α-Glucosidase | Rats' intestine | pNPG  | 72.36 ± 1.5 μg/ml (IC\textsubscript{50} of acarbose = 83.65 ± 4.7 μg/ml) |          |
|     | Hulls   | Phenolic extracts | α-Amylase | Porcine pancreatic | DNSA | 148.23 ± 4.6 μg/ml (IC\textsubscript{50} of acarbose = 7.21 ± 0.4 μg/ml) |          |
|     |         |           |                  | α-Glucosidase | Rats' intestine | pNPG  | 68.14 ± 3.8 μg/ml (IC\textsubscript{50} of acarbose = 83.65 ± 4.7 μg/ml) |          |
|     | Dehulled grain | Phenolic extracts | α-Amylase | Porcine pancreatic | DNSA | 179.5 ± 3.8 μg/ml (IC\textsubscript{50} of acarbose = 7.21 ± 0.4 μg/ml) |          |
|     |         |           |                  | α-Glucosidase | Rats' intestine | pNPG  | 116.2 ± 5.3 μg/ml (IC\textsubscript{50} of acarbose = 83.65 ± 4.7 μg/ml) |          |
|     | Milled grain | Phenolic extracts | α-Amylase | Porcine pancreatic | DNSA | 241.36 ± 9.8 μg/ml (IC\textsubscript{50} of acarbose = 7.21 ± 0.4 μg/ml) |          |
|     |         |           |                  | α-Glucosidase | Rats' intestine | pNPG  | 182.01 ± 2.0 μg/ml (IC\textsubscript{50} of acarbose = 83.65 ± 4.7 μg/ml) |          |
|     | Bran    | Phenolic extracts | α-Amylase | Porcine pancreatic | DNSA | 108.68 ± 3.1 μg/ml (IC\textsubscript{50} of acarbose = 7.21 ± 0.4 μg/ml) |          |
|     |         |           |                  | α-Glucosidase | Rats' intestine | pNPG  | 62.1 ± 3.9 μg/ml (IC\textsubscript{50} of acarbose = 83.65 ± 4.7 μg/ml) |          |
| 10  | 7 varieties of cereals | Whole grain | Methanol extracts | α-Amylase | Porcine pancreatic | DNSA | Donkor et al. (2017) |          |
|     |         |           |                  | α-Glucosidase | Rats' intestine | pNPG  |          |          |
| 11  | Yellow corn | Whole grain | Bound polyphenol | α-Amylase | Porcine pancreatic | DNSA | Gong et al. (2018) |          |
|     |         |           | Free polyphenol | α-Glucosidase | Rats' intestine | pNPG  |          |          |
| 12  | Rye     | Whole grain | Phenolic extracts | α-Amylase | Porcine pancreatic | DNSA | Mishra et al. (2017) |          |
|     |         |           |                  | α-Glucosidase | Baker's yeast | pNPG  |          |          |
| No. | Variety       | Part used  | Active compounds | Inhibited enzyme | Enzyme origin | Method      | IC$_{50}$         | Reference                      |
|-----|---------------|------------|------------------|------------------|---------------|-------------|------------------|--------------------------------|
| 13  | Foxtail millet| Whole grains| Soluble phenolic extracts | α-Amylase       | Porcine pancreatic | DNSA        | 67.28 ± 0.69 μg/ml | Pradeep and Sreerama (2017) |
|     |               |            | Bound phenolic extracts | α-Glucosidase   | Rats' intestine | pNPG         | 19.87 ± 0.69 μg/ml |
|     |               |            |                   | α-Amylase       | Porcine pancreatic | DNSA        | 98.28 ± 1.69 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 52.64 ± 0.85 μg/ml |
|     |               |            |                   | α-Amylase       | Porcine pancreatic | DNSA        | 81.85 ± 0.43 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 37.68 ± 0.31 μg/ml |
|     |               |            |                   | α-Amylase       | Porcine pancreatic | DNSA        | 115.63 ± 1.02 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 110.25 ± 0.91 μg/ml |
|     |               |            | Bound phenolic extracts | α-Amylase       | Porcine pancreatic | DNSA        | 109.91 ± 1.82 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 67.60 ± 0.41 μg/ml |
|     |               |            |                   | α-Amylase       | Porcine pancreatic | DNSA        | 162.56 ± 1.53 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 198.64 ± 1.17 μg/ml |
|     |               |            | Soluble phenolic extracts | α-Amylase       | Porcine pancreatic | DNSA        | 32.29 ± 0.59 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 10.28 ± 0.63 μg/ml |
|     |               |            |                   | α-Amylase       | Porcine pancreatic | DNSA        | 41.74 ± 0.64 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 35.21 ± 0.42 μg/ml |
|     |               |            | Bound phenolic extracts | α-Amylase       | Porcine pancreatic | DNSA        | 39.64 ± 0.57 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 12.41 ± 0.39 μg/ml |
|     |               |            |                   | α-Amylase       | Porcine pancreatic | DNSA        | 54.29 ± 0.81 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 35.26 ± 0.37 μg/ml |
|     |               |            | Soluble phenolic extracts | α-Amylase       | Porcine pancreatic | DNSA        | 61.91 ± 1.07 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 17.22 ± 0.48 μg/ml |
|     |               |            | Bound phenolic extracts | α-Amylase       | Porcine pancreatic | DNSA        | 84.31 ± 1.07 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 49.22 ± 0.72 μg/ml |
|     |               |            |                   | α-Amylase       | Porcine pancreatic | DNSA        | 74.97 ± 0.76 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 25.53 ± 0.17 μg/ml |
|     |               |            | Bound phenolic extracts | α-Amylase       | Porcine pancreatic | DNSA        | 107.45 ± 1.32 μg/ml |
|     |               |            |                   | α-Glucosidase   | Rats' intestine | pNPG         | 89.26 ± 1.65 μg/ml |
| No. | Variety       | Part used | Active compounds       | Inhibited enzyme | Enzyme origin | Method   | IC<sub>50</sub> | Reference                                      |
|-----|--------------|-----------|------------------------|------------------|---------------|----------|----------------|-----------------------------------------------|
| 14  | Foxtail millet (CO5) | Whole grains | Soluble phenolic extracts | α-Amylase         | Porcine pancreatic | DNSA     | 79.61 ± 2.58 μg/ml | Pradeep and Sreerama (2018) (IC<sub>50</sub> of acarbose = 10.54 ± 1.06 mg/ml) |
|     |              |           |                        | α-Glucosidase     | Rats' intestine   | pNPG     | 23.54 ± 0.53 μg/ml |                                           |
|     |              |           | Bound phenolic extracts | α-Amylase         | Porcine pancreatic | DNSA     | 112.62 ± 3.46 μg/ml |                                           |
|     |              |           |                        | α-Glucosidase     | Rats' intestine   | pNPG     | 60.17 ± 1.50 μg/ml |                                           |
|     | Foxtail millet (CO6) | Whole grains | Soluble phenolic extracts | α-Amylase         | Porcine pancreatic | DNSA     | 74.66 ± 2.37 μg/ml |                                           |
|     |              |           |                        | α-Glucosidase     | Rats' intestine   | pNPG     | 26.81 ± 0.45 μg/ml |                                           |
|     |              |           | Bound phenolic extracts | α-Amylase         | Porcine pancreatic | DNSA     | 117.33 ± 3.67 μg/ml |                                           |
|     |              |           |                        | α-Glucosidase     | Rats' intestine   | pNPG     | 66.29 ± 2.47 μg/ml |                                           |
| No. | Variety       | Part used | Active compounds     | Inhibited enzyme | Enzyme origin  | Method    | IC\textsubscript{50} | Reference |
|-----|---------------|-----------|----------------------|-------------------|----------------|-----------|-----------------|-----------|
|     | Foxtail millet (CO7) | Whole grains | Soluble phenolic extracts | α-Amylase | Porcine pancreatic | DNSA    | 69.92 ± 1.25 μg/ml (IC\textsubscript{50} of acarbose = 10.54 ± 1.06 mg/ml) |           |
|     |               |           |                      | α-Glucosidase      | Rats' intestine | pNPG    | 22.37 ± 0.64 μg/ml (IC\textsubscript{50} of acarbose = 91.38 ± 6.20 mg/ml) |           |
|     | Bound phenolic extracts | α-Amylase | Porcine pancreatic | DNSA    | 101.55 ± 2.85 μg/ml (IC\textsubscript{50} of acarbose = 10.54 ± 1.06 mg/ml) |           |
|     |               |           |                      | α-Glucosidase      | Rats' intestine | pNPG    | 57.26 ± 1.26 μg/ml (IC\textsubscript{50} of acarbose = 91.38 ± 6.20 mg/ml) |           |
|     | Little millet (CO2) | Whole grains | Soluble phenolic extracts | α-Amylase | Porcine pancreatic | DNSA    | 67.26 ± 1.79 μg/ml (IC\textsubscript{50} of acarbose = 10.54 ± 1.06 mg/ml) |           |
|     |               |           |                      | α-Glucosidase      | Rats' intestine | pNPG    | 20.17 ± 0.61 μg/ml (IC\textsubscript{50} of acarbose = 91.38 ± 6.20 mg/ml) |           |
|     | Bound phenolic extracts | α-Amylase | Porcine pancreatic | DNSA    | 96.22 ± 3.42 μg/ml (IC\textsubscript{50} of acarbose = 10.54 ± 1.06 mg/ml) |           |
|     |               |           |                      | α-Glucosidase      | Rats' intestine | pNPG    | 58.65 ± 1.61 μg/ml (IC\textsubscript{50} of acarbose = 91.38 ± 6.20 mg/ml) |           |
|     | Little millet (CO3) | Whole grains | Soluble phenolic extracts | α-Amylase | Porcine pancreatic | DNSA    | 69.87 ± 2.05 μg/ml (IC\textsubscript{50} of acarbose = 10.54 ± 1.06 mg/ml) |           |
|     |               |           |                      | α-Glucosidase      | Rats' intestine | pNPG    | 21.85 ± 0.75 μg/ml (IC\textsubscript{50} of acarbose = 91.38 ± 6.20 mg/ml) |           |
|     | Bound phenolic extracts | α-Amylase | Porcine pancreatic | DNSA    | 98.47 ± 2.64 μg/ml (IC\textsubscript{50} of acarbose = 10.54 ± 1.06 mg/ml) |           |
|     |               |           |                      | α-Glucosidase      | Rats' intestine | pNPG    | 56.11 ± 2.03 μg/ml (IC\textsubscript{50} of acarbose = 91.38 ± 6.20 mg/ml) |           |
Hargrove et al. (2011) compared the inhibition of α-amylase by monoflavonoids and proanthocyanidins in Sorghum bicolor bran extract. The results showed that the extract of sumac sorghum bran rich in proanthocyanidins (IC_{50} = 1.4 \mu g/ml) had a stronger inhibitory effect on α-amylase than the extract of sorghum bran (IC_{50} = 11.4 \mu g/ml) without procyanidins. In addition, flavonoids have higher IC_{50} values than proanthocyanidins. Links et al. (2015) prepared a highly efficient sorghum-condensed tannins (SCT) from sorghum. The results showed that SCT was a better α-glucosidase inhibitor (IC_{50} = 0.4 \mu g/ml) compared with acarbose (IC_{50} = 8,464.0 \mu g/ml). SCT also had a certain inhibitory effect on α-amylase. The effect of kafirin micro-particles (KEMS) as an oral administration system for SCT has potential hypoglycemic effect. Lignin can also be used as novel α-amylase inhibitor. The molecular docking studies indicated that the major binding sites are –OH in G units and β-O-4 structure of lignin on α-amylase molecule (Fan et al., 2019).

Different processing methods significantly affected the total phenolics, individual phenolic compounds, and enzyme inhibitory properties of cereals (Donkor et al., 2012; Pradeep & Sreerama, 2015). Germinated millets with higher phenolic compound levels showed highest inhibitory activities toward both the enzymes that their untreated, steamed, and microwaved treated cereal counterparts (Pradeep & Sreerama, 2015). Similar results were also obtained in germinated wheat, brown rice, barley, sorghum, oat, rye, and buckwheat cereals (Donkor et al., 2012). In the recent study of Gong et al. (2018), germination combined with extrusion on free and bound phenolic compound extracts of whole cereal corn increased the anti-α-glucosidase activity by 221 and 40%, and increased the anti-α-amylase activity by 105 and 108%. In the study of Qin et al. (2013), soaked tartary buckwheat had increased quercetin, kaempferol, total flavonoid, and total phenolic compound contents which were responsible for the highest α-glucosidase inhibitory activity as compared with raw, steamed, and dried tartary buckwheat. The findings of Irontdi et al. (2019) demonstrated that both the α-glucosidase and α-amylase inhibitory activities of sorghum decreased due to roasting, in contradictory with the report of Kunyanga et al. (2011) that indicated an increase in enzyme inhibitory activities of pearl millet. The parallel changes in phenolic compound levels and enzyme inhibitory activity with different processing methods suggest that phenolic compounds might be the major enzyme inhibitors in the cereals. Additionally, phenolic compounds are mainly concentrated in the pericarp, hull bran, and aleurone layers of whole cereals which may promote their contribution to the enzyme inhibitory activities. The phenolic extracts of these fractions usually displayed strong inhibition toward α-glucosidase and α-amylase compared with other fractions of whole cereals (Hemalatha et al., 2016; Pradeep & Sreerama, 2017). Moreover, the digestibility of phenolic compounds plays a key role in their enzyme inhibitory activity in the small intestine. Unencapsulated sorghum-condensed tannins had minimal α-amylase inhibition and no α-glucosidase inhibition after pepsin and trypsin–chymotrypsin digestion (Links et al., 2015). Hence, technologies that ensure bioaccessibility of...
4.2 Peptides

Some of the bioactive peptides generated from cereal proteins by enzymatic, or chemical hydrolysis and fermentation, have been reported to exhibit enzyme-inhibiting activities (Table 2). The inhibition activity of peptides from rice bran protein on α-amylase, ranged from 6.9 to 56.1 μg acarbose equivalent mg⁻¹ protein, was generally correlated with the degree of protein hydrolysis (Uraipong & Zhao, 2015). Moreover, different fractions (albumin, globulin, prolamin, and glutelin) of rice bran proteins, which were subjected to different protease hydrolysis (Alcalase, Neutrase, Flavourzyme, and Protamex), resulted in different activities. In general, highest inhibition activities were found with albumin and glutelin hydrolysates produced by Protamex- and Alcalase-catalyzed hydrolysis. The results of this in vitro study highlight that the bioactivity of peptides in the hydrolysates is dependent on the proteolytic enzyme used. Accordingly, hydrolysates generated by 14 different enzymes from barley and brewers' spent grain protein were evaluated for the α-glucosidase and α-amylase inhibition activities by Connolly et al. (2014). The tryptic hydrolysate resulted in the highest inhibition of α-glucosidase, which had increased from 12.43% inhibition for unhydrolyzed protein-enriched isolates to 66.81% at 7.5 mg/ml. For α-amylase inhibition, the unhydrolyzed isolates inhibited by 8.08% to 13.35% with the concentration increased from 2.5 to 7.5 mg/ml. However, no significant increases were found for all 14 hydrolysates. Additionally, the α-amylase and α-glucosidase inhibitory peptides may also be produced during digestion. Peptides released from quinoa during the in vitro duodenal phase showed the highest inhibitory effects, which reaching an IC₅₀ value of 0.19 mg protein/ml for α-amylase inhibition and 1.75 mg protein/ml for α-glucosidase inhibition, respectively (Vilcacundo et al., 2017).

The structure–activity relationships were studied for several identified peptides. The most potent α-glucosidase inhibitory peptide identified is LQAFEPLR (IC₅₀ = 35.67 μg/ml) derived from oat globulin by trypsin hydrolysis. As demonstrated by Di Stefano et al. (2018), α-glucosidase inhibitory activity appears to occur more for peptides containing serine, threonine, tyrosine, lysine, or arginine at the N-terminal, and a proline residue closer to the C-terminal with methionine or alanine occupying the C-terminal position. The roles of hydrophobic amino acids on the inhibition of α-glucosidase were confirmed by Vilcacundo et al. (2017). Potential α-glucosidase inhibitory peptides identified in quinoa after digestion were IQAEGGLT and DKKYPK. Peptide IQAEGGLT containing three hydrophobic residues showed potent inhibitory activity toward α-glucosidase via hydrophobic interaction. In case of α-amylase inhibitory peptides, the aromatic–aromatic interactions between the enzyme residues and peptide arising from hydrogen bonds, and electrostatic and Van der Waals interactions, which may form a sliding barrier via a hydrogen bonding with the residues of the active/substrate-binding region,
### TABLE 3  A summary of newly discovered nonstarch polysaccharides as α-glucosidase and α-amylase inhibitors

| No. | Variety          | Part used | Active compounds                | Inhibited enzyme | Enzyme origin | Method | IC50             | Reference                  |
|-----|------------------|-----------|---------------------------------|------------------|---------------|--------|------------------|----------------------------|
| 1   | Corn             | Silk      | Carboxymethylated polysaccharide| α-Amylase        | DNSA          |        | 5.33 mg/ml (IC50 of acarbose = 9.38 ± 6.20 mg/ml) | Shuhan et al. (2013) |
|     |                  |           | Sulfated polysaccharide         |                  |               |        | 8.54 mg/ml       |                            |
|     |                  |           | Raw polysaccharide              |                  |               |        | 10.07 mg/ml      |                            |
|     |                  |           | Acetylated polysaccharide       |                  |               |        | 10.31 mg/ml      |                            |
| 2   | Barely           | Seed      | Oligosaccharides (BP)           | α-Glucosidase    | pNPG          |        | 22.49 mg/ml      | Qian et al. (2015)         |
| 3   | Fagopyrum tartaric| Seed      | Neutral polysaccharide          | α-Glucosidase    | Glucose oxidase method |        |                  | Wang et al. (2016)        |

### TABLE 4  A summary of newly discovered lipids as α-glucosidase and α-amylase inhibitors

| No. | Variety | Part used | Active compounds                | Inhibited enzyme | Enzyme origin | Method | IC50      | Reference                  |
|-----|---------|-----------|---------------------------------|------------------|---------------|--------|-----------|----------------------------|
| 1   | Wheat   | Bran      | 1,2-Dilinoleylglycerol-3-phosphate| α-Glucosidase    | Baker’s yeast | pNPG   | 38.9 μM   | Li et al. (2009)            |
|     |         | Bran      | 1-Palmitoyl-2-linoleyl glycerol-3-phosphate| α-Glucosidase    | Baker’s yeast | pNPG   | 47.9 μM   |                            |
| 2   | Wheat   | Bran and germ | 1,2-Dilinoleylglycerol-3-phosphate| α-Glucosidase    | Baker’s yeast | pNPG   | 27.1 μg/ml | Liu et al. (2011)           |
|     |         | Bran and germ | 1-Palmitoyl-2-linoleyl glycerol-3-phosphate| α-Glucosidase    | Baker’s yeast | pNPG   | 32.2 μg/ml |                            |
| 3   | Wheat   | Bran      | Alkylresorcinol                   | α-Glucosidase    | Rats’ intestine | pNPG | 37.58 μg/ml | Tu et al. (2013)            |
4.3 | Nonstarch polysaccharides

Nonstarch polysaccharides with α-glucosidase and α-amylase inhibitory activities have been identified in barley, wheat, buckwheat, and corn silk (Table 3). The barley polysaccharide exhibited a noncompetitively inhibitory process toward α-glucosidase with IC<sub>50</sub> at 22.49 mg/ml. The sulfation can significantly raise the enzyme inhibitory activity with increases in dose and the degree of substitution of sulfate group. However, the mechanism of sulfated polysaccharides against α-glucosidase was reversible as a mixed one (Qian et al., 2015). The oligosaccharide from barley malt denoted as α-pyran glucosan composed of four glucoses with (1 → 3) linkage was an effective α-glucosidase inhibitors as acarbose (Shelat et al., 2011). The IC<sub>50</sub> of crude oligosaccharides, pure oligosaccharides, and acarbose was 1.30, 0.48, and 0.26 mg/ml, respectively. A novel purified neutral polysaccharide (TBP-II, 26 kDa) from buckwheat was reported to exhibit α-glucosidase inhibitory activity (Wang et al., 2016). TBP-II was mainly consisted of galactose, arabinose, xylose, and glucose with a molar ratio of 0.7:1.3:6.3:74.2. The backbone of TBP-II was composed of (1 → 4)-linked-d-glucopyranosyl (GlcP), while the branches comprised of (1 → 3)-linked-d-glucopyranosyl (GlcP), (1 → 6)-linked-d-galactopyranosyl (Galp), and (1 → 2,4)-linked-d-rhamnopyranosyl (Rhap). TBP-II exhibited an excellent inhibitory activity on α-glucosidase, which was superior to acarbose and crude polysaccharide, and the percentage inhibition depended on the concentration of polysaccharides.

In case of α-amylase, cellulose (either purified or as a component of wheat bran) was demonstrated to bind α-amylase and inhibit the activity of the enzyme through a mixed-type inhibition mechanism (Sushil et al., 2015). Cereal arabinoxylan and β-glucan can impair diffusion of the polymer probes similar in size to α-amylase, which slowed starch hydrolysis in the small intestine (Shelat et al., 2010, 2011). The α-amylase inhibitory activities among water-soluble corn silk polysaccharides and their sulfated, acetylated, and carboxymethylated derivatives were compared by Shushan et al. (2013). The carboxymethylated polysaccharide, which exhibited the highest inhibitory activity among the four polysaccharides samples, had a high solubility, a narrow molecular weight distribution, and a hyperbranched conformation. The IC<sub>50</sub> of acarbose, carboxymethylated, sulfated, raw, and acetylated derivatives was 2.51, 5.33, 8.54, 10.07, and 10.31 mg/ml. However, limited work has been conducted on the structure–function relationship of nonstarch polysaccharides against α-glucosidase or α-amylase.

4.4 | Lipids

Lipids derived from cereals are another potential α-glucosidase and α-amylase inhibitors (Table 4). The Soxhlet hexane and ethyl acetate extracts of wheat bran were effective inhibitors of α-glucosidase in vitro (Liu, 2009). The isolated phosphatidic acids in wheat germ, 1,2-dilinoleylglycerol-3-phosphate and 1-palmitoyl-2-linoleoyl glycerol-3-phosphate (Figure 2), showed the highest α-glucosidase inhibitory activity among the test lipids with the IC<sub>50</sub> of 38.9 and 47.9 μM (Liu et al., 2011). The structure–activity relationship studies suggested that the unsaturated fatty acids and phosphate group in the glycerides were significant structural requirements for the inhibitory activity. Alkylresorcinols are another important components that are responsible for the α-glucosidase inhibitory activity of wheat bran lipids (Tu et al., 2013). Alkylresorcinols showed IC<sub>50</sub> of 37.58 μg/ml by noncompetitive type of inhibition. It has been reported that the important biological role of alkylresorcinols is to directly regulate enzyme activity, such as inhibition of acetylcholinesterase, and the inhibitory activity is affected by the length of the alkyl side chain (Athukorala et al., 2010; Stasiuk et al., 2008). However, its effects on inhibition of α-glucosidase still require further investigation. Additionally, there is some evidence that fatty acids, saponins, and terpenes found in fruits, vegetables, and mushrooms contribute to the in vitro α-glucosidase and α-amylase inhibition activities of hexane extracts (Papoutsis et al., 2020). However, limited work has been conducted on elucidation of the α-glucosidase and α-amylase inhibition activities of different lipophilic compounds found in cereals. Future studies are encouraged to investigate the individual inhibitors of cereal lipids and their inhibition mechanism.

4.5 | Crude extracts

Distinguishable differences among cereal species were proved based on the results of inhibitory activities of the cereal crude extracts against these two starch digestive enzymes (Table 5). Kim et al. (2011) studied...
| No. | Variety                | Part used       | Active compounds | Inhibited enzyme   | Enzyme origin          | Method | IC50       | Reference                  |
|-----|------------------------|-----------------|------------------|---------------------|------------------------|--------|------------|---------------------------|
| 1   | Purple pigmented       | Kernel          | Water extracts   | α-Glucosidase       | Baker’s yeast          | pNPG   |            | Ranilla et al. (2008)     |
|     | Yellow, purple-red     | Kernel          | Water extracts   | α-Glucosidase       | Baker’s yeast          | pNPG   |            |                           |
|     | mottled                |                 |                  |                     |                        |        |            |                           |
|     | Yellow, red blotched   | Kernel          | Water extracts   | α-Glucosidase       | Baker’s yeast          | pNPG   |            |                           |
|     | Half yellow-half red   | Kernel          | Water extracts   | α-Glucosidase       | Baker’s yeast          | pNPG   |            |                           |
|     | Purple mottled         | Kernel          | Water extracts   | α-Glucosidase       | Baker’s yeast          | pNPG   |            |                           |
| 2   | Sorghum (Mongdang-susu)| Whole grains     | Ethanol extracts | α-Amylase           | Porcine                | DNSA   | 4.5 ± 0.0 μg/ml | Kim et al. (2011)         |
|     | (SS-1)                 |                 |                  |                     |                        |        |            |                           |
|     | Sorghum (Me-susu(SS-2))| Whole grains     | Ethanol extracts | α-Amylase           | Porcine                | DNSA   | 2.9 ± 0.5 μg/ml |                           |
|     | Sorghum (Susongsaeengi-susu (SS-3)) | Whole grains | Ethanol extracts | α-Amylase           | Porcine                | DNSA   | 11.8 ± 0.1 μg/ml |                           |
|     | Sorghum (Sikyung-susu (SS-4)) | Whole grains | Ethanol extracts | α-Amylase           | Porcine                | DNSA   | 9.0 ± 0.4 μg/ml  |                           |
|     | Sorghum (Jangsu-susu (SS-5)) | Whole grains | Ethanol extracts | α-Amylase           | Porcine                | DNSA   | 194.1 ± 3.1 μg/ml |                           |
|     | Sorghum (Heuin-susu (SS-6)) | Whole grains | Ethanol extracts | α-Amylase           | Porcine                | DNSA   | >666 μg/ml     |                           |
| 3   | 13 kind of barely      | Seed            | Hot water, cold  | α-Amylase           | DNSA                   |        |            | Ramakrishna et al. (2017) |
|     |                        |                 | water, and ethanol extracts | α-Glucosidase       |                        |        |            |                           |
|     |                        |                 |                  |                     |                        |        |            |                           |
the inhibition of α-glucosidase and α-amylase by 70% ethanol extracts of different varieties of sorghum, foxtail millet, and proso millet. The results showed that in 6 sorghum varieties, compared with the existing α-glucosidase inhibitor anti-diabetic acarbose (IC$_{50}$ = 2.1 μg/ml), Mongdang-susu (SS-1), Me-susu (SS-2), Susongsaengi-Susu (SS-3), and Sikyung-Susu (SS-4) extracts had significantly higher inhibitory activity against α-glucosidase (IC$_{50}$ = 1.1–1.4 μg/ml). Moreover, these extracts have a strong inhibitory effect on α-amylase in pancreas and saliva, while foxtail and proso millets extracts have no significant inhibitory effect on α-amylase or α-glucosidase activity. Ramakrishna et al. (2017) screened the antihyperglycemic function of 13 barley varieties and evaluated the α-amylase and α-glucosidase inhibitory activities of barley extracts (hot water, cold water, and 12% ethanol). The results showed that the cold water and ethanol extracts of most barley varieties had significant inhibitory effects on α-amylase, but the differences among most varieties were not significant. Additionally, it was observed that for all extraction methods, the black barley variety had the highest α-glucosidase inhibitory activity (34%) and exhibited a dose-dependent pattern among all barley varieties. Ranilla et al. (2009) used in vitro enzyme assays to determine the α-glucosidase and α-amylase inhibition associated with early type 2 diabetes in 10 kinds of Peruvian Andean hot-processed cereals (five cereals, three pseudocereals, and two legumes). The results showed that the purple corn (Zea mays L.) water extract had the highest α-glucosidase inhibitory activity (51%, 5 mg sample weight). No α-amylase inhibitory activity was observed in all of the evaluated Andean grains.

5 | CONCLUSIONS

The increased interest in whole cereal foods has coincided with an increase in the prevalence of chronic diseases such as T2DM. α-Amylase and α-glucosidase inhibitors are significant for the control of postprandial blood glucose in diabetic patients. Cereal-derived phenolic compounds, peptides, nonstarch polysaccharides, and lipids inhibit α-amylase and α-glucosidase activity. These inhibitors may be associated with the prevention of hypoglycemia by whole cereal food intake (Figure 3). To increase the utilization of whole cereals and their bioactive ingredients in diabetes management foods, it is mandatory to understand the inhibitory mechanisms and further investigate the structure–activity relationships between the compounds and enzymes. For example, the number and location of hydroxyl groups of phenolic acids, the molecular weight of polysaccharides, acetylation, and methylation all affect the enzyme inhibition activities. Of note, processing technologies will be able to affect the distribution, compounds, chemical structures, amount, and thus health benefits of the end whole cereal food subject to cereal types. The cereal-derived α-amylase and/or α-glucosidase inhibitor could be targeted for developing valuable whole cereal foods in T2DM dietary managements. Noteworthy, most data about the impact of whole cereal flour or whole cereal food on enzyme activities are from in vitro studies, and further in vivo investigations are needed.

ACKNOWLEDGMENTS

This work was supported by Beijing Municipal Natural Science Committee—Beijing Municipal Education Committee Joint Fund (KZ201810011014), the First-Class Disciplines Fund (PXM2019_014213_000010), and Support Project of High-level Teacher in Beijing Municipal Universities (IDHT 20180506).

CONFLICT OF INTEREST

The authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.
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How to cite this article: Gong L, Feng D, Wang T, Ren Y, Liu Y, Wang J. Inhibitors of α-amylase and α-glucosidase: Potential linkage for whole cereal foods on prevention of hyperglycemia. *Food Sci Nutr*. 2020;8:6320–6337. [https://doi.org/10.1002/fsn3.1987](https://doi.org/10.1002/fsn3.1987)