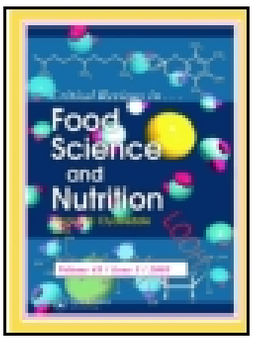

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REVIEW

Bioactive compounds, health benefits, and industrial applications of Tartary buckwheat (*Fagopyrum tataricum*)

Liang Zou[a†], Dingtao Wu[a†], Guixing Ren[b], Yichen Hu[a], Lianxin Peng[a], Jianglin Zhao[a], Pascual Garcia-Perez[c], Maria Carpena[c], Miguel A. Prieto[c], Hui Cao[c,d], Ka-Wing Cheng[e], Mingfu Wang[e], Jesus Simal-Gandara[c], Oliver D. John[f], Kannan R. R. Rengasamy[g], Gang Zhao[a], and Jianbo Xiao[c,h]

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ABSTRACT

Tartary buckwheat belongs to the family Polygonaceae, which is a traditionally edible and medicinal plant. Due to its various bioactive compounds, the consumption of Tartary buckwheat is correlated to a wide range of health benefits, and increasing attention has been paid to its potential as a functional food. This review summarizes the main bioactive compounds and important bioactivities and health benefits of Tartary buckwheat, emphasizing its protective effects on metabolic diseases and relevant molecular mechanisms. Tartary buckwheat contains a wide range of bioactive compounds, such as flavonoids, phenolic acids, triterpenoids, phenylpropanoid glycosides, bioactive polysaccharides, and bioactive proteins and peptides, as well as D-chiro-inositol and its derivatives. Consumption of Tartary buckwheat and Tartary buckwheat-enriched products is linked to multiple health benefits, *e.g.*, antioxidant, anti-inflammatory, antihyperlipidemic, anticancer, antidiabetic, antiobesity, antihypertensive, and hepatoprotective activities. Especially, clinical studies indicate that Tartary buckwheat exhibits remarkable antidiabetic activities. Various tartary buckwheat -based foods presenting major health benefits as fat and blood glucose-lowering agents have been commercialized. Additionally, to address the safety concerns, *i.e.*, allergic reactions, heavy metal and mycotoxin contaminations, the quality control standards for Tartary buckwheat and its products should be drafted and completed in the future.

KEYWORDS

Tartary buckwheat; flavonoids; phenylpropanoid; polysaccharides; benefits; antidiabetic

Introduction

Tartary buckwheat (*Fagopyrum tataricum* (L.) Gaertn) belongs to the family Polygonaceae, subfamily Polygonoideae, which is a traditionally edible and medicinal plant (Ruan et al. 2020). Tartary buckwheat (TB) possesses a great ecological adaptability, which is appropriate for harsh climates and marginal lands (Huda et al. 2021; Zhu 2016, 2021), and it is self-pollinated, conferring a reproductive advantage regarding its stable production (Ruan et al. 2020). Generally, TB has been cultivated since ancient times, and it is currently distributed in Asia (especially in China), America, and Europe (Huda et al. 2021; Ruan et al. 2020). Moreover, the global buckwheat production has been constantly increasing worldwide, reaching about 4 million tons in 2021 (Zhu 2021).

TB has been used as a food, as well as in the folk medicine of different Asian countries, mostly in China, where various TB-based food products, such as tea, vinegar, alcoholic beverages, noodles, and cakes, are becoming popular (Huda et al. 2021; Zhu 2016). Modern phytochemical studies have revealed that TB presents a plethora of bioactive compounds, such as flavonoids, polysaccharides, and proteins (Huda et al. 2021; Ji et al. 2019; Zhu 2021). As a consequence, such bioactive compounds have been identified as the major responsible for the health-promoting effects attributed to TB, such as antioxidant (Chen, Qin, et al. 2021; Zhou et al. 2020), hypolipidemic (Zhou et al. 2018; Zhang, Zhang, et al. 2017; Zhou, Zhao, et al. 2019), antidiabetic (Lee et al. 2016; Hu et al. 2017; Wu et al. 2021), anticancer (Dzah et al. 2020; Li et al. 2017; Zhou, Chen, et al. 2019), anti-inflammatory (Hwang et al. 2019; Nam et al.

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†Liang Zou and Dingtao Wu contributed equally to this work.

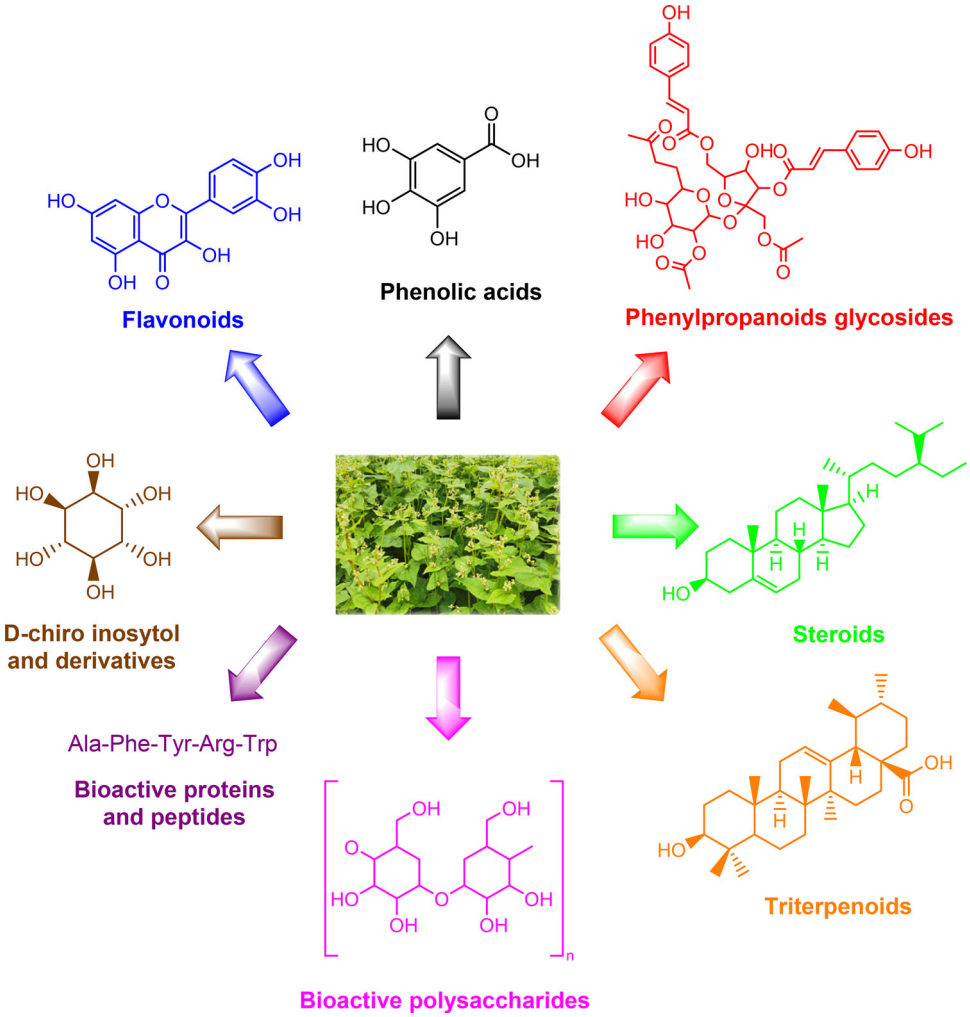

Figure 1. The basic skeletons of some representative bioactive compounds isolated from Tartary buckwheat.

2017), and hepatoprotective agents (Lee et al. 2019; Yang et al. 2020), as demonstrated by a great number of in vitro and in vivo studies. Therefore, TB can be considered as an exceptional candidate to be developed as a functional ingredient and/or food to improve human health.

In this sense, different TB-based traditional food, snacks, and healthy drinks are being currently developed worldwide, and thus, lots of commercial products related to TB or its derived extracts have been patented in China (China National Intellectual Property Administration 2021) and authorized as healthy food by the Chinese State Administration for Market Regulation (State Administration for Market Regulation 2021). However, the commercialization of TB and derivatives is not exempt from difficulties, since safety concerns must be addressed, including the promotion of allergic reactions and heavy metals and mycotoxins contaminations.

Usually, the allergy due to TB takes place as an immunoglobulin E (IgE)-mediated immunological response, which can occur by either the consumption or the manipulation of TB food products during handling and manufacturing (Norbäck and Wieslander 2021). Additionally, TB and its related products may be susceptible to invasion by toxigenic fungi during planting, storage, and processing, resulting in mycotoxin contaminations (Keriene et al. 2016; Ren et al. 2018). Furthermore, special attention should be paid to the accumulation of heavy metals, particularly in the case of lead (Pb) (Huang et al. 2013; Peng et al. 2014) and chromium (Cr), being associated with a high carcinogenic risk (Li, Li, et al. 2020).

Taking into account the most recent developments and novelties, this review is focused on the bioactive compounds found on TB, together with their associated bioactivities and benefits on human health, as well as the safety concerns and industrial applications leading to the commercialization of TB and its derived products.

Bioactive compounds

To date, different families of bioactive compounds have been isolated and purified from seeds, flowers, leaves, and roots of TB, including flavonoids, phenolic acids, triterpenoids, stilbenes, steroids, anthraquinones, phenylpropanoid glycosides, bioactive polysaccharides, and bioactive proteins and peptides, among others (Figure 1).

Flavonoids

Flavonoids constitute the most prominent group of polyphenolic secondary metabolites in plants and diets. The

Table 1. Bioactive compounds isolated from different TB raw materials and derived products, together with their identification methodology.

Family	Compounds	Original isolation	Identification methodology	References
Flavonols	Rutin, kaempferol, quercetin glycosides	Seeds, sprouts, leaves, roots, fruits, grains, flowers	HPLC-DAD-ESI-MS, HPLC-DAD-FTICR-MS, NMR	(Borovaya and Klykov 2020; Jiang et al. 2015; Joshi et al. 2020; Ren et al. 2013; Sytar et al. 2018; Zhu 2016)
Flavones	Vitexin, orientin, isovitexin, isoorientin	Seeds, grains, fruits, sprouts	HPLC-DAD-ESI-MS, NMR	(Borovaya and Klykov 2020; Sytar et al. 2018)
Isoflavones	2,6-dihydroxydaidzein, sissotrin, glycitin, genistin, ononin	Leaves	UPLC-ESI-MS/MS	(Li et al. 2019)
Flavanones	(-)-liquiritigenin, hesperidin, hesperetin derivatives, naringenin, naringenin chalcone	Leaves and roots	UPLC-ESI-MS/MS	(Li et al. 2019)
Flavan-3-ols	Catechin, epicatechin, epicatechin gallate, epigallocatechin	Seeds, roots, leaves, stems, sprouts	HPLC-PAD-LIT-MS, HPLC-FTICR-MS	(Borovaya and Klykov 2020; Jing et al. 2016; Zhu 2016)
Anthocyanins	Cyanidin glycosides, proanthocyanidins A2, A3, B2, B3	Flowers, sprouts, seeds, stems, leaves	HPLC-ESI-MS/MS, UPLC-ESI-MS/MS	(Borovaya and Klykov 2020; Li et al. 2019; Zhu 2016)
Flavonolignans	Tricin ether derivatives	Seeds, leaves	UPLC-ESI-MS/MS	(Li et al. 2019)
Fagopyrins	Fagopyrins A-F	Flowers, grains, seeds	UV-Vis absorption, MS, NMR	(Joshi et al. 2020)
Phenolic acids	Gallic acid, 4-hydroxybenzoic acid, *p*-hydroxybenzoic acid, vanillic acid, protocatechuic acid, syringic acid, salicylic acid, *p*-coumaric acid, *o*-coumaric acid, caffeic acid, ferulic acid, chlorogenic acid	Whole plants, flour, seeds, grains	UPLC-ESI-MS, HPLC-DAD-ESI-MS, NMR	(Chen, Wu, et al. 2021; Liu et al. 2019; Zhu 2016)
Phenylpropanoid glycosides	1,3,6,6′-tetra-feruloyl sucrose, 1,3,6-tri-p-coumaroyl-6′-feruloyl sucrose 3,6-di-*p*-coumaroyl-1,6′-di-feruloyl sucrose, 1,3,6′-tri-feruloyl-6-*p*-coumaroyl sucrose, tatarisides A-G, diboside A	Roots, seeds, whole plants	HPLC-PDA/LIT-FTICR-MS, NMR	(Ren et al. 2013; Zheng et al. 2012; Zhu 2016)
Steroids	β-sitosterol, daucosterol, β-sitosterol palmitate, peroxidize-ergosterol, stigmsat-4-ene-3,6-dione	Seeds	HPLC-EI-MS, NMR	(Lee, Lee, et al. 2013; Lv et al. 2017)
Triterpenoids	Ursolic acid, α-thujene, α-terpineol	Seeds, roots, leaves	HPLC-ESI-MS	(Lv et al. 2017)
Bioactive polysaccharides	TBP-II, TBP-1, TBP-2, TBP-3	Seeds, grains	SEC, DEAE-CC	(Wang et al. 2016; Wu et al. 2021; Yan et al. 2011)
Bioactive proteins and peptides	Pep-1, Pep-2, Pep-3, Pep-4, Pep-5, Pep-6, P1, P2, P3	Flour, TB albumin hydrolysate	RP-HPLC-Q-TOF/MS, RP-HPLC-ESI-MS	(Luo et al. 2020; Zhou et al. 2020)
D-chiro-inositol derivatives	D-chiro-inositol, fagopyritols	Seeds	PC, GC-MS, NMR	(Wu et al. 2018)

HPLC, high-performance liquid chromatography; DAD, diode array detector; ESI, electrospray ionization; MS, mass spectrometry; FTICR, Fourier-transform ion cyclotron resonance; NMR, nuclear magnetic resonance; UPLC, ultrahigh-performance liquid chromatography; MS/MS, tandem mass spectrometry; LIT, linear ion trap; EI, direct electron ionization; SEC, size-exclusion chromatography; DEAE-CC, di-ethyl-amino-ethyl column chromatography; RP, reverse phase; Q-TOF, quadrupole-time-of-flight; GC, gas chromatography.

content of flavonoids found in TB seeds is about 40 mg/g, whereas it reaches about 100 mg/g in its leaves, stems, and flowers (Huda et al. 2021). Different flavonoid subfamilies have been identified in TB by multiple detection methods, such as high-performance liquid chromatography (HPLC), HPLC coupled to mass spectrometry (HPLC-MS), ultra-HPLC coupled to MS by electrospray ionization (UPLC-ESI-MS), and nuclear magnetic resonance (NMR), and they are classified into flavonols, flavones, isoflavones, flavanones, flavanols/flavan-3-ols, anthocyanins, fagopyrins, proanthocyanidins, and flavonolignans (Huda et al. 2021) (Table 1). Additionally, for the extraction of flavonoids from TB, a simple, effective, and efficient matrix solid-phase dispersion extraction method has been developed for the extraction of major flavonoids (orientin, isoorientin, vitexin, isovitexin, quercetin-3-O-robinobioside, and rutin) from TB sprouts (Mansur et al. 2020). Indeed, the ionic liquid-loaded microcapsules were prepared for the selective separation of main flavonoids (rutin and quercetin) from TB extract (He et al. 2021).

Several flavonols, such as rutin, kaempferol and quercetin derivatives, have been determined in TB (Borovaya and Klykov 2020; Jiang et al. 2015; Jing et al. 2016; Li et al. 2019; Ren et al. 2013; Zhu 2016). Among all the isolated and identified flavonoids in this plant, rutin was determined as the most abundant compound, accounting for the 90% of the total phenolics (Sytar et al. 2018). Generally, the content of rutin is about 14 mg/g of dry weight (DW) in TB seeds (Zhu 2016), and is about 110 mg/100 g of fresh weight (FW) in TB sprouts (Joshi et al. 2020). Recent studies have

revealed that the content of rutin is highly influenced by the treatments involved in TB processing, showing that it significantly improves after fermentation treatment (Chen, Qin, et al. 2021; Huang et al. 2017), whereas infrared roasting, thermal assisted roasting, steaming, boiling, and microwaving, can promote a significant decrease (Bhinder et al. 2019; Chen, Qin, et al. 2021; Klepacka and Najda 2021; Liu et al. 2019). Interestingly, the contents of rutin and kaempferol-3-rutinoside in TB flour significantly decreased during the dough formation and dough fermentation processes, which were changed into quercetin and kaempferol, respectively (Xiao et al. 2021).

Furthermore, four flavones, including vitexin, orientin, isoorientin, and isovitexin, have been determined in TB by HPLC-MS and NMR (Huda et al. 2021; Zhu 2016), although these compounds were found in a lower concentration in TB in comparison to common buckwheat (Sytar et al. 2018). Some isoflavones have also been isolated from TB leaves, such as 2,6-dihydroxydaidzein, sissotrin, glycitin, genistin, and ononin (Li et al. 2019). Moreover, several flavanones have been detected in the leaves and roots of TB by UPLC-ESI-MS/MS (Table 1), such as (-)-liquiritigenin, hesperidin, hesperetin derivatives, naringenin, and naringenin chalcone (Li et al. 2019). Concerning flavan-3-ols, catechin, epicatechin, epicatechin gallate, and epigallocatechin have been detected in TB, by different methods, including HPLC equipped with photodiode array detector (PAD), coupled to linear ion trap (LIT) MS (HPLC-PAD-LIT-MS) and Fourier-transform ion cyclotron resonance MS (FTICR-MS) (Borovaya and Klykov 2020; Jing et al. 2016; Zhu 2016). In addition, two anthocyanins, represented by cyanidin glycosides (cyanidin 3-*O*-glucoside and cyanidin 3-*O*-rutinoside), and four proanthocyanidins (procyanidin A2, procyanidin A3, procyanidin B2, and procyanidin B3) were determined in the aerial parts of TB, as well as in seeds (Borovaya and Klykov 2020; Li et al. 2019). Furthermore, several flavonolignans were found in TB leaves and seeds, including tricin 4′-O-(syringyl alcohol) ether 7-O-hexoside, tricin 4′-O-(syringyl alcohol) ether 5-O-hexoside, tricin 4′-O-syringic acid, tricin 4′-O-*β*-guaiacylglycerol, tricin 7-O-*β*-guaiacylglycerol, and tricin 4′-O-(*β*-guaiacylglyceryl) ether O-hexoside (Li et al. 2019).

Besides these ubiquitous flavonoids, specific flavonoids have been found on TB, as it is the case of fagopyrins, namely fagopyrin A to fagopyrin F, considered as phytochemical determinants of different *Fagopyrum* species and identified by different techniques (Joshi et al. 2020).

Phenolic acids

Phenolic acids and their derivatives are widely distributed in plants, and thus both hydroxybenzoic acids and hydroxycinnamic acids have been detected in TB (Table 1) (Huda et al. 2021; Zhu 2016). In particular, gallic acid, 4-hydroxybenzoic acid, *p*-hydroxybenzoic acid, vanillic acid, protocatechuic acid, syringic acid, salicylic acid, *p*-coumaric acid, *o*-coumaric acid, caffeic acid, ferulic acid, and chlorogenic acid, were identified in TB by UPLC-ESI-MS (Liu et al. 2019). As it occurred with rutin, the phenolic acid content of TB is influenced by the processing methodologies, showing that syringic acid, ferulic acid, and 4-hydroxybenzoic acid concentrations significantly improved after fermentation treatment (Chen, Qin, et al. 2021), whereas the contents of salicylic acid, syringic acid, chlorogenic acid, protocatechuic acid, and gallic acid showed a significant decrease after thermal-assisted roasting and microwave cooking (Liu et al. 2019).

Phenylpropanoid glycosides

Twelve phenylpropanoid glycosides have been found in the roots and seeds of TB (Table 1). Four phenylpropanoid glycosides, including 1,3,6,6′-tetra-feruloyl sucrose, 1,3,6-tri-*p*-coumaroyl-6′-feruloyl sucrose 3,6-di-*p*-coumaroyl-1,6′-di-feruloyl sucrose, and 1,3,6′-tri-feruloyl-6-*p*-coumaroyl sucrose, have been detected in the seeds of TB by HPLC-PAD/LIT-FTICR-MS (Huda et al. 2021; Zhu 2016). Moreover, specific phenylpropanoid glycosides were found in TB, represented by seven tatarisides (tatarisides A to tatarisides G) and diboside A, were determined in TB roots (Zheng et al. 2012).

Steroids

Steroids constitute a large class of cyclopentane perhydrophenanthrene derivatives, widely distributed in the biological world, including the plant kingdom. A total of 5 steroids have been identified exclusively in the roots of TB (Table 1), being *β*-sitosterol, daucosterol, *β*-sitosterol palmitate, peroxidized-ergosterol, and stigmsat-4-ene-3,6-dione the most representative compounds (Lee, Lee, et al. 2013).

Triterpenoids

Triterpenoids are C_{30} isoprenoid derivatives, usually found in plants in both free and glycosylated forms with potent associated biological activities (Mäki-Opas et al. 2019). In the case of TB, a total of 3 triterpenoids have been isolated from seeds, roots, and leaves: being ursolic acid, α-thujene, and α-terpineol (Table 1) (Lv et al. 2017).

Bioactive polysaccharides

Generally, polysaccharides are considered as the major abundant components in TB (Table 1), presenting obvious in vitro α-D-glucosidase inhibitory activity and in vivo antidiabetic activity (Wang et al. 2016; Wu et al. 2021). The extraction yields of polysaccharides from buckwheat range from 7.23% to 25.16% (Ji et al. 2019). A non-starch polysaccharide (TBP-II) with an average molecular weight of 26 kDa has been isolated and purified from TB seeds by using size exclusion chromatography (SEC), and its constitutive monosaccharidic subunits are galactose, arabinose, xylose, and glucose in a molar ratio of 0.7: 1.0: 6.3: 74.2 (Wang et al. 2016). Regarding the structure of TBP-II, 1,4-α-D-glucopyranosyl has been identified as its linear backbone, and 1,3-α-D-glucopyranosyl, 1,6-α-D-galactopyranosyl, and 1,2(4)-α-D-rhamnopyranosyl were identified as the ramifications (Wang et al. 2016).

Table 2. Biological activities attributed to TB, and their bioactive compounds, and their mechanisms of action.

Bioactivity	Mechanisms of action	References
Antioxidant activity	Strong radical scavenging activity	(Chen, Wu, et al. 2021)
	Improvement of total antioxidation capacity	(Zhou et al. 2020)
	Increase of GSH/GSSG ratio	(Luo et al. 2020)
	ROS reduction	(Choi et al. 2015)
	SOD, CAT, and GSH-Px induction	(Zhou et al. 2020)
	Inhibition of lipid perioxidation	(Luo et al. 2020)
Anti-inflammatory activity	Decrease of TNF-α, IL-6, NFκB and nitric oxide	(Hwang et al. 2019; Nam et al. 2017)
	Inhibition of iNOS, COX-2, and MCP-1	(Hwang et al. 2019; Lee et al. 2017)
Hypolipidemic activity	Decrease of serum TC, TG, LDL, and MDA levels	(Wang et al. 2009; Zhou, Chen, et al. 2019)
	Decrease of liver TC and TG levels	(Giménez-Bastida and Zieliński 2015; Wang et al. 2009)
	Decrease of atherogenic index	(Wang et al. 2009)
	Increase of serum HDL level	(Zhang, Zhang, et al. 2017)
	Enhancement of gut microbiota	(Zhou et al. 2018)
Anticancer activity	Cytotoxicity against liver HepG2, colon Caco-2, breast Bcap37, MCF-1 and MDA-MB-231, gastric MGC80-3, lung A549 and H460, and leukemia THP-1 cancer cell lines	(Dzah et al. 2020; Guo et al. 2010; Jia et al. 2018; Lee et al. 2015; Li et al. 2017; Li, Zhang, et al. 2020; Wu and Lee 2011; Zhou, Chen, et al. 2019)
Antidiabetic activity	Serum glucose level reduction	(Lee et al. 2012; Lee et al. 2016)
	Insulin resistance decrease	(Wu et al. 2018)
	Enhancement of glucose uptake and tolerance	(Shanzao Chen et al. 2017; Wu et al. 2021)
	Inhibition of oxidative stress	(Ramos-Romero et al. 2018)
Antiobesity activity	Body weight reduction	(Nishimura et al. 2016)
	Body fat percentage reduction	(Peng et al. 2020)
	Inhibition of oxidative stress and adipose tissue inflammation	(Kim et al. 2019)
Hepatoprotective activity	Serum AST, ALT, ALP, LDH, and CRP levels reduction	(Lee, Shen, et al. 2013)
	ROS, TBARS, MDA, TC, TG, LDL levels reduction	(Hu, Zhao, Ren, et al. 2015)
	Decrease of TNF-α, IL-1β, and IL-6	(Lee, Lee, et al. 2013)
	GSH, GSH-Px, CAT, GR, GST, and SOD induction	(Lee, Shen, et al. 2013)
Other activities	Antibacterial activity	(Zhao et al. 2018)
	CVS dysfunction prevention	(Zhu 2016)
	Antihypertensive activity	(Hou et al. 2017; Ramos-Romero et al. 2020)
	DNA structural prevention	(Huang et al. 2017)
	Psoriasis-like dermatitis alleviation	(Chen et al. 2017)

GSH/GSSG, reduced/oxidized glutathione; MDA, malondialdehyde; ROS, reactive oxygen species; SOD, superoxide dismutase; CAT, catalase; GSH-Px, glutathione peroxidase; ; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; NF, nuclear factor κB; iNOS, inducible nitric oxide synthase; COX2, cyclooxygenase-2; MCP-1, monocyte chemoattractant protein-1; TC, total cholesterol; TG, triglycerides level; LDL, low-density lipoproteins; HDL, high-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; LDH, lactate dehydrogenase; CRP, C-reactive protein; TBARS, thiobarbituric acid reaction substance; IL-1β, interleukin-1β; GSH, glutathione; GR, glutathione reductase; GST, glutathione-S-transferase; CVS, cardiovascular system.

In another study, a neutral polysaccharide (TBP1) with an average molecular weight of 19.6 kDa has been obtained from TB bran, which has been seen to exert excellent hypoglycemic and hypolipidemic effects in diabetic mice (Wu et al. 2021). Concerning TBP1 composition, glucose (93.98%) was determined as the main monosaccharide subunit. Furthermore, three different polysaccharide fractions, named as TBP-1, TBP-2, and TBP-3, have been isolated from TB by diethylaminoethyl (DEAE)-cellulose column chromatography, with molecular weights of 144.5 kDa, 445.7 kDa, and 636.8 kDa, respectively (Yan et al. 2011). Moreover, it was shown that TBP-1 and TBP-2 fractions were essentially composed of glucose, while TBP-3 presents a heterogeneous composition, including mannose, rhamnose, glucuronic acid, glucose, galactose, and arabinose with a molar ratio of 4.32: 2.41: 1.00: 39.8: 9.64: 2.02 (Yan et al. 2011). Due to the prevalence of polysaccharides as phytoconstituents of TB, their purification and characterization requires to be further investigated.

Bioactive proteins and peptides

The protein contents in different *Fagopyrum* species range from 7.8% to 21.3% (Zhu 2021). A comprehensive study showed that the contents of proteins in the flour of different TB varieties ranged from 9% to 15% (Bhinder et al. 2020). Protein isolates and its derived peptides from TB possess diverse in vitro and in vivo bioactivities, such as cholesterol-lowering (Zhang, Zhang, et al. 2017), antioxidant (Zhou et al. 2020; Luo et al. 2020), hypoglycemic (Tao et al. 2019), antimicrobial (Cui et al. 2018), and gut microbiota regulation effects (Zhou et al. 2018). One of the most relevant bioactive protein hydrolysates found on TB, named TB crude protein product (TBP), was obtained from TB flour, by alkali extraction and isoelectric precipitation, exhibiting inhibitory effect against hypercholesterolemia in cholesterol-fed rats and higher lithogenic index in cholesterol-fed mice by higher fecal excretion of sterols (Tomotake et al. 2007). The content of protein in TBP is 45.8%, and its amino acid composition is composed of Asp, Thr, Ser, Glu, Gly, Ala, Cys, Val, Met, Ile, Leu, Tyr, Phe, Lys, His, Arg, Pro, and Trp, being characterized by a high Lys, Glu, Gly, and Arg content.

Furthermore, another crude protein (TB-P) was also isolated from TB by alkali extraction and isoelectric precipitation, which also possessed a cholesterol-lowering effect (Zhang, Zhang, et al. 2017). The protein content of TB-P is 63.1%, and its amino acid composition includes Asp, Glu,

Thr, Leu, Cys, Gly, Val, Ile, Arg, Lys, Ala, Met, Ser, His, Pro, Tyr, Phe, and Trp, presenting a high Glu and Arg content. Moreover, six active peptides were obtained from the enzymatic hydrolysates of 13S globulin acidic subunit, namely Pep-1, Pep-2, Pep-3, Pep-4, Pep-5, and Pep-6 (Zhou et al. 2020).

Additionally, three new antioxidant peptides (P1, P2, and P3) were obtained from the hydrolysates of TB albumin by the action of alkaline protease, and their sequences have been identified as Gly-Glu-Val-Pro-Trp, Tyr-Met-Glu-Asn-Phe, and Ala-Phe-Tyr-Arg-Trp, respectively (Luo et al. 2020). More studies are also required for the extraction and purification of bioactive proteins from TB, and the detailed structural features of purified proteins also require to be systematically characterized.

Other compounds

Additional compounds presenting significant bioactivities can be also found in TB. For instance, resveratrol, a stilbene synthesized during polyphenol biosynthesis, was recently isolated from TB for the first time (Němcová et al. 2011). D-fagomine, an iminosugar found on TB, effectively strengthens the body sensitivity to insulin and alleviates sucrose-induced hypertension (Ramos-Romero et al. 2020). D-chiro-inositol and its derivatives (fagopyritol A and fagopyritol B) determined in TB bran have potential anti-diabetic effects in KK-A^y type 2 diabetic mice (Wu et al. 2018). Furthermore, different anthraquinones, such as aurantio-obtusin, aloe-emodin, rhein, emodin, chrysophanol, and physcion, were found in the seeds of TB, which may possess different bioactivities, such as antibacterial and anticancer effects (Zhu 2016). Finally, bioactive amines, such as N-trans-feruloyltyramine, have also been determined in TB, which presents a potent neuroprotective activity (Huda et al. 2021).

Biological activities

Multiple in vitro and in vivo studies have demonstrated that TB and its bioactive compounds possess diverse health-promoting effects, acting as antioxidant (Chen, Qin, et al. 2021; Dzah et al. 2020; Zhou et al. 2020; Luo et al. 2020), hypolipidemic (Wang et al. 2009; Zhou et al. 2018; Zhang, Zhang, et al. 2017; Zhou, Zhao, et al. 2019), antidiabetic (Lee et al. 2016; Hu et al. 2017; Wu et al. 2018; Wu et al. 2021; Cheng et al. 2019), anticancer (Dzah et al. 2020; Li, Zhang, et al. 2020; Li et al. 2017; Zhou, Chen, et al. 2019), anti-inflammatory (Hwang et al. 2019; Nam et al. 2017; Huang et al. 2017), and hepatoprotective agents (Lee, Shen, et al. 2013; Hu, Zhao, Ren, et al. 2015; Lee et al. 2019; Yang et al. 2020). Table 2 summarizes the diverse biological activities and health benefits associated with TB and its bioactive components. Herein, an updated review on the in vitro and in vivo of health benefits of TB and its bioactive components is presented, with a special focus on the mechanisms of action attributed to bioactive components.

Antioxidant activity

Many studies have demonstrated that TB and its products exhibit a potent in vitro and in vivo antioxidant activity due to the presence of several bioactive components, such as polyphenols and peptides (Giménez-Bastida and Zieliński 2015; Ji et al. 2019; Zhu 2021).

Generally, a higher polyphenol content is positively correlated with the in vitro antioxidant activity and, interestingly, different food processing technologies are likely to significantly affect the antioxidant activities of TB and its products (Zhu 2016). For example, higher antioxidant activity was observed in 70% ethanolic TB extracts (TBEs) compared with 80% acetone and ethyl acetate extracts (Chen, Qin, et al. 2021). Additionally, the single subcritical water extraction method appears to be more beneficial for the extraction of antioxidant compounds from TB, compared with other methods, such as hot water extraction, ultrasound-assisted extraction, and ultrasound-assisted subcritical water extraction (Dzah et al. 2020). Other treatments, *e.g.* suitable roasting, brewing, boiling, steaming, autoclaving, fermentation, and germination pretreatments are able to improve the total polyphenol content, thereby increasing antioxidant activity (Ling et al. 2018; Liu et al. 2019; Zhang, Chen et al. 2017). In addition, during the dough formation and fermentation stages of steamed TB bread preparation, flavonoid glycosides (rutin and kaempferol-3-rutinoside) are converted into aglycones (quercetin and kaempferol) accompanied by an increase of antioxidant activity (Xiao et al. 2021). Moreover, the by-products of TB such as bran, hull, leaves, and flowers should be considered as non-ignorable source of natural antioxidants, due to their potent associated antioxidant activity (Dziadek et al. 2018; Li, Zhang, et al. 2020; Park et al. 2019; Zhao et al. 2018).

Besides polyphenols, TB-derived peptides also exhibit a remarkable antioxidant activity. For instance, peptides effectively promoted an enhancement of total antioxidation capacity (T-AOC), superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GSH-Px) activities in HepG2 cells *via* the peroxisome proliferator-activated receptor alpha/heme oxygenase-1 (PAR-α/HO-1) pathway (Zhou et al. 2020). In another study, the new antioxidant peptides proceeding from TB albumin exhibited an inhibitory effect on lipid peroxidation and reducing power, as observed by the improvement of the ratio reduced glutathione/oxidized glutathione (GSH/GSSG) (Luo et al. 2020).

Anti-inflammatory activity

Inflammation is a common bioprocess in response to tissue injury, microbial pathogens, and chemical irritation, and it has also been considered as an initial step in the onset of chronic diseases, such as cancer, alzheimer, obesity and diabetes (García-Pérez et al. 2021). Previous evidences have reported that TB and its bioactive components possess an outstanding anti-inflammatory activity (Giménez-Bastida and Zieliński 2015; Huda et al. 2021; Zhu 2016). In this sense, recent studies have demonstrated that kaempferol-3-*O*-*β*-rutinoside, isolated from TB sources, exert a potent

anti-inflammatory effect in lipopolysaccharide (LPS)-induced RAW 264.7 macrophage cells (Hwang et al. 2019). Moreover, this compound can inhibit the production of nitric oxide (NO), interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α), and suppress the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) in LPS-induced RAW 264.7 cells through the nuclear factor kappa B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways (Hwang et al. 2019). This observation was assessed by the evaluation of the flavonoid-rich extract of TB, which also promoted an anti-inflammatory effect on LPS-induced RAW 264.7 cells through the NF-κB and MAPK pathways (Nam et al. 2017).

Furthermore, different fractions of TBE, including *n*-hexane, methylene chloride, ethyl acetate, and *n*-butanol fractions, effectively inhibited the production of reactive oxygen species (ROS), NO, and IL-6, and the mRNA expression levels of NF-κB, COX-2, and iNOS in LPS-stimulated RAW 264.7 cells (Choi et al. 2015). Additionally, TBEs are able to inhibit the inflammatory response in 3T3-L1 cells, which can reduce the mRNA expression levels of TNF-α, IL-6, monocyte chemoattractant protein-1 (MCP-1), and iNOS, and decrease the production of NO (Lee et al. 2017). Interestingly, recent studies have shown that different TB processing methods may enhance the anti-inflammatory activity of TB on LPS-induced RAW 264.7 cells, as already reported for fermentation (Huang et al. 2017) and the laser light treatment of flavonoid-rich TB sprout extract (Almuhayawi et al. 2021).

Therefore, these studies suggest that TB flavonoids exhibit anti-inflammatory activity in LPS-induced RAW 264.7 cell through the NF-κB and MAPK pathways, which can be beneficial for the prevention and treatment of inflammatory diseases in humans. Nevertheless, more in vivo and human studies are required to further confirm the anti-inflammatory activities of TB and its compounds.

Hypolipidemic activity

Hyperlipidemia is defined as a metabolic disease characterized by elevated levels of triglycerides (TG), total cholesterol (TC), low-density lipoproteins (LDL) and low levels of high-density lipoproteins (HDL) (Giménez-Bastida and Zieliński 2015).

As a matter of fact, the antioxidant activity of TB bran ethanolic extract (TBBE) and its effect on the lipid profile of hyperlipidemic rats induced by a high-fat diet were discussed (Wang et al. 2009). Results indicated that TBBE significantly decreased TG and TC serum and liver levels, up-regulated serum GSH-Px activity, and downregulated the serum malondialdehyde (MDA) level, atherogenic index of plasma (AIP), and atherogenic index (AI) (Wang et al. 2009).

Furthermore, a bioactive protein isolated from TB sources, BWP, can prevent dyslipidemia in high-fat diet-fed mice associated with the changes of gut microbiota, reducing the levels of blood TC and TG and decrease the levels of TNF-α and IL-6 (Zhou et al. 2018). Indeed, BWP significantly promoted the growth of *Lactobacillus* and *Bifidobacterium*, and inhibited the growth of *Escherichia coli*, thus contributing to the increase of the excretion of total bile acids and short-chain fatty acids (Zhou et al. 2018).

Additionally, the TB flour-derived protein TB-P also possesses remarkable cholesterol-lowering effect in hypercholesterolemic hamsters (Zhang, Zhang, et al. 2017), by enhancing the excretion of bile acids *via* up-regulation of hepatic cholesterol-7α-hydroxylase (CYP7A1), and also by inhibition of the absorption of dietary cholesterol *via* down-regulation of intestinal Niemann-Pick C1-like protein 1 (NPC1L1), acyl CoA-cholesterol acyltransferase 2 (ACAT2), and ATP binding cassette transporters G5 and G8 (ABCG5/8) (Zhang, Zhang, et al. 2017).

Moreover, the TB resistant starch (BRS) could lower cholesterol in mice fed a high-fat diet, by reducing the plasma levels of TG, TC, TNF-α, IL-6 and glucose (Zhou, Zhao, et al. 2019). The increased short-chain fatty acids excretion through the amelioration of gut microbiota dysbiosis was also noted, thus possibly preventing cholesterol increase and glucose metabolic disorder, suggesting that polyphenols, proteins, and resistant starch from TB exert an excellent hypolipidemic activity through the downregulation of TG and TC, the increase in the ratio HDL/LDL, and the up-regulation of the excretion of bile acids (Zhou, Zhao, et al. 2019). In conclusion, due to the high contents in flavonoids, bioactive proteins and polysaccharides, TB has potential applications as functional foods for the prevention of hyperlipidemia.

Anti-cancer activity

TBEs and its components have been widely examined for their in vitro and in vivo anticancer activity (Giménez-Bastida and Zieliński 2015; Jing et al. 2016; Zhu 2016). Recent studies have revealed that TB polyphenols exert cytotoxicity on human liver carcinoma cells (Dzah et al. 2020) and human colon cancer Caco-2 cells (Li, Zhang, et al. 2020). Furthermore, the anticancer effect and possible molecular mechanisms attributed to TB and its bioactive compounds were investigated, indicating that TB phenolics are responsible for the anticancer activity against human breast cancer MDA-MB-231 cells in a dose-dependent manner, through the induction of cell apoptosis by p38/MAPK pathway, and the cell cycle arrest from G1 to S phase (Li et al. 2017). Additionally, TB flavonoids exhibit a remarkable anticancer activity against human gastric cancer MGC80-3 cells, which is mediated by the promotion of the expression of apoptotic proteins, such as caspase-8 (Zhou, Chen, et al. 2019).

Moreover, a previous study has demonstrated that TB-derived quercetin presents strong cytotoxic effects against human hepatoma HepG2 cells, by increasing the production of ROS, and inducing cell cycle arrest at G_2/M phase, leading to an increase in apoptotic cell death (Li et al. 2014). Indeed, quercetin can also suppress the mobility of human breast cancer MCF-7 cells and MDA-MB-23 cells by suppressing glycolysis through protein kinase B (Akt)-mTOR

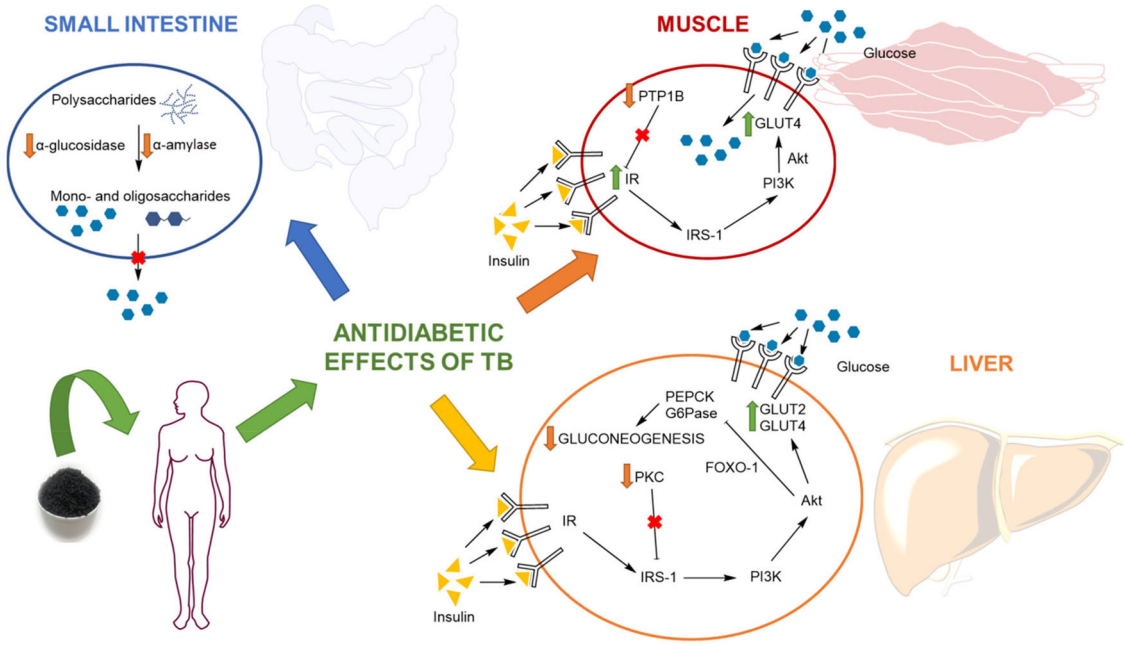

Figure 2. The antidiabetic mechanisms of Tartary buckwheat and its bioactive components. The antidiabetic effect of Tartary buckwheat (TB) and its bioactive components mainly target the small intestine, muscle, and liver. (1) In the small intestine, TB and its bioactive components inhibit the activities of α-glucosidase and α-amylase, and suppress the decomposition of dietary polysaccharides into easily absorbed oligosaccharides and monosaccharides, thus reducing the postprandial blood glucose level. (2) In the muscle, TB and its bioactive components improve insulin resistance by downregulating the expression of PTP1B and up-regulating the expression of PI3K. (3) In the liver, TB and its bioactive components promote glucose uptake by activating the expression of GLUT2 and GLUT4, and downregulate gluconeogenesis by inhibiting the expression of PEPCK and G6-Pase. PTP1B, protein-tyrosine phosphatase 1B; IR, insulin receptor; IRS-1, insulin receptor substrate-1; PI3K, phosphoinositide-3-kinase; Akt, protein kinase B; GLUT, glucose transporter; FOXO1, forkhead box protein O1; PEPCK, phosphoenolpyruvate carboxykinase; G6Pase, glucose-6-phosphatas.

pathway-mediated autophagy induction (Jia et al. 2018). Furthermore, quercetin has been proved to enhance the efficacy of gemcitabine-induced cell death in lung cancer A549 and H460 cells by increasing caspase-3 and caspase-9 activities (Lee et al. 2015).

Besides polyphenols, TB polysaccharides also exhibit anticancer properties against THP-1 human leukemia cells, by directly inducing cell differentiation and maturity, and promoting the phagocytic activity in mature cells (Wu and Lee 2011). Additionally, TBWSP31, a purified protein isolated from TB, promoted an anticancer activity against breast cancer Bcap37 cells, inducing the cell cycle arrest at G_0/G_1 phase, which might be associated with the up-regulation of Fas expression and the down-regulation of Bcl-2 expression (Guo et al. 2010).

Overall, these studies provide a wide of evidence about the effectiveness of TB polyphenols, polysaccharides and proteins as anticancer compounds against a great variety of cancer cell lines. Nevertheless, increasing efforts should be made for the development of in vivo animal studies to further understand the underlying molecular mechanisms attributed to these compounds.

Anti-diabetic activity

Diabetes is a metabolic disease characterized by hyperglycemia, which is considered as one of the major health concerns in modern society. Previous studies have demonstrated that TB and its bioactive compounds possess an excellent in vitro and in vivo antidiabetic activity, promoting an integrated effect on intestine, muscle and hepatic tissues (Figure 2) (Giménez-Bastida and Zieliński 2015; Zhu 2016). In this sense, TB-derived polyphenols, including rutin and quercetin, proteins and non-starch polysaccharides exhibit potent inhibitory effects on α-glucosidase and α-amylase, thus preventing the release of glucose and other mono- and oligosaccharides to bloodstream (Figure 2) (Wang et al. 2016; Zhu 2021).

Recently, the antidiabetic activities of TB ethanolic extract (EEB) (rich in rutin and quercetin), rutin, and quercetin were systematically evaluated on high glucose- induced FL83B hepatocytes and C57BL/6 mice fed a fructose-rich diet (FRD) (Lee et al. 2012). Results showed that the administration of EEB and rutin could significantly decrease the serum glucose and insulin levels, improve insulin sensitivity, decrease the hepatic and serum TC, TG, and LDL levels, and increase CAT, glutathione reductase (GR), SOD, and GSH-Px activities in the liver of FRD-induced C57BL/6 mice (Lee et al. 2012). At the same time, EEB and rutin could alleviate insulin resistance by enhancing the glucose transporter 2 (GLUT2) translocation into the plasma membrane of FL83B hepatocytes, thus resulting in an increase of glucose uptake (Lee et al. 2012). Concerning the molecular mechanisms behind these effects, both EEB and rutin were reported to induce Akt pathway and promote the up-regulation of AMP-dependent protein kinase (AMPK) and the downregulation of protein tyrosine phosphatase 1B (PTP1B) (Lee et al. 2012). In this sense, TB-derived rutin contribute to the decrease in the serum glucose level in type-2 diabetes by alleviating insulin resistance through the down-regulation of PTP1B in C2C12 myocytes and, consequently, the

overexpression of the insulin receptor (IR) in the membrane of muscle cells, promoting glucose uptake *via* insulin receptor substrate 1/phosphatidylinositol-3-kinase (IRS-1/PI3K)-mediated glucose transporter 4 (GLUT4) up-regulation (Figure 2) (Lee et al. 2016). Furthermore, the continuous administration of TB-derived flavonoids could improve the insulin sensitivity and glucose intolerance in high fructose-fed mice, which could also reverse the reduced level of insulin action on the phosphorylation of IRS-1, Akt, PI3K, and translocation of glucose transporter type 4 (GLUT4) in the insulin-resistant liver (Hu et al. 2017).

In addition to flavonoids, TB-derived D-chiro-inositol (DCI) also presents an excellent antidiabetic activity. The oral administration of DCI-enriched TBE has been seen to reduce plasma glucose, C-peptide, glucagon, TG, and urea nitrogen in type-2 diabetic KK-A^y mice, thus enhancing glucose tolerance and insulin sensitivity (Yao et al. 2008). Furthermore, the effects and molecular mechanisms associated with DCI on hepatic gluconeogenesis in mice fed a high-fat diet and in saturated palmitic acid-treated hepatocytes were investigated (Cheng et al. 2019). Results showed that DCI could reduce the hepatic gluconeogenesis rate in human HepG2 cell line in vitro and in insulin-resistant mouse in vivo models, by regulating the diacylglycerol-mediated protein kinase C (PKC)-PI3K/Akt pathway-mediated inhibition of cytosolic phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase) by FOXO-1 transcription factor activation (Figure 2) (Cheng et al. 2019). Moreover, two DCI derivatives, including fagopyritol A1 and fagopyritol B1, also exhibit antidiabetic effects (Wu et al. 2018): the administration of fagopyritol B1 in KK-A^y mice was found to be the most effective DCI derivative in suppressing the progressive rise of blood glucose, improving impaired glucose tolerance, and increasing insulin sensitivity, in comparison with DCI and fagopyritol A1 (Wu et al. 2018). In fact, fagopyritols improved lipid homeostasis and increased the expression of insulin receptor and PI3K in liver and skeletal muscle, showing an increase in glucose consumption in both normal and insulin resistant HepG2 cells, and up-regulating the phosphorylation of PI3K and Akt. As a result, fagopyritols were suggested to exert a parallel mode of action than DCI, presenting a potential antidiabetic effect *via* activation of the PI3K/Akt insulin-dependent pathway (Wu et al. 2018).

Furthermore, studies have shown that buckwheat-isolated D-fagomine can reduce fat-induced impaired glucose tolerance and inflammation markers and mediators (hepatic microgranulomas and lobular inflammation, plasma IL-6, prostaglandin E_2 and leukotriene B_4), as well as reduce the changes in *Enterobacteria* and *Bifidobacteria* populations, which may improve the prophase of diabetic rats by regulating intestinal flora and anti-inflammatory effects (Ramos-Romero et al. 2018).

Recently, the anti-diabetic effects of a soluble dietary fiber (SDF) extracted from TB bran in diabetic mice have been systematically investigated (Wu et al. 2021). The dietary SDF administration of SDF could reduce the levels of fasting blood glucose, improve oral glucose tolerance, increase the levels of liver glycogen and insulin, and improve both serum and hepatic lipid profiles in diabetic mice (Wu et al. 2021).

In conclusion, these results suggest that the antidiabetic activity of TB is mainly attributed to its bioactive components, such as flavonoids (mostly rutin and quercetin), D-chiro-inositol and its derivatives, and polysaccharides. Thus, TB has potential applications as functional foods for the prevention of diabetes and hyperlipidemia, due to the multifaceted antidiabetic mechanisms attributed to its phytoconstituents (Figure 2).

Anti-obesity activity

Obesity is an increasingly serious, obvious, but also the most neglected global health problem (Walls et al. 2011). It constitutes the main risk for serious diet-related noncommunicable diseases, including diabetes, cardiovascular diseases like hypertension and stroke, and certain cancer forms.

As a coarse grain, rutin-rich TB shows some effects on decreasing body weight, body fat percentage, and oxidative stress in a randomized, double-blind, and placebo-controlled study (Nishimura et al. 2016). Moreover, BRS has been shown to prevent obesity (Zhou, Zhao, et al. 2019). In the same way, TB quercetin can significantly reduce body weight, serum TG, LDL, TNF-α, and insulin levels, and ameliorate glucose tolerance of rats fed a high-fat diet, which suggests that quercetin can attenuate obesity and related metabolic disorders in this in vivo model (Peng et al. 2020). Particularly, both BRS and quercetin may regulate the intestinal microbial community structure to play an antiobesity effect (Peng et al. 2020; Zhou, Zhao, et al. 2019). Furthermore, the effect of TBEs on adipogenesis in 3T3-L1 cells was discussed, reporting that TBEs could inhibit lipid accumulation, TG accumulation, and glycerol-3-phosphate dehydrogenase activity (GPDH) in 3T3-L1 cells during adipocyte differentiation (Lee et al. 2017). Indeed, the mRNA expression levels of enzymes involved in fatty acid synthesis, including peroxisome proliferator-activated receptor-γ (PPAR-γ), CCAAT/enhancer binding protein-α (CEBP-α), adipocyte protein 2 (aP2), acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), and stearoylcoenzyme A desaturase-1 (SCD-1), were suppressed by TBEs (Lee et al. 2017).

Besides their influence on fat and weight reduction, TBEs may attenuate critical side effects associated with obesity, as it was proven in the inhibition of the obesity-induced adipose tissue inflammation in rats fed a high-fat diet (Kim et al. 2019). In detail, the administration of TBEs can reduce the TNF-α, interleukin-1β (IL-1β), and IL-6 levels in the liver of ethanol- and CCl_4-induced animals, thus preventing obesity-mediated liver inflammatory injury (Lee, Shen, et al. 2013). Overall, these studies suggest that TB exerts a potent antiobesity effect, requiring further in vivo animal and human clinical studies to confirm such bioactivity and understand its mechanisms of action.

Hepatoprotective activity

Liver damage is a chronic disease caused by ROS and several chemicals, such as alcohol. In this sense, about 90% of

consumed alcohol is metabolized in the liver by alcohol dehydrogenase, resulting in the production of acetaldehyde, superoxide ions, and hydrogen peroxide, which may covalently bind to lipids and proteins, resulting in denaturation and alcoholic fatty liver (Wu and Cederbaum 2009).

A previous study has demonstrated that rutin, quercetin, and TBE exert an hepatoprotective effect *via* the promotion of antioxidant and anti-inflammatory properties against oxidative liver damage in ethanol-induced C57BL/6 mice and CCl4-induced Sprague-Dawley rats (Lee, Shen, et al. 2013). Rutin- and quercetin-enriched TBE, together with the individual compounds could inhibit the increase in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) levels in ethanol-induced mice and CCl_4-induced rats with liver damage (Lee, Shen, et al. 2013). Additionally, TBEs could improve the activities of antioxidant-related enzymes, including CAT, GSH-Px, GR, and SOD, and inhibit the levels of hepatic inflammation in the same animal models (Lee, Shen, et al. 2013). Indeed, both rutin and quercetin can significantly prevent ethanol-induced hepatotoxicity by decreasing hepatic aminotransferase activities and inflammatory response in HepG2 cells *via* the nuclear factor E2 related factor 2/antioxidant response element (Nrf2/ARE) antioxidant pathway (Lee et al. 2019).

Furthermore, the purified flavonoid-enriched TBE exhibited an outstanding hepatoprotective effect in high trimethylamine-N-oxide (TMAO) diet-fed mice, significantly increasing serum HDL level and decreasing serum TC, TG, and LDL levels (Hu, Zhao, Yuan, et al. 2015). In fact, TB flavonoids also reduced serum AST and ALT activities, and hepatic non-esterified fatty acid (NEFA) and MDA levels, and increased the hepatic GSH-Px and SOD activities (Hu, Zhao, Ren, et al. 2015). Additionally, the same extract can also ameliorate high fructose-induced oxidative stress associated with Nrf2/HO-1 pathways in mice (Hu et al. 2017).

Moreover, TBEs can alleviate alcohol-induced acute and chronic liver damages through the inhibition of oxidative stress and the mitochondrial cell death pathway (Yang et al. 2020). Furthermore, the DCI-enriched TBE also exhibits a hepatoprotective effect in high fructose-fed mice promoting the reduction of serum TC, TG, MDA and LDL levels, and ATL, AST, C-reactive protein (CRP), and lactate dehydrogenase (LDH) activities, as well as increasing HDL level and enhancing SOD and GSH-P*x* activities (Hu, Zhao, Ren, et al. 2015).

In general, these studies suggest that TB exerts an excellent in vitro and in vivo hepatoprotective activity, mainly induced by rutin, quercetin, and DCI. However, greater efforts should be made to increase the number of studies conducted on humans to further confirm the effect of such TB hepatoprotective activity on health.

Other activities

Besides the bioactivities mentioned above, TB and its bioactive compounds have also been documented to possess other bioactivities. For example, the volatile oils from TB flowers exhibit antibacterial activity (Zhao et al. 2018). Furthermore, TB flavonoids exert protective effects on high TMAO diet-induced vascular dysfunction, thus preventing hypertension through the attenuation of vascular insulin resistance and oxidative stress in spontaneously hypertensive rats (Hou et al. 2017). Additionally, TB-derived D-fagomine can counter sucrose-induced steatosis and hypertension by reducing liver fructose levels after meals, which may be effective at preventing metabolic syndrome risk (Ramos-Romero et al. 2020). In the same way, TB polyphenols exhibit an in vitro DNA damage protection effect (Huang et al. 2017), and quercitrin can alleviate imiquimod-induced psoriasis-like dermatitis in mice by inhibiting the T-cell response (Chen et al. 2017).

Health benefits in humans

Most clinical studies regarding the effect of TB on human health have been mainly focused on its antidiabetic effects (Figure 2). Clinical observations have shown that TB intake significantly alleviates type-1 and type-2 diabetes symptomatology, by reducing the levels of fasting blood glucose, glycosylated hemoglobin (GH), and glycosylated serum proteins, as well as enhancing the concentration of fasting serum insulin (Jing et al. 2016).

The intake of 50 g of TB flour for three months in non-insulin-dependent diabetes has been shown to promote a significant decrease in serum cholesterol concentration (Zheng et al. 1991). Additionally, the intake of 15 g of TB tea in patients with hyperlipidemia for sixty days decreased serum TC, LDL, and TG concentrations. Furthermore, the intake of 200 g of TB flour in patients with diabetes for three months significantly decreased fasting blood glucose, serum TC and TG (Qin et al. 1992).

Thus, TB has been reported to reduce of type-2 diabetes mellitus (T2DM) risk. In a parallel, randomized, open-label controlled trial, the daily replacement of a portion of staple food with TB in T2DM patients significantly decreased the relative changes in urinary albumin to creatinine ratio (UACR) and urea nitrogen (UN) after four weeks (Qiu, Li, et al. 2016). Furthermore, the subgroup analysis based on different diabetic kidney stages also manifested a significant reduction in UACR and UN for the T2DM patients with normoalbuminuria and microalbuminuria, suggesting that UN's reduction was due to an increase of amino acid synthesis from improved nitrogen metabolism, which resulted in a TB-mediated attenuation of diabetes-induced renal dysfunction (Qiu, Li, et al. 2016). Moreover, additional studies pointed at the effectiveness of TB in the enhancement of insulin resistance and lipid profile on T2DM patients, by significantly decreasing fasting insulin, TC, and LDL levels, compared to control diet group (Qiu, Liu, et al. 2016).

In a double-blind crossover study, the consumption of TB cookies, which contains a higher concentration of rutin (359.7 mg rutin equivalents/day) than common buckwheat (16.5 mg rutin equivalents/day), was found to reduce the serum concentration of myeloperoxidase (MPO) by a factor of 0.84 ($p = 0.02$) (Wieslander et al. 2011). When

Table 3. Known buckwheat allergens derived from different protein families. Adapted from Norbäck and Wieslander (2021) and Satoh, Jensen-Jarolim, and Teshima (2020).

Name	Sources	Protein family/characteristics	M_w (kDa)
Fag e 1	Common buckwheat	13S globulin	24
Fag e 2	Common buckwheat	2S globulin	16
Fag e 3	Common buckwheat	7S globulin/vicilin	19
Fag e 4	Common buckwheat	Antimicrobial peptide	4
Fag e 5	Common buckwheat	Vicilin-like protein	55
Fag e 10	Common buckwheat	α-amylase inhibitor/ trypsin inhibitor	10
Fag e T1	Common buckwheat	Trypsin inhibitor	9
Fag t 1	Tartary buckwheat	Legumin-type protein	24
Fag t 2	Tartary buckwheat	2S albumin	16
Fag t 3	Tartary buckwheat	Storage protein	56

M_w, molecular weight.

factoring both intakes of common buckwheat and TB, the reduction of serum cholesterol concentration and improved lung vital capacity and forced vital capacity were observed, suggesting that TB intake can decrease serum MPO concentration, an important inflammatory marker (Wieslander et al. 2011).

In a similar double-blind crossover study, the consumption of TB-made cookies was also found to show a marked reduction in nasal irritation, headache, and fatigue symptoms during the 4-week study period (Wieslander et al. 2012). Moreover, the study noted that consumption of TB firstly reduced fatigue symptoms in normal-weight participants, by the consumption of 359.7 mg rutin equivalents/day in the form of TB cookies (Wieslander et al. 2012).

In a double-blind, placebo-controlled trial, the rutin-rich 'Manten-Kirari' TB variety was used to prepare an active test food, finding out that the participants who consumed TB-derived food experienced a reduction in oxidative stress (in terms of thiobarbituric acid reactive substances, TBARS) and significantly reduced body weight, body mass index, and body fat percentage compared to the placebo group, although AI, LDL, and other lipid metabolism-related parameters were not altered (Nishimura et al. 2016).

Although a recent systematic review indicated that the effect of increased buckwheat consumption on cardiovascular risk was unclear, the weighted mean difference of post-intervention concentrations of blood glucose, TG, and TC were markedly decreased (Li, Lietz, and Seal 2018). In general, clinical trials specifically involving TB intake are still deficient. Moreover, only a few published data on clinical efficacy, toxicity or adverse effects of buckwheat and its constituents is available (Li, Lietz, and Seal 2018). Thus, to validate the efficacy and safety of TB consumption, more rigorous, well-controlled, and double-blind clinical trials are warranted.

Safety concerns

TB has attracted more attention in recent years due to its multiple health benefits. However, little attention has been paid to several safety concerns associated with TB and their derived products, including allergic reactions, heavy metal, and mycotoxins accumulation.

Buckwheat allergens

TB can cause allergy, resulting in clinical symptoms, such as eczema, asthma, dermatitis, and anaphylactic shock (Li et al. 2011; Satoh, Jensen-Jarolim, and Teshima 2020). In the same way, buckwheat has been recognized as one of the essential food allergens manifested by severe and dangerous symptoms induced by ingestion or inhalation of small amounts of TB flour and related products (Satoh et al. 2008).

Buckwheat allergy and anaphylaxis are commonly described in school children in Japan and Korea, with estimated prevalence values of 0.10% in Korea (Oh et al. 2004) and 0.22% in Japan (Takahashi et al. 1998) accounting for the fourth most common cause of food-induced anaphylaxis in Japan and the fifth in Korea. Moreover, Yang et al. also reported a case of biphasic buckwheat anaphylaxis in a 57-year-old male patient who lost consciousness twice in the same day after having buckwheat noodles (Yang et al. 2018). In this sense, TB allergy has been described worldwide, being considered as an emerging problem in Australia (Fok et al. 2015, 2019). Thus, such allergy-inducing negative effects attributed to buckwheat limit its broad use as an ingredient and/or additive of alternative foods.

Concerning the immunologic process, buckwheat allergy is an immediate hypersensitivity reaction mediated by specific IgE antibodies, which have been reported to be possible clinically relevant buckwheat allergens (Table 3). To date, allergens in common buckwheat are identified as Fag e 1, Fag e 2, Fag e 3, Fag e 4, Fag e 5, Fag e 10 kD, and Fag e T1 (Norbäck and Wieslander 2021; Satoh, Jensen-Jarolim, and Teshima 2020), being Fag e 1 and Fag e 2 considered as the main allergens in common buckwheat, showing a greater prevalence than Fag e 3, Fag e 4, and Fag e 5 (Geiselhart et al. 2018; Katayama et al. 2018). Furthermore, three major allergenic proteins, including Fag t 1, Fag t 2, and Fag t 3, have also been identified in TB (Norbäck and Wieslander 2021). Nowadays, several methods have been developed for the determination of buckwheat allergens, such as IgE-binding based enzyme-linked immunosorbent assay, liquid chromatography (LC)-MS/MS, and real-time qualitative polymerase chain reaction (PCR), aimed at improving the safety assessment of TB and its products (Zhu 2021).

Furthermore, several physical, biochemical, chemical, and genetic methods have been applied to decrease the allergenicity of buckwheat proteins, such as protease hydrolysis, high pressure treatment, genetic transformation and mutations, and Maillard reaction (Yang et al. 2013; Zhu 2021). As buckwheat is becoming a popular healthy food, there is an increasing prevalence of buckwheat anaphylaxis, and the disclosure of buckwheat on packaged food labels should be strongly encouraged as an important public health measure.

Mycotoxin and heavy metal contaminations

Recently, buckwheat has been added in the list of cereals that may be susceptible to invasion by toxigenic fungi, such as *Aspergillus*, *Fusarium*, and *Penicillium*, during planting, ripening, processing, and storage (Keriene, Mankeviciene,

Table 4. Healthy food products related to Tartary buckwheat (TB) authorized by the State Administration for Market Regulation of China, health benefits, and conditions for recommended consumption.

Products	Ingredients	Health benefits	Conditions for recommended consumption
Capsule	TBE as the main ingredient	GL, FL	HGFL
Capsule	TBE	GL	HGL
Capsule	TBF as the main ingredient	GL	HGL
Capsule	TBF	GL, FL	HGFL
Capsule	TBF as the main ingredient	RHP	RE
Capsule	TBF	RHP	RE
Capsule	TBF as the main ingredient	GI	Constipation
Vinegar	TBS as the main ingredient	FL	Hyperlipidemia
Tablet	TBE as the main ingredient	GL	HGL
Powder	TBF as the main ingredient	WR	Simple obesity
Powder	TBF as the main ingredient	GL, FL	HGFL
Tea	TBF as the main ingredient	GL, FL	HGL
Biscuit	TBF as the main ingredient	GL, FL	HGFL

TBE, TB extract; TBF, TB flour; TBS, TB seed; GL, blood glucose lowering; FL, blood fat lowering; RHP, radiation hazard protection; GI, gastro-intestinal function improvement; WR, weight reduction; HGFL, high blood glucose and fat levels; HGL, high blood glucose level; RE, radiation exposure.

and Cesnuleviciene 2018; Ren et al. 2018). *Aspergillus*, *Fusarium*, and *Penicillium* are not only considered as harmful pathogens of TB, but they also result in mycotoxin contaminations (Chitarrini et al. 2014). Various different mycotoxins, such as zearalenone, aflatoxins, ochratoxins, fumonisins, and trichothecenes, have been found as secondary fungal metabolites in these fungi-contaminated foods or crops (Alshannaq and Yu 2017; Ren et al. 2018).

In particular, aflatoxin B1, and its metabolic precursor sterigmatocystin, have been identified as being Class I carcinogenic by the World Health Organization's (WHO) International Agency for Research on Cancer (IARC) Monographs Program. Recent studies showed that a high concentration of aflatoxin B1 was detected in buckwheat (Keriene, Mankeviciene, and Cesnuleviciene 2018), even exceeding the maximum residue limits set by European Union regulation (Ren et al. 2018). Such high aflatoxin B1 contents found in grains question the quality of buckwheat and its products and, consequently, so as to achieve TB safety and quality assessment, an ultra-fast liquid chromatography coupled with triple quadrupole mass spectrometry (UPLC-QQQ-MS) method was developed for the simultaneous determination of multi-class mycotoxins in TB, conferring several advantages as simple pretreatment, time-efficiency, and high selectivity and accuracy (Ren et al. 2018). However, more reliable, convenient, low cost, and simple methods are required to be established for the determination of mycotoxins in TB and its products in order to ensure their safety and quality.

On the other hand, the irrigation with contaminated water, the usage of fertilizers and metal-based plant protective agents, and the rapid industrialization of agricultural regions can result in a heavy metal contamination of crops (Kovač et al. 2021). Due to the increase of soil pollution, several studies have raised concerns about the health issues of crop products containing heavy metals, such as lead, chromium, cadmium, and nickel, since their dose in the human body can reach a threshold level that seriously endangers health because of their cumulative properties (Li, Li, et al. 2020). Among all the toxic heavy metals, lead has attracted much attention as a paramount representative of heavy metal pollutants, becoming a serious hazard. Unfortunately, recent studies have determined a high lead concentration in TB and its products, such as buckwheat tea, whose consumption has been restricted to avoid lead toxicity (Huang et al. 2013; Peng et al. 2014).

Furthermore, a recent study evaluated the contents of heavy metals (copper, zinc, lead, cadmium, chromium, and nickel) in different types of TB teas and evaluated their potential health risks (Li, Li, et al. 2020). Results showed that all tested TB teas were contaminated with certain heavy metals, although most of them were identified in suitable concentrations to meet healthy food standards, which indicated that the buckwheat tea was still safe to drink (Li, Li, et al. 2020). Nevertheless, as it occurred with aflatoxin B1, the chromium intake from TB tea infusions may result in a strong carcinogenic risk for consumers (Li, Li, et al. 2020).

Keeping this in mind, the quality control standards for TB foods should be drafted and completed in the future, thus contributing to the systematical evaluation of TB foods.

Industrial applications of tartary buckwheat

Recent findings indicate that the functional components of TB and its derived products have good benefits in preventing and controlling chronic diseases. In recent years, with the improvement of people's awareness of the nutritional and health value of TB and the rapid development of modern food processing technology and equipment, the varieties of TB products are more abundant and diversified. As shown in Table 4, several healthy foods related to TB have been authorized by the State Administration for Market Regulation of China (State Administration for Market Regulation 2021). Among the different authorized healthy foods, TB flour or its extract constitute the only functional ingredients in the healthy combination formula. Other healthy food products include TB capsule, TB vinegar, TB tablet, TB powder, and TB tea (Table 4). Indeed, about 57% of TB healthy foods are in the form of capsules, being the most popular form of products for the general population (State Administration for Market Regulation 2021). Additionally, it is worth mentioning that the efficacy of these TB-based healthy foods is capable of lowering blood glucose level, lowering blood fat level, lowering blood pressure level, improving gastrointestinal

function, and protecting from radiation hazard (Table 4). Indeed, about 88.6% of TB-based healthy foods present hypoglycemia and hypolipidemic effects, which is in agreement with many studies that suggest that TB has lowering blood fat and sugar in vivo effects (Huda et al. 2021; Ruan et al. 2020; Zhu 2016).

Moreover, more than 210 types of traditional foods, healthy drinks, and pharmaceutical formulations related to TB have also been authorized as invented patents by the China National Intellectual Property Administration (China National Intellectual Property Administration 2021). Among these patented TB products, about 28% of them are in the form of TB tea and TB healthy tea, presenting hypoglycemic and hypolipidemic effects. Additionally, about 20% of TB products are in the form of beer and healthy wine, presenting high flavonoids contents. Furthermore, TB and its products are also popular in the USA, Canada, and Europe (Giménez-Bastida and Zieliński 2015), and noodles, breads, biscuits, and teas are widely consumed in different countries, such as China, Japan, Korea, India, Nepal, and Canada (Huda et al. 2021).

In particular, TB tea is being increasingly welcomed worldwide due to its unique malt fragrance and health-promoting benefits (Li, Li, et al. 2020). TB tea in the global consumer market can generally be divided into three types: whole plant tea, whole bran tea, and whole embryo tea, according to the different raw materials (Li, Li, et al. 2020). It is estimated that there are over 30 well-known enterprises producing TB tea in China, and its annual output value exceeds 2.5 billion RMB. Various types of TB teas are commercially available according to general e-commerce sites, such as "JD.com" and "TMALL.com" in China, and "Amazon.com" and "eBay Inc." in USA. However, the quality and safety evaluation of TB tea is still poorly understood, which requires to be further systematically investigated.

Conclusion and perspectives

TB is a traditional edible and medicinal plant containing diverse functional components, such as flavonoids, phenolic acids, triterpenoids, bioactive polysaccharides, and bioactive proteins and peptides. Flavonoids, such as rutin and quercetin, are major bioactive components in TB. However, the changes of these bioactive compounds during different food processing methods are yet to be clarified, and further studies are required to improve the applications of TB in the functional food industry. In vitro and in vivo epidemiological and experimental studies have demonstrated that TB and its bioactive components possess a plethora of health-enhancing benefits. However, only crude extracts are used in many studies, and it is necessary to explore effective methods to extract and isolate bioactive compounds from TB. Although some studies have investigated the potential molecular mechanisms of TB and its bioactive compounds, potential molecular targets need to be further clarified, and more investigations should be conducted to deeply illustrate TB's mechanisms of action. According to the current literature, the long-term TB consumption and related products can prevent and control chronic diseases, such as hyperglycemia, hypertension, and hyperlipidemia. Generally, most of bioactive compounds that work in mice are not effective or safe in humans, and conducting human clinical trials is the only fool-proof method for determining TB's efficacy and related products in human beings. Therefore, more well-designed clinical trials should be carried out to confirm the health benefits of TB and related products.

Furthermore, more than 100 kinds of TB products, such as healthy drinks and functional foods, are widely consumed by the general population. To ensure the efficacy and safety of healthy food, the quality evaluation of TB and its functional components in these products is necessary, by the application of reliable scientific tools. Indeed, greater attention should be paid to TB allergens, and heavy metals and mycotoxin contaminations, and specific food processing techniques should be developed to minimize allergens' content in TB products.

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Conflicts of interest

The authors state no conflicts of interest.

List of abbreviations

ABC	ATP-Binding Cassette
ACAT	Acyl-CoA-Cholesterol Acyltransferase
ACC	Acetyl-CoA Carboxylase
AI	Atherogenic Index
AIP	Atherogenic Index of Plasma
AMPK	AMP-dependent protein Kinase
Akt	Protein kinase B pathway
aP2	Adipocyte Protein 2
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotranferase
BRS	TB resistant starch
BWP	Bioactive TB protein
CAT	Catalase
CEBP-α	CCAAT/ enhancer binding protein α
CoA	Coenzyme A
COX-2	Cyclooxygenase-2
CRP	C reactive protein
CYP7A1	Cholesterol-7α-hydroxylase
DAD	Diode array detector
DCI	D-chiro-inositol
DEAE	Diethyl-aminoethyl
DW	Dry Weight
EEB	TB ethanolic extract

ESI	Electrospray Ionization
FAS	Fatty Acid Synthase
FTICR	Fourier-Transform Ion Cyclotron Resonance
FW	Fresh Weight
G6Pase	Glucose-6-phosphatase
GH	Glycosylated hemoglobin
GLUT2	Glucose transporter 2
GLUT4	Glucose transporter 4
GPDH	Glycerol-3-phosphate dehydrogenase
GR	Glutathione reductase
GSH/GSSG	Reduced/oxidized glutathione
GSH-Px	Glutathione peroxidase
HDL	High-Density Lipoproteins
HPLC	High-Performance Liquid Chromatography
IARC	International Agency for Research on Cancer
IgE	Immunoglobulin E
IL-1β	Interleukin 1β
IL-6	Interleukin-6
iNOS	Inducible Nitric Oxide Synthase
IR	Insulin Receptor
IRS	Insulin Receptor Substrate
LDH	Lactate Dehydrogenase
LDL	Low-Density Lipoproteins
LIT	Linear Ion Trap
LPS	Lipopolysaccharide
MAPK	Mitogen-Activated Protein Kinase
MCP-1	Monocyte Chemoattractant Protein-1
MDA	Malondialdehyde
MPO	Myeloperoxidase
MS	Mass Spectrometry
NEFA	Non-Esterified Fatty Acid
NF-κB	Nuclear factor κB
NMR	Nuclear Magnetic Resonance
NO	Nitric Oxide
NPC1L1	Niemann-Pick C1-like protein
Nrf2/ARE	Nuclear factor E2/Antioxidant Response Element
PAD	Photodiode Array Detector
PAR-α/HO-1	Peroxisome proliferator-activated receptor α/ hemeoxigenase-1 pathway
PCR	Polymerase Chain Reaction
PEPCK	Phosphoenolpyruvate carboxykinase
PI3K	Phosphatidylinositol-3-kinase
PKC	Protein Kinase C
PPAR-γ	Peroxisome Proliferator-Activated Receptor γ
PTP1B	Protein Tyrosine Phosphatase 1B
QQQ	Triple quadrupole
ROS	Reactive Oxygen Species
SDF	Soluble Dietary Fiber
SEC	Size Exclusion Chromatography
SCD-1	Stearoyl-CoA desaturase-1
SOD	Superoxide dismutase
T2DM	Type-2 Diabetes Mellitus
T-AOC	Total Antioxidant Capacity
TB	Tartary Buckwheat
TB-P	TB crude protein
TBARS	Thiobarbituric Acid Reactive Substance
TBBE	TB Bran Ethanolic Extract
TBE	TB Extract
TBP	TB Crude Protein Product
TBP1	Neutral Polysaccharide
TBP-II	Non-starch Polysaccharide
TBWSP31	Purified protein isolated from TB
TC	Total Cholesterol
TG	Triglycerides
TMAO	Trimethylamine-N-oxide
TNF-α	Tumor Necrosis Factor A
UACR	Urinary Albumin/Creatinine Ratio
UN	Urea Nitrogen
UPLC	Ultrahigh-Performance Liquid Chromatography
WHO	World's Health Organization

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References

Almuhayawi, M. S., A. H. A. Hassan, M. Abdel-Mawgoud, G. Khamis, S. Selim, S. K. Al Jaouni, and H. AbdElgawad. 2021. Laser light as a promising approach to improve the nutritional value, antioxidant capacity and anti-inflammatory activity of flavonoid-rich buckwheat sprouts. *Food Chemistry* 345:128788. doi: 10.1016/j.foodchem.2020.128788.

Alshannaq, A., and J. H. Yu. 2017. Occurrence, toxicity, and analysis of major mycotoxins in food. *International Journal of Environmental Research and Public Health* 14 (6):632. doi: 10.3390/ijerph14060632.

Bhinder, S., A. Kaur, B. Singh, M. P. Yadav, and N. Singh. 2020. Proximate composition, amino acid profile, pasting and process characteristics of flour from different Tartary buckwheat varieties. *Food Research International* 130:108946. doi: 10.1016/j.foodres.2019.108946.

Bhinder, S., B. Singh, A. Kaur, N. Singh, M. Kaur, S. Kumari, and M. P. Yadav. 2019. Effect of infrared roasting on antioxidant activity, phenolic composition and Maillard reaction products of Tartary buckwheat varieties. *Food Chemistry* 285:240–51. doi: 10.1016/j.foodchem.2019.01.141.

Borovaya, S. A., and A. G. Klykov. 2020. Some aspects of flavonoid biosynthesis and accumulation in buckwheat plants. *Plant Biotechnology Reports* 14 (2):213–25. doi: 10.1007/s11816-020-00614-9.

Chen, S., H. Li, Y. Liu, Z. Zhu, and Q. Wei. 2017. Quercitrin extracted from Tartary buckwheat alleviates imiquimod-induced psoriasis-like dermatitis in mice by inhibiting the Th17 cell response. *Journal of Functional Foods* 38:9–19. doi: 10.1016/j.jff.2017.08.034.

Chen, S., L. Wu, H. Zhu, L. Yao, and L. Wang. 2021. Effects of processing methods on phenolic compositions, anti-oxidant activities and α-glucosidase inhibitory ability of two buckwheat varieties. *Chemical Papers* 75 (3):1029–39. doi: 10.1007/s11696-020-01356-2.

Chen, Y., L. Qin, A. Wen, M. Mazhar, H. Wang, and Y. Zhu. 2021. Three-solvent extracting method comprehensively evaluates phenolics profile and antioxidant activities of Tartary buckwheat. *Journal of Food Processing and Preservation* 45 (1):1–10. doi: 10.1111/jfpp.15020.

Cheng, F., L. Han, Y. Xiao, C. Pan, Y. Li, X. Ge, Y. Zhang, S. Yan, and M. Wang. 2019. D-chiro-inositol ameliorates high fat diet-induced hepatic steatosis and insulin resistance via PKCε-PI3K/AKT pathway. *Journal of Agricultural and Food Chemistry* 67 (21):5957–67. doi: 10.1021/acs.jafc.9b01253.

China National Intellectual Property Administration. 2021. Accessed March 30, 2021. http://epub.cnipa.gov.cn/.

Chitarrini, G., C. Nobili, F. Pinzari, A. Antonini, P. De Rossi, A. Del Fiore, S. Procacci, V. Tolaini, V. Scala, M. Scarpari, et al. 2014. Buckwheat achenes antioxidant profile modulates Aspergillus flavus growth and aflatoxin production. *International Journal of Food Microbiology* 189:1–10. doi: 10.1016/j.ijfoodmicro.2014.07.029.

Choi, S. Y., J. Y. Choi, J. M. Lee, S. Lee, and E. J. Cho. 2015. Tartary buckwheat on nitric oxide-induced inflammation in RAW264.7 macrophage cells. *Food & Function* 6 (8):2664–70. doi: 10.1039/c5fo00639b.

Cui, X., J. Du, J. Li, and Z. Wang. 2018. Inhibitory site of α-hairpinin peptide from Tartary buckwheat has no effect on its antimicrobial activities. *Acta Biochimica et Biophysica Sinica* 50 (4):408–16. doi: 10.1093/abbs/gmy015.

Dzah, C. S., Y. Duan, H. Zhang, D. A. Authur, and H. Ma. 2020. Ultrasound-, subcritical water- and ultrasound assisted subcritical water-derived Tartary buckwheat polyphenols show superior antioxidant activity and cytotoxicity in human liver carcinoma cells. *Food Research International* 137:109598. doi: 10.1016/j.foodres.2020.109598.

Dziadek, K., A. Kopeć, E. Piątkowska, T. Leszczyńska, E. Pisulewska, R. Witkowicz, B. Bystrowska, and R. Francik. 2018. Identification of

polyphenolic compounds and determination of antioxidant activity in extracts and infusions of buckwheat leaves. *European Food Research and Technology* 244 (2):333–43. doi: 10.1007/s00217-017-2959-2.

Fok, J., F. Kette, W. Smith, A. Smith, A. Ahmadie, R. Heddle, and P. Hissaria. 2015. Buckwheat allergy: An emerging problem in Australia. *Internal Medicine Journal* 45:6.

Fok, J. S., F. Kette, W. B. Smith, A. Smith, A. Ahmadie, R. Heddle, and P. Hissaria. 2019. Buckwheat allergy in Australia. *Internal Medicine Journal* 49 (12):1552–1553. doi: 10.1111/imj.14660.

García-Pérez, P., M. Ayuso, E. Lozano-Milo, C. Pereira, M. I. Dias, M. Ivanov, R. C. Calhelha, M. Soković, I. C. F. R. Ferreira, L. Barros, et al. 2021. Phenolic profiling and *in vitro* bioactivities of three medicinal *Bryophyllum* plants. *Industrial Crops and Products* 162: 113241. doi: 10.1016/j.indcrop.2021.113241.

Geiselhart, S., C. Nagl, P. Dubiela, A. C. Pedersen, M. Bublin, C. Radauer, C. Bindslev-Jensen, K. Hoffmann-Sommergruber, and C. G. Mortz. 2018. Concomitant sensitization to legumin, Fag e 2 and Fag e 5 predicts buckwheat allergy. *Clinical and Experimental Allergy* 48 (2):217–224. doi: 10.1111/cea.13068.

Giménez-Bastida, J. A., and H. Zieliński. 2015. Buckwheat as a functional food and its effects on health. *Journal of Agricultural and Food Chemistry* 63 (36):7896–7913. doi: 10.1021/acs.jafc.5b02498.

Guo, X., K. Zhu, H. Zhang, and H. Yao. 2010. Anti-tumor activity of a novel protein obtained from tartary buckwheat. *International Journal of Molecular Sciences* 11 (12):5201–5211. doi: 10.3390/ijms11125201.

He, Q., Z. X. Guo, Y. Cao, M. Yang, and S. Yao. 2021. Selective separation of main flavonoids by combinational use of ionic liquid-loaded microcapsules from crude extract of Tartary buckwheat. *Food Chemistry* 362:130255. doi: 10.1016/j.foodchem.2021.130255.

Hou, Z., Y. Hu, X. Yang, and W. Chen. 2017. Antihypertensive effects of Tartary buckwheat flavonoids by improvement of vascular insulin sensitivity in spontaneously hypertensive rats. *Food Function* 8 (11): 4217–4228. doi: 10.1039/c7fo00975e.

Hu, Y., Z. Hou, R. Yi, Z. Wang, P. Sun, G. Li, X. Zhao, and Q. Wang. 2017. Tartary buckwheat flavonoids ameliorate high fructose-induced insulin resistance and oxidative stress associated with the insulin signaling and Nrf2/HO-1 pathways in mice. *Food & Function* 8 (8):2803–2816. doi: 10.1039/c7fo00359e.

Hu, Y., Y. Zhao, D. Ren, J. Guo, Y. Luo, and X. Yang. 2015. Hypoglycemic and hepatoprotective effects of D-chiro-inositol-enriched tartary buckwheat extract in high fructose-fed mice. *Food & Function* 6 (12):3760–3769. doi: 10.1039/C5FO00612K.

Hu, Y., Y. Zhao, L. Yuan, and X. Yang. 2015. Protective effects of tartary buckwheat flavonoids on high TMAO diet-induced vascular dysfunction and liver injury in mice. *Food & Function* 6 (10): 3359–3372. doi: 10.1039/C5FO00581G.

Huang, S., Y. Ma, D. Sun, J. Fan, and S. Cai. 2017. *In vitro* DNA damage protection and anti-inflammatory effects of Tartary buckwheats (*Fagopyrum tataricum* L. Gaertn) fermented by filamentous fungi. *International Journal of Food Science & Technology* 52 (9): 2006–2017. doi: 10.1111/ijfs.13474.

Huang, Y. F., L. X. Peng, Y. Liu, Z. F. Zhang, L. Y. Lv, and G. Zhao. 2013. Evaluation of essential and toxic elements concentrations in different parts of buckwheat. *Czech Journal of Food Sciences* 31 (No. 3):249–255. doi: 10.17221/148/2012-CJFS.

Huda, M. N., S. Lu, T. Jahan, M. Ding, R. Jha, K. Zhang, W. Zhang, M. I. Georgiev, S. U. Park, and M. Zhou. 2021. Treasure from garden: Bioactive compounds of buckwheat. *Food Chemistry* 335: 127653. doi: 10.1016/j.foodchem.2020.127653.

Hwang, D., M. J. Kang, C. W. Kang, and G. D. Kim. 2019. Kaempferol-3-O-β-rutinoside suppresses the inflammatory responses in lipopolysaccharide-stimulated RAW264.7 cells via the NF-κB and MAPK pathways. *International Journal of Molecular Medicine* 44 (6):2321–2328. doi: 10.3892/ijmm.2019.4381.

Ji, X., L. Han, F. Liu, S. Yin, Q. Peng, and M. Wang. 2019. A mini-review of isolation, chemical properties and bioactivities of polysaccharides from buckwheat (*Fagopyrum* Mill). *International Journal of Biological Macromolecules* 127:204–209. doi: 10.1016/j.ijbiomac.2019.01.043.

Jia, L., S. Huang, X. Yin, Y. Zan, Y. Guo, and L. Han. 2018. Quercetin suppresses the mobility of breast cancer by suppressing glycolysis through Akt-mTOR pathway mediated autophagy induction. *Life Sciences* 208 (157):123–130. doi: 10.1016/j.lfs.2018.07.027.

Jiang, S., Q. Liu, Y. Xie, H. Zeng, L. Zhang, X. Jiang, and X. Chen. 2015. Separation of five flavonoids from tartary buckwheat (*Fagopyrum tataricum* (L.) Gaertn) grains via off-line two dimensional high-speed counter-current chromatography. *Food Chemistry* 186:153–159. doi: 10.1016/j.foodchem.2014.08.120.

Jing, R., H. Q. Li, C. L. Hu, Y. P. Jiang, L. P. Qin, and C. J. Zheng. 2016. Phytochemical and pharmacological profiles of three *Fagopyrum* buckwheats. *International Journal of Molecular Sciences* 17 (4):589. doi: 10.3390/ijms17040589.

Joshi, D. C., K. Zhang, C. Wang, R. Chandora, M. Khurshid, J. Li, M. He, M. I. Georgiev, and M. Zhou. 2020. Strategic enhancement of genetic gain for nutraceutical development in buckwheat: A genomics-driven perspective. *Biotechnology Advances* 39:107479. doi: 10.1016/j.biotechadv.2019.107479.

Katayama, S., D. Yamaguchi, Y. Suzuki, A. M. A. Athamneh, T. Mitani, R. Satoh, R. Teshima, Y. Mine, and S. Nakamura. 2018. Oral immunotherapy with a phosphorylated hypoallergenic allergen ameliorates allergic responses more effectively than intact allergen in a murine model of buckwheat allergy. *Molecular Nutrition & Food Research* 62 (21):1800303–8. doi: 10.1002/mnfr.201800303.

Keriene, I., A. Mankeviciene, S. Bliznikas, R. Cesnuleviciene, S. Janaviciene, D. Jablonskyte-Rasce, and S. Maiksteniene. 2016. The effect of buckwheat groats processing on the content of mycotoxins and phenolic compounds. *CYTA - Journal of Food* 14 (4):565–571. doi: 10.1080/19476337.2016.1176959.

Keriene, I., A. Mankeviciene, and R. Cesnuleviciene. 2018. Risk factors for mycotoxin contamination of buckwheat grain and its products. *World Mycotoxin Journal* 11 (4):519–529. doi: 10.3920/WMJ2018.2299.

Kim, S. Y., M. S. Lee, E. Chang, S. Jung, H. Ko, E. Lee, S. Lee, C. T. Kim, I. H. Kim, and Y. Kim. 2019. Tartary buckwheat extract attenuated the obesity-induced inflammation and increased muscle PGC-1a/SIRT1 expression in high fat diet-induced obese rats. *Nutrients* 11 (3):e654. doi: 10.3390/nu11030654.

Klepacka, J., and A. Najda. 2021. Effect of commercial processing on polyphenols and antioxidant activity of buckwheat seeds. *International Journal of Food Science & Technology* 56 (2):661–670. doi: 10.1111/ijfs.14714.

Kovač, M., M. Bulaić, J. Jakovljević, A. Nevistić, T. Rot, T. Kovač, I. D. Šarkanj, and B. Šarkanj. 2021. Mycotoxins, pesticide residues, and heavy metals analysis of Croatian cereals. *Microorganisms* 9 (2):e216. doi: 10.3390/microorganisms9020216.

Lee, C. C., W. H. Hsu, S. R. Shen, Y. H. Cheng, and S. C. Wu. 2012. *Fagopyrum tataricum* (Buckwheat) improved high-glucose-induced insulin resistance in mouse hepatocytes and diabetes in fructose-rich diet-induced mice. *Experimental Diabetes Research* 2012:e375673. doi: 10.1155/2012/375673.

Lee, C. C., S. R. Shen, Y. J. Lai, and S. C. Wu. 2013. Rutin and quercetin, bioactive compounds from tartary buckwheat, prevent liver inflammatory injury. *Food & Function* 4 (5):794–802. doi: 10.1039/c3fo30389f.

Lee, D. G., I. S. Jang, K. E. Yang, S. J. Yoon, S. Baek, J. Y. Lee, T. Suzuki, K. Y. Chung, S. H. Woo, and J. S. Choi. 2016. Effect of rutin from tartary buckwheat sprout on serum glucose-lowering in animal model of type 2 diabetes. *Acta Pharmaceutica* 66 (2):297–302. doi: 10.1515/acph-2016-0021.

Lee, J. M., K. H. Lee, Y. H. Yoon, E. J. Cho, and S. Lee. 2013. Identification of triterpenoids and flavonoids from the seeds of tartary buckwheat. *Natural Product Sciences* 19 (2):137–144.

Lee, M. S., Y. Shin, S. Jung, S. Y. Kim, Y. H. Jo, C. T. Kim, M. K. Yun, S. J. Lee, J. Sohn, H. J. Yu, et al. 2017. The inhibitory effect of tartary buckwheat extracts on adipogenesis and inflammatory response. *Molecules* 22 (7):e1160. doi: 10.3390/molecules22071160.

Lee, S., J. Lee, H. Lee, and J. Sung. 2019. Relative protective activities of quercetin, quercetin-3-glucoside, and rutin in alcohol-induced liver injury. *Journal of Food Biochemistry* 43 (11):e13002. doi: 10.1111/jfbc.13002.

Lee, S. H., E. J. Lee, K. H. Min, G. Y. Hur, S. H. Lee, S. Y. Lee, J. H. Kim, C. Shin, J. J. Shim, K. H. In, et al. 2015. Quercetin enhances chemosensitivity to gemcitabine in lung cancer cells by inhibiting

heat shock protein 70 expression. *Clinical Lung Cancer* 16 (6): e235–e243. doi: 10.1016/j.cllc.2015.05.006.

Li, F., X. Zhang, Y. Li, K. Lu, R. Yin, and J. Ming. 2017. Phenolics extracted from tartary (*Fagopyrum tartaricum* L. Gaerth) buckwheat bran exhibit antioxidant activity, and an antiproliferative effect on human breast cancer MDA-MB-231 cells through the p38/MAP kinase pathway. *Food & Function* 8 (1):177–188. doi: 10.1039/c6fo01230b.

Li, J., P. Yang, Q. Yang, X. Gong, H. Ma, K. Dang, G. Chen, X. Gao, and B. Feng. 2019. Analysis of flavonoid metabolites in buckwheat leaves using UPLC-ESI-MS/MS. *Molecules* 24 (7):e1310. doi: 10.3390/molecules24071310.

Li, L., G. Lietz, and C. Seal. 2018. Buckwheat and CVD risk markers: A systematic review and meta-analysis. *Nutrients* 10 (5):e619. doi: 10.3390/nu10050619.

Li, P., X. Cui, Y. Li, and Z. Wang. 2011. Epitope mapping and identification on a 3D model built for the tartary buckwheat allergic protein TBb. *Acta Biochimica et Biophysica Sinica* 43 (6):441–447. doi: 10.1093/abbs/gmr036.

Li, W., X. Zhang, X. He, F. Li, J. Zhao, R. Yin, and J. Ming. 2020. Effects of steam explosion pretreatment on the composition and biological activities of tartary buckwheat bran phenolics. *Food & Function* 11 (5):4648–4658. doi: 10.1039/d0fo00493f.

Li, Y., S. Duan, H. Jia, C. Bai, L. Zhang, and Z. Wang. 2014. Flavonoids from tartary buckwheat induce G2/M cell cycle arrest and apoptosis in human hepatoma HepG2 cells. *Acta Biochimica et Biophysica Sinica* 46 (6):460–470. doi: 10.1093/abbs/gmu023.

Li, Z., Z. Li, Y. Huang, Y. Jiang, Y. Liu, W. Wen, H. Li, J. Shao, C. Wang, and X. Zhu. 2020. Antioxidant capacity, metal contents, and their health risk assessment of tartary buckwheat teas. *ACS Omega* 5 (17):9724–9732. doi: 10.1021/acsomega.9b04007.

Ling, A., X. Li, X. Hu, Z. Ma, K. Wu, H. Zhang, M. Hao, and S. Wei. 2018. Dynamic changes in polyphenol compounds, antioxidant activity, and PAL gene expression in different tissues of buckwheat during germination. *Journal of the Science of Food and Agriculture* 98 (15):5723–5730. doi: 10.1002/jsfa.9119.

Liu, Y., C. Cai, Y. Yao, and B. Xu. 2019. Alteration of phenolic profiles and antioxidant capacities of common buckwheat and tartary buckwheat produced in China upon thermal processing. *Journal of the Science of Food and Agriculture* 99 (12):5565–5576. doi: 10.1002/jsfa.9825.

Luo, X., Y. Fei, Q. Xu, T. Lei, X. Mo, Z. Wang, L. Zhang, X. Mou, and H. Li. 2020. Isolation and identification of antioxidant peptides from tartary buckwheat albumin (*Fagopyrum tataricum* Gaertn.) and their antioxidant activities. *Journal of Food Science* 85 (3):611–617. doi: 10.1111/1750-3841.15004.

Lv, L., Y. Xia, D. Zou, H. Han, Y. Wang, H. Fang, and M. Li. 2017. *Fagopyrum tataricum* (L.) Gaertn.: A review on its traditional uses, phytochemical and pharmacology. *Food Science and Technology Research* 23 (1):1–7. doi: 10.3136/fstr.23.1.

Mäki-Opas, I., M. Hämäläinen, L. J. Moilanen, R. Haavikko, T. J. Ahonen, S. Alakurtti, V. M. Moreira, K. Muraki, J. Yli-Kauhaluoma, and E. Moilanen. 2019. Pyrazine-fused triterpenoids block the TRPA1 ion channel *in vitro* and inhibit TRPA1-mediated acute inflammation in vivo. *ACS Chemical Neuroscience* 10 (6):2848–2857. doi: 10.1021/acschemneuro.9b00083.

Mansur, A. R., K. J. Kim, D.-B. Kim, M. Yoo, H. W. Jang, D.-O. Kim, and T. G. Nam. 2020. Matrix solid-phase dispersion extraction method for HPLC determination of flavonoids from buckwheat sprouts. *LWT - Food Science and Technology* 133:110121. doi: 10.1016/j.lwt.2020.110121.

Nam, T. G., T. G. Lim, B. H. Lee, S. Lim, H. Kang, S. H. Eom, M. Yoo, H. W. Jang, and D. O. Kim. 2017. Comparison of anti-inflammatory effects of flavonoid-rich common and tartary buckwheat sprout extracts in lipopolysaccharide-stimulated RAW 264.7 and peritoneal macrophages. *Oxidative Medicine and Cellular Longevity* 2017:9658030. doi: 10.1155/2017/9658030.

Němcová, L., J. Zima, J. Barek, and D. Janovská. 2011. Determination of resveratrol in grains, hulls and leaves of common and tartary buckwheat by HPLC with electrochemical detection at carbon paste electrode. *Food Chemistry* 126 (1):374–378. doi: 10.1016/j.foodchem.2010.10.108.

Nishimura, M., T. Ohkawara, Y. Sato, H. Satoh, T. Suzuki, K. Ishiguro, T. Noda, T. Morishita, and J. Nishihira. 2016. Effectiveness of rutin-rich Tartary buckwheat (*Fagopyrum tataricum* Gaertn.) 'Manten-Kirari' in body weight reduction related to its antioxidant properties: A randomised, double-blind, placebo-controlled study. *Journal of Functional Foods* 26:460–469. doi: 10.1016/j.jff.2016.08.004.

Norbäck, D., and G. Wieslander. 2021. A review on epidemiological and clinical studies on buckwheat allergy. *Plants* 10 (3):e607. https://doi.org/10.2500/aap.2006.27.2879. doi: 10.3390/plants10030607.

Oh, J. W., B. Y. Pyun, J. T. Choung, K. M. Ahn, C. H. Kim, S. W. Song, J. A. Son, S. Y. Lee, and S. I. Lee. 2004. Epidemiological change of atopic dermatitis and food allergy in school-aged children in Korea between 1995 and 2000. *Journal of Korean Medical Science* 19 (5):716–723. doi: 10.3346/jkms.2004.19.5.716.

Park, B. I., J. Kim, K. Lee, T. Lim, and K. T. Hwang. 2019. Flavonoids in common and tartary buckwheat hull extracts and antioxidant activity of the extracts against lipids in mayonnaise. *Journal of Food Science and Technology* 56 (5):2712–2720. doi: 10.1007/s13197-019-03761-2.

Peng, L. x., Y. f Huang, Y. Liu, Z. f Zhang, L. y Lu, and G. Zhao. 2014. Evaluation of essential and toxic element concentrations in buckwheat by experimental and chemometric approaches. *Journal of Integrative Agriculture* 13 (8):1691–1698. doi: 10.1016/S2095-3119(13)60724-8.

Peng, L., Q. Zhang, Y. Zhang, Z. Yao, P. Song, L. Wei, G. Zhao, and Z. Yan. 2020. Effect of tartary buckwheat, rutin, and quercetin on lipid metabolism in rats during high dietary fat intake. *Food Science & Nutrition* 8 (1):199–213. doi: 10.1002/fsn3.1291.

Qiu, J., Z. Li, Y. Qin, Y. Yue, and Y. Liu. 2016. Protective effect of tartary buckwheat on renal function in type 2 diabetics: A randomized controlled trial. *Therapeutics and Clinical Risk Management* 12: 1721–1727. doi: 10.2147/TCRM.S123008.

Qiu, J., Y. Liu, Y. Yue, Y. Qin, and Z. Li. 2016. Dietary tartary buckwheat intake attenuates insulin resistance and improves lipid profiles in patients with type 2 diabetes: A randomized controlled trial. *Nutrition Research* 36 (12):1392–1401. doi: 10.1016/j.nutres.2016.11.007.

Qin, W., T. S. Qian, J. J. Jiang, C. F. Lun, Y. Y. Ding, and H. M. Wang. 1992. The clinical observation of Tartary buckwheat for the treatment of diabetes. *Chinese Journal of Endocrinology and Metabolism*, 52–53.

Ramos-Romero, S., M. Hereu, L. Atienza, S. Amézqueta, J. Casas, S. Muñoz, I. Medina, B. Miralles-Pérez, M. Romeu, and J. L. Torres. 2020. The buckwheat iminosugar D-fagomine attenuates sucrose-induced steatosis and hypertension in rats. *Molecular Nutrition & Food Research* 64 (1):e1900564. doi: 10.1002/mnfr.201900564.

Ramos-Romero, S., M. Hereu, L. Atienza, J. Casas, N. Taltavull, M. Romeu, S. Amézqueta, G. Dasilva, I. Medina, and J. L. Torres. 2018. Functional effects of the buckwheat iminosugar D-fagomine on rats with diet-induced prediabetes. *Molecular Nutrition & Food Research* 62 (16):e1800373. doi: 10.1002/mnfr.201800373.

Ren, G., Y. Hu, J. Zhang, L. Zou, and G. Zhao. 2018. Determination of multi-class mycotoxins in tartary buckwheat by ultra-fast liquid chromatography coupled with triple quadrupole mass spectrometry. *Toxins* 10 (1):e28. doi: 10.3390/toxins10010028.

Ren, Q., C. Wu, Y. Ren, and J. Zhang. 2013. Characterization and identification of the chemical constituents from tartary buckwheat (*Fagopyrum tataricum* Gaertn) by high performance liquid chromatography/photodiode array detector/linear ion trap FTICR hybrid mass spectrometry. *Food Chemistry* 136 (3-4):1377–1389. doi: 10.1016/j.foodchem.2012.09.052.

Ruan, J., Y. Zhou, J. Yan, M. Zhou, S. H. Woo, W. Weng, J. Cheng, and K. Zhang. 2020. Tartary buckwheat: An under-utilized edible and medicinal herb for food and nutritional security. *Food Reviews International*, 1–15. doi: 10.1080/87559129.2020.1734610.

Satoh, R., E. Jensen-Jarolim, and R. Teshima. 2020. Understanding buckwheat allergies for the management of allergic reactions in humans and animals. *Breeding Science* 70 (1):85–92. doi: 10.1270/jsbbs.19051.

Satoh, R., S. Koyano, K. Takagi, R. Nakamura, R. Teshima, and J. I. Sawada. 2008. Immunological characterization and mutational analysis of the recombinant protein BWp16, a major allergen in

buckwheat. *Biological & Pharmaceutical Bulletin* 31 (6):1079–1085. doi: 10.1248/bpb.31.1079.

State Administration for Market Regulation. 2021. Accessed March 30, 2021. http://www.samr.gov.cn/tssps/index.html.

Sytar, O., W. Biel, I. Smetanska, and M. Brestic. 2018. Bioactive compounds and their biofunctional properties of different buckwheat germplasms for food processing. In *Buckwheat germplasm in the world*, ed. M. Zhou, I. Kreft, G. Suvorova, Y. Tang, and S. H. Woo, 191–204. San Diego, CA: Elsevier Inc. doi: 10.1016/b978-0-12-811006-5.00019-7.

Tao, T., D. Pan, Y. Y. Zheng, and T. J. Ma. 2019. Optimization of hydrolyzed crude extract from Tartary buckwheat protein and analysis of its hypoglycemic activity *in vitro*. *IOP Conference Series: Earth and Environmental Science* 295:032065. doi: 10.1088/1755-1315/295/3/032065.

Takahashi, Y., S. Ichikawa, Y. Aihara, and S. Yokota. 1998. Buckwheat allergy in 90,000 school children in Yokohama. *Arerugi = [Allergy]* 47 (1):26–33.

Tomotake, H., N. Yamamoto, H. Kitabayashi, A. Kawakami, J. Kayashita, H. Ohinata, H. Karasawa, and N. Kato. 2007. Preparation of tartary buckwheat protein product and its improving effect on cholesterol metabolism in rats and mice fed cholesterol-enriched diet. *Journal of Food Science* 72 (7):S528–S533. doi: 10.1111/j.1750-3841.2007.00474.x.

Walls, H. L., A. Peeters, J. Proietto, and J. J. McNeil. 2011. Public health campaigns and obesity—A critique. *BMC Public Health* 11 (1):136. doi: 10.1186/1471-2458-11-136.

Wang, M., J. R. Liu, J. M. Gao, J. W. Parry, and Y. M. Wei. 2009. Antioxidant activity of tartary buckwheat bran extract and its effect on the lipid profile of hyperlipidemic rats. *Journal of Agricultural and Food Chemistry* 57 (11):5106–5112. doi: 10.1021/jf900194s.

Wang, X. T., Z. Y. Zhu, L. Zhao, H. Q. Sun, M. Meng, J. Y. Zhang, and Y. Zhang. 2016. Structural characterization and inhibition on α-D-glucosidase activity of non-starch polysaccharides from *Fagopyrum tartaricum*. *Carbohydrate Polymers* 153:679–685. doi: 10.1016/j.carbpol.2016.08.024.

Wieslander, G., N. Fabjan, M. Vogrincic, I. Kreft, C. Janson, U. Spetz-Nyström, B. Vombergar, C. Tagesson, P. Leanderson, and D. Norbäck. 2011. Eating buckwheat cookies is associated with the reduction in serum levels of myeloperoxidase and cholesterol: A double blind crossover study in day-care centre staffs. *The Tohoku Journal of Experimental Medicine* 225 (2):123–130. doi: 10.1620/tjem.225.123.

Wieslander, G., N. Fabjan, M. Vogrincic, I. Kreft, B. Vombergar, and D. Norbäck. 2012. Effects of common and tartary buckwheat consumption on mucosal symptoms, headache and tiredness: A double-blind crossover intervention study. *Journal of Food, Agriculture & Environment* 10 (2):107–110.

Wu, D., and A. I. Cederbaum. 2009. Oxidative stress and alcoholic liver disease. *Seminars in Liver Disease* 29 (2):141–154. doi: 10.1055/s-0029-1214370.

Wu, S. C., and B. H. Lee. 2011. Buckwheat polysaccharide exerts anti-proliferative effects in THP-1 human leukemia cells by inducing differentiation. *Journal of Medicinal Food* 14 (1-2):26–33. doi: 10.1089/jmf.2010.1252.

Wu, W., Z. Li, F. Qin, and J. Qiu. 2021. Anti-diabetic effects of the soluble dietary fiber from tartary buckwheat bran in diabetic mice and their potential mechanisms. *Food & Nutrition Research* 65:e4998. doi: 10.29219/fnr.v65.4998.

Wu, W., L. Wang, J. Qiu, and Z. Li. 2018. The analysis of fagopyritols from tartary buckwheat and their anti-diabetic effects in KK-A^y type 2 diabetic mice and HepG2 cells. *Journal of Functional Foods* 50 (17):137–146. doi: 10.1016/j.jff.2018.09.032.

Xiao, Y., C. Yang, H. N. Xu, J. Zhang, and L. F. Zhang. 2021. Study on the change of flavonoid glycosides to aglycones during the process of steamed bread containing tartary buckwheat flour and antioxidant, α-glucosidase inhibitory activities evaluation *in vitro*. *LWT - Food Science and Technology* 145:111527. doi: 10.1016/j.lwt.2021.111527.

Yan, J., X. C. Sun, Z. J. Xie, G. He, Y. Yi, C. Fang, and X. J. Gou. 2011. Purification and monosaccharide composition analysis of tartary buckwheat polysaccharides. *Food Science* 32 (19):33–36.

Yang, P. H., S. D. Shyur, M. J. Liu, and H. H. Chuang. 2018. Biphasic buckwheat anaphylaxis: Case report and systematic review. *Asian Pacific Journal of Allergy and Immunology* 36 (4):244–247. doi: 10.12932/AP-290317-0060.

Yang, Q., C. Luo, X. Zhang, Y. Liu, Z. Wang, P. Cacciamani, J. Shi, Y. Cui, C. Wang, B. Sinha, et al. 2020. Tartary buckwheat extract alleviates alcohol-induced acute and chronic liver injuries through the inhibition of oxidative stress and mitochondrial cell death pathway. *American Journal of Translational Research* 12 (1):70–89.

Yang, Z. H., C. Li, Y. Y. Li, and Z. H. Wang. 2013. Effects of Maillard reaction on allergenicity of buckwheat allergen Fag t 3 during thermal processing. *Journal of the Science of Food and Agriculture* 93 (6):1510–1515. doi: 10.1002/jsfa.5928.

Yao, Y., F. Shan, J. Bian, F. Chen, M. Wang, and G. Ren. 2008. D-chiro-inositol-enriched tartary buckwheat bran extract lowers the blood glucose level in KK-A^y mice. *Journal of Agricultural and Food Chemistry* 56 (21):10027–10031. doi: 10.1021/jf801879m.

Zhang, C., R. Zhang, Y. M. Li, N. Liang, Y. Zhao, H. Zhu, Z. He, J. Liu, W. Hao, R. Jiao, et al. 2017. Cholesterol-lowering activity of tartary buckwheat protein. *Journal of Agricultural and Food Chemistry* 65 (9):1900–1906. doi: 10.1021/acs.jafc.7b00066.

Zhang, X. Y., J. Chen, X. L. Li, K. Yi, Y. Ye, G. Liu, S. F. Wang, H. L. Hu, L. Zou, and Z. G. Wang. 2017. Dynamic changes in antioxidant activity and biochemical composition of tartary buckwheat leaves during *Aspergillus niger* fermentation. *Journal of Functional Foods* 32 (1):375–381. doi: 10.1016/j.jff.2017.03.022.

Zhao, J., L. Jiang, X. Tang, L. Peng, X. Li, G. Zhao, and L. Zhong. 2018. Chemical composition, antimicrobial and antioxidant activities of the flower volatile oils of *Fagopyrum esculentum*, *Fagopyrum tataricum* and *Fagopyrum cymosum*. *Molecules* 23 (1):e182. doi: 10.3390/molecules23010182.

Zheng, C., C. Hu, X. Ma, C. Peng, H. Zhang, and L. Qin. 2012. Cytotoxic phenylpropanoid glycosides from *Fagopyrum tataricum* (L.) Gaertn. *Food Chemistry* 132 (1):433–438. doi: 10.1016/j.foodchem.2011.11.017.

Zheng, G., X. Pan, Z. An, and Y. Wang. 1991. Preliminary observation of lipid-decreasing effects of compound Tartary buckwheat flour on NIDDM patients. *Beijing Medical Journal* 5:280.

Zhou, X. L., Z. D. Chen, Y. M. Zhou, R. H. Shi, and Z. J. Li. 2019. The effect of tartary buckwheat flavonoids in inhibiting the proliferation of MGC80-3 cells during seed germination. *Molecules* 24 (17):e3092. doi: 10.3390/molecules24173092.

Zhou, X. L., B. B. Yan, Y. Xiao, Y. M. Zhou, and T. Y. Liu. 2018. Tartary buckwheat protein prevented dyslipidemia in high-fat diet-fed mice associated with gut microbiota changes. *Food and Chemical Toxicology* 119:296–301. doi: 10.1016/j.fct.2018.02.052.

Zhou, Y., Y. Jiang, R. Shi, Z. Chen, Z. Li, Y. Wei, and X. Zhou. 2020. Structural and antioxidant analysis of Tartary buckwheat (*Fagopyrum tartaricum* Gaertn.) 13S globulin. *Journal of the Science of Food and Agriculture* 100 (3):1220–1229. doi: 10.1002/jsfa.10133.

Zhou, Y., S. Zhao, Y. Jiang, Y. Wei, and X. Zhou. 2019. Regulatory function of buckwheat-resistant starch supplementation on lipid profile and gut microbiota in mice fed with a high-fat diet. *Journal of Food Science* 84 (9):2674–2681. doi: 10.1111/1750-3841.14747.

Zhu, F. 2016. Chemical composition and health effects of tartary buckwheat. *Food Chemistry* 203:231–245. doi: 10.1016/j.foodchem.2016.02.050.

Zhu, F. 2021. Buckwheat proteins and peptides: Biological functions and food applications. *Trends in Food Science & Technology* 110:155–167. doi: 10.1016/j.tifs.2021.01.081.