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Buckwheat phenolic metabolites in health and disease

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Abstract

Buckwheat (*Fagopyrum esculentum* Moench, *F. tataricum* Gaertner) groats and flour have been established globally as nutritional foods because of their high levels of proteins, polyphenols and minerals. In some regions, buckwheat herb is used as a functional food. In the present study, reports of *in vitro* studies, preclinical and clinical trials dealing with the effect of buckwheat and its metabolites were reviewed. There are numerous reports of potential health benefits of consuming buckwheat, which may be in the form of food, dietary supplements, home remedies or possibly pharmaceutical drugs; however, adverse effects, including those resulting from contamination, must be considered. There are reports of antioxidative activity of buckwheat, which contains high levels of rutin and quercetin. On the other hand, both cytotoxic and antigenotoxic effects have been shown. Reduction of hyperlipidaemia, reduction of blood pressure and improved weight regulation have been suggested. Consuming buckwheat may have a beneficial effect on diabetes, since lower postprandial blood glucose and insulin response have been reported. In addition, buckwheat metabolites, such as rutin, may have intrinsic protective effects in preserving insulin signalling. Rutin has also been suggested to have potential therapeutic applications for the treatment of Alzheimer's disease. The literature indicates that buckwheat is safe to consume and may have various beneficial effects on human health.

Key words: **Buckwheat: Rutin: Adverse effects: Flavonoids: Tartary buckwheat**

Introduction

Two types of buckwheat are used globally: common buckwheat (*Fagopyrum esculentum* Moench) and Tartary buckwheat (*F. tataricum* Gaertner). Buckwheat groats and flour have been established as nutritional foods because of their high levels of proteins, rutin, quercetin and minerals[1,2], such as Se[3]. In Europe, buckwheat bread is gaining significance due to its nutritional properties, antioxidant capacity and the possibility of preparing gluten-free bread[4]. Recently, buckwheat herb was suggested as a functional food. Milled dried plants may be added as colorant to pasta and other products[5]. There are numerous reports of potential health benefits of consuming buckwheat, which may be in a form of food, dietary supplements, home remedies or possibly pharmaceutical drugs. Safety of any food and drugs is of great importance. Recently, a report of severe adverse effect of taking buckwheat tablets was published[6]. The authors reported five cases of new-onset polyneuropathy with dyskinesia induced by composite tablets of black tea and Tartary buckwheat used as a hypoglycaemic food supplement. The diagnosed polyneuropathy was relatively rare but severe; for this the present review of known potential health effects of buckwheat products is instrumental to assess the safety of using buckwheat products. First, it is important to note that the medical history of the affected patients revealed that all took tablets from the same batch[6]. This makes a strong assumption that contamination may have been the cause of reported acute symptoms, which developed quickly after taking this drug and ceased quickly after withdrawing from taking the tablets. The majority of patients had numbness and weakness of the limbs, paraesthesias, hoarseness and bladder dysfunction; one had either shortness of breath, dysphagia or facial paralysis. No heavy metal or other toxic contaminants were found in the tablet. This may indicate that some highly toxic contaminants present in low quantities were missed by the analyses[6].

The present review addresses known potential health-related effects of buckwheat products. This topic is especially important in view of recent increased public interest in buckwheat (Fig. 1).

Adverse effects as a result of contamination of herbal medicinal products

The safety and quality of medicinal plant materials and herbal medicinal products are a major concern for health authorities and the public[7]. However, numerous adverse effects have been found as a result of adulteration or contamination of herbal medicinal products, such as agranulocytosis, meningitis, organ failure, perinatal stroke and heavy metal poisoning[8]. Reports include neurological adverse effects such as paraesthesia and seizures[9]. Unfortunately, the data are largely anecdotal. Plant products may be susceptible to attack by pathogenic, often mycotoxigenic, fungi with consequent increase of mycotoxins. *Aspergillus flavus* may produce aflatoxin B1 (AFB1), the most carcinogenic compound of fungal

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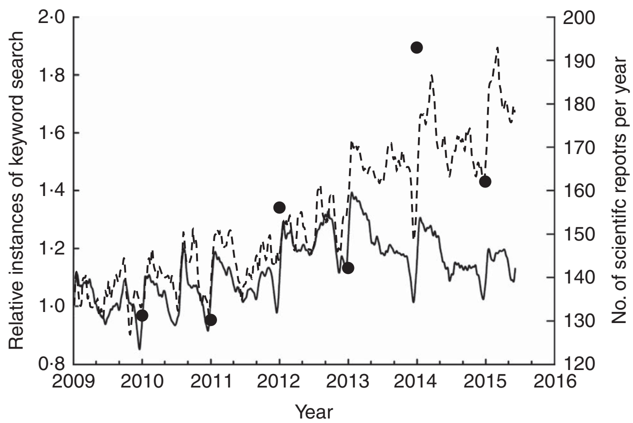

Fig. 1. Increase in public interest in buckwheat. Relative instances of the keyword 'buckwheat' (- - -) have increased in the last 3 years compared with the keyword 'wheat' (——). Data were taken from Google Trends, which provides an index of the relative volume of search queries conducted through Google. Similarly, an increase in the number of publications on buckwheat (●), indexed in the Web of Science (Thomson Reuters), is noticeable.

origin. Seeds of *F. tataricum* are less susceptible to *A. flavus* infection compared with *F. esculentum*[10].

Neuropathy described after taking buckwheat tablets[6] may be attributed to contamination with other herbs such as *Psychotria rubra*[11]. Another example of a neurotoxic plant is hemlock (*Conium maculatum*), which contain piperidine alkaloids, and was probably the cause of death of Socrates[12]. Plants from the genus *Senecio* (Compositae), which contain hepatotoxic pyrrolizidine alkaloids, are a common cause of poisoning with herbal products[13]. Chronic toxicity was found in daily doses of pyrrolizidine alkaloids as low as 25 μg[14]. Botulinum toxins from the bacterium *Clostridium botulinum* are the most potent toxins, with the lethal dose for an individual by the oral route being 30 ng[15]. Clostridia should be absent in all herbal materials, preparations and finished herbal products, as recommended by Annex 5 of WHO guidelines[7]. Foods that are fermented and consumed without cooking pose a substantial risk: first, because Clostridia are obligate anaerobes; second, the toxin is degraded by cooking[16]. The clinical syndrome of botulism includes symmetrical cranial nerve palsies and flaccid paralysis. This may manifest as an expressionless face, dysphagia, dry mouth, shortness of breath[16,17] and paraesthesia[18]. The signs of botulism resemble some signs described in poisoning with buckwheat product[6]. *Clostridium* spp. bacteria have been previously discovered in traditional Chinese herbal medicines, such as Xiyangshen root and Dangshen root[19]. Other than possible contaminants, adverse effects may also be due to plant metabolites, naturally present in food and plant products. Here the current literature to elucidate if there is any previous indication that peripheral nerve damage could appear in patients taking buckwheat is reviewed[6]. Bibliographic data, analysed in the year 2015, are summarised in Tables 1, 2 and 3.

Phenolic metabolites in buckwheat

Buckwheat is mainly grown for the production of seeds[20]. It is an important functional food, rich in vitamins, essential amino acids and phenolic compounds[21]. The content of rutin in Tartary buckwheat herb is as high as 3 % dry weight, and up to 1·7 % in seeds[22]. In common buckwheat milling products rutin content is two orders of magnitude less than in Tartary buckwheat seeds and is highly variable (from 19 to 160 mg/kg in different flour fractions and 480 mg/kg in bran)[23]. In milling fractions darker colour was also correlated with higher protein and minerals content[24]. This variability indicates that rutin and nutrients are not equally distributed in the seed, and is attributed to specific seed morphology[25,26].

Therapeutic doses of rutin have been estimated to be between 180 and 350 mg[27]. Thus, the daily intake of 100 g of buckwheat flour or bran in food would cover 10 % of the therapeutic dose. This contributes to average doses of flavonols and flavons otherwise consumed by at least 2-fold[28].

The composition and differential content of phenolic compounds in seeds of common buckwheat were recently analysed[29]. The list of flavonoids, including rutin, is shown in Table 4. The most detected hydroxycinnamic acids in seeds are caffeic and chlorogenic acid derivatives[29].

From Tartary buckwheat (*F. tataricum*) grains a preparative separation successfully purified five flavonoids: quercetin, kaempferol, quercetin 3-*O*-rutinoside-3′-*O*-β-glucopyranoside, rutin and kaempferol 3-rutinoside[30] (Fig. 2). Flavonoid metabolism is related to responses to UVB radiation[31]. Recently, a new Tartary buckwheat cultivar, 'Manten-Kirari', has been developed, whose grains contain only trace amounts of rutinosidase and lack bitterness. This is a promising variety for preparing non-bitter, rutin-rich foods[32]. The bread-baking procedure using Tartary buckwheat has an impact on rutin, quercetin and polyphenol concentration and antioxidant activity. Rutin concentration during the bread-baking process decreases, while the concentration of quercetin remains stable[33]. Similarly, there is much less rutin in noodles compared with flour made from buckwheat[34].

A much higher rutin level than in seeds is found in fresh buckwheat shoots, which are consumed as a salad or cooked[35]. The buckwheat plant has the highest concentration of rutin and epicatechin in the leaves and flowers[36], depending on UV irradiation[37]. Interestingly, shoots grown from seeds soaked in selenite or selenate solution had higher total flavonoids content compared with soaking seeds in water[38]. Additionally to flavonoids, found in seeds, common buckwheat sprouts also contain vitexin, isovitexin and quercetin-3-*O*-robinobioside[39].

It is important to note that before absorption, dietary phenolic compounds may be transformed in the small intestine by digestive enzymes and in the colon by the intestinal microbiota system[40]. For example, rutin may be converted to quercetin, depending on its concentration and composition of the gut microflora[41]. Although quercetin is metabolised preferentially to carbon dioxide, the biological half-life is very long, ranging from 20 to 72 h[42]. Furthermore, the absorption of quercetin taken orally is surprisingly high, ranging from 36 to 53 %[42], but relatively slow, since it takes 6 h for the plasma concentration to steadily reach the peak concentration[43,44].

Other metabolites of buckwheat

In addition, buckwheat sprouts contain naphthodianthrone fagopyrins that can cause photosensitisation[45,46], manifested

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Table 1. *In vitro* tests of buckwheat activity and activity of its metabolites

Compound	Dose	Test used	Main effect	Reference
Common buckwheat water extract	1 mg/ml	*In vitro* human digestion model and antioxidant activity of lipids in mouse brain	Increase in antioxidative activity	Hur *et al.*[54]
Quercetin, isoquercetin and rutin from Tartary buckwheat seeds and bran	12·5–100 μM	Cytotoxicity and antioxidant activity on human hepatoma cell line HepG2	Quercetin exhibited cytotoxic effects via the production of reactive oxygen species. Up-regulation of p53 and p21, and down-regulation of cyclin D1, Cdk2 and Cdk7	Li *et al.*[55]
Methanol extracts of common and Tartary buckwheat	0·1 μM-rutin, 2·86 μM-quercetin	Induced DNA damage in human hepatoma cell line (HepG2), comet assay	Antigenotoxic effect	Vogrinčič *et al.*[57]
70 % aqueous methanol extract of common buckwheat	0·4 to 20 mg buckwheat/ml	Radical-scavenging activity against DPPH free radical, TEAC and ORAC assay	Increase of antioxidant activities after 36 h of seed germination	Zhang *et al.*[59]
Ethanol extracts of Tartary and common buckwheat sprouts	2·5 mg/ml of sprouts	Radical-scavenging activity against DPPH free radical, ferrous ion-chelating capability, antioxidative capability on lecithin lipid micelles	Tartary buckwheat sprouts possess higher reducing power, free radical-scavenging activity, and superoxide anion-scavenging activity than common buckwheat sprouts	Lin *et al.*[62]
60 % aqueous ethanol extracts from Tartary buckwheat sprouts	Results expressed as μmol Trolox equivalents per g dry weight	Scavenge effects of DPPH, ABTS and superoxide free radicals	Elevated antioxidant activities during germination are related to increases in vitamin C, total flavonoids and rutin, but not vitamin E and quercetin	Zhou *et al.*[64]
Hot water rutin-free extract of Tartary buckwheat	Isolates from the acidic fraction (0·5 – 2·5 mg/ml)	Contractile experiment using Sprague – Dawley rat thoracic aorta rings contracted by phenylephrine	The acidic fraction of the extract elicited an endothelium-dependent vasorelaxation effect via NO/cGMP pathways (EC_{50} value of 0·25 mg/ml)	Matsui *et al.*[72]
Hot water rutin-free extract of Tartary buckwheat	Isolates from the acidic fraction (0·5 – 2·5 mg/ml)	Contractile experiment using Sprague – Dawley rat thoracic aorta rings contracted by phenylephrine	The acidic fraction of the extract elicited an endothelium-dependent vasorelaxation effect	Ushida *et al.*[73]
Buckwheat rutin isolate	0·8–8·8 mg/l rutin	Measurements of Ca^{2+}, calcineurin and c-fos mRNA expression in cultured neonatal rat cardiomyocytes	Inhibition of angiotensin II-induced hypertrophy in cultured neonatal rat cardiomyocytes via Ca^{2+}	Chu *et al.*[74]
Ethanol extract of buckwheat sprouts	10–500 μg extract/ml	Scavenge effects of DPPH, NO, serum peroxidation and chelating assays	Extract of buckwheat sprouts inhibited serum oxidation and possessed chelating activity. Inhibition of pro-inflammatory mediators IL-6 and TNF-α production in macrophages	Karki *et al.*[81]
Rutin	Rutin hydrate 1 μg/ml	HT22 cell viability test after treatment with 200 mM-ethanol	Protection against ethanol neurotoxicity	Song *et al.*[86]
Ethanol extract of buckwheat and rutin	50–200 μg/ml extract or 40 μg/ml rutin	Albumin–fructose glycation assay	Attenuation of protein glycation	Lee *et al.*[88]
Buckwheat bran extracts and rutin	100 μl of extract/500 ml of enzyme solution	*In vitro* sucrase enzymic assay	Buckwheat bran extracts and not pure rutin inhibits sucrase activity	Hosaka *et al.*[90]
Rutin	0·1–10 μM	RIN-m5F rat insulinoma pancreatic β-cells, ATP detection assay and insulin secretion detection	Attenuate the induced glucotoxicity in β-cells by stimulating insulin receptor substrate 2 signalling	Cai & Lin[92]

DPPH, 1,1-diphenyl-2-picrylhydrazyl; TEAC, Trolox equivalent antioxidant capacity; ORAC, oxygen radical absorbance capacity; ABTS, 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulphonic acid); EC_{50}, half maximal effective concentration.

Table 2. Main published preclinical trials dealing with the effect of buckwheat and its metabolites on experimental animals

Compound	Dose	Model animal	Study population	Study design	Main outcome	Reference
Ethanol extracts of Tartary and common buckwheat sprouts	2·5 mg/ml of sprouts	Syrian hamsters	Thirty-six animals	Six groups fed for 28 d: control meal, high fat, plus 2·5 % or 25 % of buckwheat seeds, plus 2·5 % or 25 % of sprouts	Buckwheat meals reduced total cholesterol level and serum TAG levels	Lin *et al.*[62]
Raw common buckwheat extract and germinated buckwheat extract	300–600 mg/kg	Spontaneously hypertensive rats and normotensive Wistar–Kyoto rats	Sixty animals	Six groups fed for 5 weeks: water, 300 and 600 mg/kg of raw and germinated extract-treated groups, and 2·5 mg/kg captopril-treated (positive control) group	Reduced oxidative damage in aortic endothelial cells by lowering nitrotyrosine immunoreactivity	Kim *et al.*[63]
Tartary and common buckwheat protein product	Buckwheat protein product (Tartary: 1710 mg quercetin/100 g), (common: 5·4 mg quercetin/100 g)	Male Sprague–Dawley rats and male ddY mice	Three groups of eight or nine rats, three groups of nine mice	Three groups of rats and mice were given experimental diets. Cholesterol and sodium cholate were added to the diets including casein, common or Tartary buckwheat protein extract	Reductions in serum cholesterol, in rats, enhanced excretion of faecal neutral sterols. Reduction in the lithogenic index	Tomotake *et al.*[68]
70 % ethanol extracts of germinated common buckwheat seeds	100–200 mg germinated buckwheat extract/kg body weight daily	C57BL/6 male mice	Thirty animals	Control high-fat diet group and two germinated buckwheat extract-fed groups. 100 mg and 200 mg germinated buckwheat extract/kg body weight daily	Increased concentrations of serum HDL-cholesterol. Down-regulation of mRNA expressions of PPARγ and C/EBPα in hepatocytes	Choi *et al.*[69]
Dry Tartary buckwheat sprouts, used in the production of pasta	5 g of pasta per rat per d (contained 30 % of Tartary sprouts)	Spontaneously hypertensive rats normotensive counterpart, Wistar–Kyoto rats	Twenty animals	Two strains of rats were randomly divided into two diet groups: durum wheat flour pasta and Tartary buckwheat sprouts	Higher plasma levels of vasodilators, a lower level of the vasoconstrictor, and improved antioxidant capacity	Merendino *et al.*[71]
Tartary flour digested with pepsin, chymotrypsin and trypsin	100 mg of buckwheat digest per kg body weight	Spontaneously hypertensive rats	Ten animals	Two groups: one fed a diet with the Tartary buckwheat digest	Tartary buckwheat protein and not rutin exhibit angiotensin I-converting enzyme inhibition	Li *et al.*[75]
Common buckwheat flour and wheat germ	20 % (w/w) of wheat germ and buckwheat flour relative to control diet	Female ICR/CD-1 mice	260 animals screened, eighty-eight used	The non-prematurely ageing mice as control group, prematurely ageing mice randomly divided into control group (*n* 26) and wheat germ and buckwheat flour groups	Prematurely ageing mice that received cereal buckwheat showed improved parameters of innate and acquired immune responses	Alvarez *et al.*[76]
75 % ethanol extracts from Tartary buckwheat	Extract contained 228·8 mg/g of rutin and 58·6 mg/g of quercetin	Male C57BL/6 mice and male Sprague–Dawley rats	Six groups of six rats and six groups of six mice	Increase of liver enzymes in serum was monitored in the ethanol- and carbon tetrachloride-induced animals. Antioxidant enzyme activities were also monitored	Hepatoprotection via promoting antioxidative and anti-inflammatory properties against oxidative liver damage	Lee *et al.*[82]
Common buckwheat protein extract	38·1 % of the daily diet	Female Sprague–Dawley rats	Two groups of twenty animals	The 7,12-dimethylbenz anthracene-treated rats examined for palpable mammary tumours and serum level of oestradiol was measured	Retardation of the development of mammary tumour in rats, correlated with lower serum oestradiol	Kayashita *et al.*[83]
Rutin and *n*-butanol extracted from Tartary buckwheat	100 mg/kg per d of rutin; 100–200 mg/kg per d of *n*-butanol	Male ICR mice	Five groups of five animals	*n*-Butanol- and rutin-administered animals (model of amyloid β-induced Alzheimer's disease) assessed using the T-maze, object recognition, and Morris water maze tests	Administration of buckwheat extracts alleviated induced cognitive impairments	Choi *et al.*[85]
Rutin	25–100 mg/kg per d	Male Wistar rats	Six groups of animals	Haloperidol-induced orofacial dyskinesia evaluated by behavioural tests (orofacial dyskinetic movements, stereotypic rearing, locomotor activity, percent retention)	Pretreatment with rutin reversed behavioural changes induced by haloperidol	Bishnoi *et al.*[87]
Ethanol extract of buckwheat, rutin and quercetin	Extract (100 μg/ml, 50 mg/kg), quercetin (6 μg/ml; 3 mg/kg), and rutin (23 μg/ml; 11·5 mg/kg)	C57BL/6 mice	Six groups of twelve animals	Oral glucose tolerance test and assay for blood glucose and insulin	Inhibited increases in blood glucose and insulin levels induced by fructose-rich diet	Lee *et al.*[89]
Buckwheat leaf and flower	5 % buckwheat in the diet	Male Wistar rats	Forty animals in five groups	Rats fed a high-fat diet were analysed for weight gain, plasma lipid levels and differential plasma fatty acid concentration	Reduction of weight gain, plasma lipid concentrations and atherogenic index	Đurendić-Brenesel *et al.*[96]

ICR, Imprinting Control Region.

Table 3. Main published clinical trials dealing with the effect of buckwheat consumption on human health

Compound	Dose	Disorder	Study population	Study design	Main outcome	Reference
Tablets of black tea and Tartary buckwheat	Not known	Treatment of diabetes	Not known (five reported adverse effects)	Case report after pharmacovigilance reports	Polyneuropathy	Yang *et al.*[6]
Cookies made of common and Tartary buckwheat	360 mg of rutin/d, or 17 mg of rutin/d in four cookies	None	Sixty-two volunteers	Double-blind experimental cross-over study	Decrease in myeloperoxidase (indicator of inflammation) in Tartary buckwheat group and decrease in serum cholesterol in both groups	Wieslander *et al.*[67]
A single dose of buckwheat honey, dextromethorphan	5 ml	Nocturnal cough and sleep difficulty associated with upper respiratory tract infections	105 children aged 2–18 years	A partially double-blinded randomised study	In paired comparisons, honey was superior to no treatment for cough frequency, dextromethorphan was not better than no treatment	Paul *et al.*[78]
Buckwheat herb tea	1·8 g of herb per cup, three cups daily	Chronic venous insufficiency	Sixty-seven patients	Single-centre randomised double-blind placebo-controlled clinical trial	Prevention of further development of oedema	Ihme *et al.*[79]
Cookies made of common and Tartary buckwheat	360 mg of rutin/d, or 17 mg of rutin/d in four cookies	None	Sixty-two healthy women	Double-blind cross-over intervention study	Reduction of mucosal symptoms (ocular, nasal and throat), decreased headache and tiredness	Wieslander *et al.*[84]
Bread of buckwheat and wheat flour	Dose corresponding to 50 g carbohydrate. 50 % of buckwheat groats in bread	None	Ten healthy subjects	Randomised trial	Lower postprandial blood glucose and insulin response	Skrabanja *et al.*[93]

Table 4. Flavonoids from common buckwheat seeds[29]

Catechin
Epiafzelechin-epicatechin
Epicatechin
Isoorientin
Kaempferol-3-rutinoside
Kaempferol-hexoside
Orientin
Procyanidin B2 dimetilygallate
Procyanidin dimer (catechin-catechin)
Procyanidin dimer monogalate
Procyanidin tetramer isomer (four epicatechin units)
Procyanidin trimer 1
Procyanidin trimer 2 (three epicatechin units)
Procyanidin trimer 3 [epiafzelechin-(4–8)-epicatechin-*O*-(3,4-dimethyl)-gallate]
Quercetin-3-galactoside (hyperin)
Quercetin-3-glucoside (isoquercitrin)
Quercetin-3-rhamnoside (quercitrin)
Quercetin-3-rutinoside (rutin)
Quercetin-hexoside gallate

as skin irritation after sunlight exposure. The highest levels of fagopyrins have been found in flowers and leaves[47]. Levels of fagopyrins increase gradually in sprout growth, especially in the light[48].

Products prepared from common buckwheat grains have a characteristic aroma, which is attributed mainly to salicylaldehyde[49]. Other significant odorants are (*E,E*)-2,4-decadienal, (*E*)-2-nonenal, 2-pheniletanol, (*E,E*)-2,4-nonadienal, hexanal, decanal, nonanal, and, in Tartary buckwheat, naphthalene[50–53]. The pharmacological and medical effects of these volatile compounds need to be further investigated.

Antioxidant activity of buckwheat

Experiments using an *in vitro* human digestion model showed that the antioxidative activity of common buckwheat is increased by digestion in the small intestine via an increase in the antioxidants rutin and quercetin[54]. The antioxidant capacity of quercetin from Tartary buckwheat was the strongest, compared with isoquercetin and rutin[55]. On the other hand, by reducing the intracellular antioxidase activity, flavonoid compounds could increase cell oxidative stress[56]. It has been shown that quercetin exhibits the strongest cytotoxic effects against the human hepatoma cell line, which is due to the G2/M phase arrest accompanied by an increase of apoptotic cell death. The p53 and p21 were found to be up-regulated, and cyclin D1, Cdk2 and Cdk7 down-regulated[55]. Further, it has been shown that in the human hepatoma cell line, common and Tartary buckwheat has antigenotoxic effects[57]. The potential anti-tumour effect of flavonoids of buckwheat has not yet been thoroughly studied. An epidemiological study on 738 men showed that intake of flavonoids does not predict a reduced risk of cancer in elderly men[58].

With germination of buckwheat seeds, phenolic compounds, such as rutin, vitexin, isovitexin, orientin, isoorientin, chlorogenic acid, *trans*-3-hydroxycinnamic acid and *p*-hydroxybenzoic acid increased significantly, which may be due to the activation of phenylalanine ammonialyase[59]. This leads to significant

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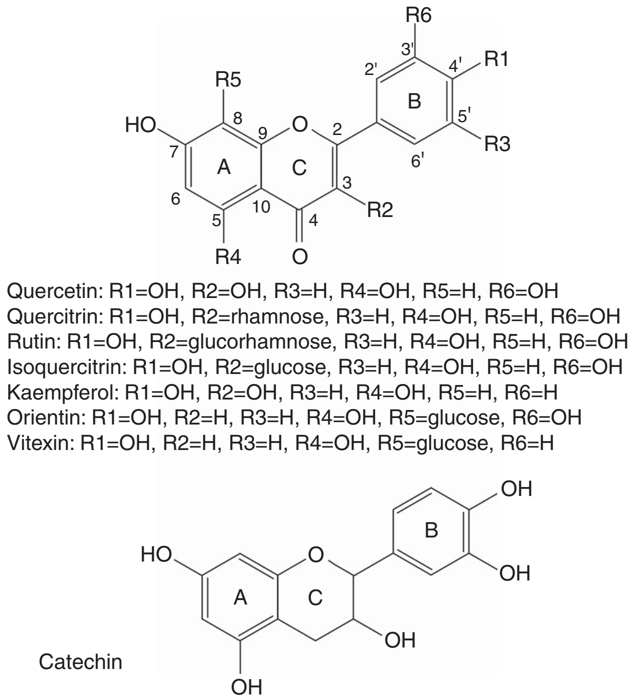

Fig. 2. Structures of main flavonoids found in buckwheat. Flavones have A, C and B ring structures, with substitutions as indicated at B4′ (R1), C3 (R2), B5′ (R3), A5 (R4), A8 (R5) and B3′ (R6).

enhancement of the antioxidant activities of germinated buckwheat and may be used as a promising functional food[59]. Buckwheat sprouts are suggested as a new vegetable[60]. The highest total phenols in buckwheat sprouts of germinated soaked buckwheat seeds is at day 6[61] or day 8[62]. Specifically, compared with buckwheat seeds, the sprouts contain relatively large amounts of rutin[48,60].

Common buckwheat and Tartary buckwheat sprouts have different antioxidant activities. It has been shown that the ethanol extracts of Tartary buckwheat sprouts have higher reducing power, free radical scavenging activity, and superoxide anion scavenging activity than those of common buckwheat sprouts, possibly because of their higher rutin and quercetin content[62]. Treatment with raw common buckwheat extract and germinated buckwheat extract reduced oxidative damage in aortic endothelial cells by lowering nitrotyrosine immunoreactivity, which suggests an antihypertensive effect and may protect arterial endothelial cells from oxidative stress[63]. In Tartary buckwheat, the compounds which play a key role in the elevated antioxidant activities during germination consisted of vitamin C, total flavonoids and rutin, but not vitamin E and quercetin[64].

CVD, hypertension and plasma cholesterol

Food rich in polyphenols possess cardiovascular protective properties[65], and antihypertensive properties[66]. Specifically, buckwheat products reduce the serum levels of myeloperoxidase and cholesterol[67]. The reduction of serum cholesterol by common and Tartary buckwheat protein products is associated with enhanced excretion of faecal neutral sterols bile acids in mice and rats[68]. Extract of germinating common buckwheat seeds, administered orally to mice, reduces hepatic TAG and total cholesterol, and down-regulates the expression of adipogenic transcription factors PPARγ and C/EBPα in hepatocytes[69]. Some earlier studies indicated reduced senile hyperlipidaemia, reduced blood pressure and reduction of weight; however, these trials were without control groups (for a review, see Wieslander & Norbäck[70]).

It has been shown that spontaneously hypertensive rats fed Tartary buckwheat sprouts exhibit higher plasma levels of the endogenous vasodilators bradykinin and NO, a lower level of the vasoconstrictor endothelin-1, and an improved antioxidant capacity, which may collectively reduce hypertension and oxidative stress *in vivo*[71]. A potent vasorelaxant effect was found in the (+)-osbeckic acid dimer, which was isolated from rutin-free Tartary buckwheat extract[72]. Tartary buckwheat rutin-free extracts exert endothelium-dependent vasorelaxation action in isolated rat aorta rings, probably by NO/cGMP signalling pathways[73]. Buckwheat rutin exhibits an inhibitory effect on angiotensin II-induced hypertrophy in cultured neonatal rat cardiomyocytes via Ca^{2+} antagonism action, thus blocking the calcineurin-dependent signal pathway[74]. Tartary buckwheat protein and not rutin exhibit angiotensin I-converting enzyme inhibition. Oral administration of Tartary buckwheat digest has been found to lower the blood pressure of hypertensive rats[75].

Immune system and inflammation

Dietary supplementation with buckwheat flour appears to have a protective effect on immune cell functions in mice with premature senescence[76]. Several parameters of innate immune response were increased: macrophage chemotaxis, phagocytosis, microbicidal activity, natural killer activity, as well as parameters of acquired immune response: lymphoproliferative response to concanavalin A and lipopolysaccharide, and IL-2 release[76].

Flavonoids including quercetin have shown viral inhibition properties such as antiherpetic activity against *Herpes simplex* virus, types 1 and 2[77]. A survey on parents of 105 children with upper respiratory tract infections was performed to compare the effects of a single dose of buckwheat honey or honey-flavoured dextromethorphan with no treatment. Significant differences in symptom improvement were detected between treatment groups, with honey consistently scoring the best and no treatment scoring the worst[78]. However, it was not yet established if honey in general or buckwheat honey specifically was favourable for the relief of coughing.

Ihme *et al.*[79] investigated the effect of buckwheat herb tea in treating leg oedema in patients with chronic venous insufficiency. Results of a randomised double-blind placebo-controlled clinical trial indicated potential use in patients to prevent the further development of oedema. As importantly, the study on sixty-seven patients confirmed the safety of this treatment[79].

Rutin has potential anti-inflammatory properties[80]. It is a potent inhibitor of phorbol-12-myristate 13-acetate (PMA), TNF-α, IL-1β, and caecal ligation and puncture (CLP)-mediated endothelial cell protein C receptor shedding[80]. Extract of

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buckwheat sprouts was shown to inhibit pro-inflammatory mediators IL-6 and TNF-α production in macrophages[81]. Extracts from Tartary buckwheat were shown to exert hepato-protection via promoting antioxidative and anti-inflammatory properties against oxidative liver damage in mice. This was manifested as inhibiting the increase in serum aspartate transaminase, alanine transaminase and alkaline phosphatase levels in challenged animals[82]. A buckwheat protein diet may retard the development of mammary tumours in female rats, which was found to be correlated with lower serum oestradiol[83].

A double-blind cross-over intervention study was conducted to study the effects of common and Tartary buckwheat consumption on mucosal symptoms, i.e. ocular, nasal and throat symptoms; further, headache and tiredness were evaluated[84]. Both types of buckwheat had generally positive effects on these symptoms.

Neurological disorders

It was recently shown that the *n*-butanol fraction and rutin extracted from Tartary buckwheat are protective against and have possible therapeutic applications for the treatment of Alzheimer's disease[85]. This was confirmed by studying learning and memory deficits in a mouse model of amyloid β-induced Alzheimer's disease. Animals' impaired cognition and memory were alleviated by the oral administration of an *n*-butanol fraction and rutin extracted from Tartary buckwheat[85].

Rutin's protective effects against acetaldehyde-based ethanol neurotoxicity have been found. Rutin protects hippocampal neuronal cells against ethanol-induced neurotoxicity by increasing aldehyde dehydrogenase 2 (ALDH2) activity. Its metabolite, acetaldehyde, is critically toxic. ALDH2 metabolises acetaldehyde into non-toxic acetate[86]. Rutin was suggested as a protective compound against the haloperidol-induced motor disorder orofacial dyskinesia, resulting from the chronic neuroleptic treatment of schizophrenia[87]. Haloperidol induces oxidative damage in all regions of the brain in rats, which was prevented by rutin, which may be a possible therapeutic to treat this motor disorder[87].

Weight regulation and diabetes

Tartary buckwheat is used for the treatment of type 2 diabetes mellitus in Taiwan. It has been shown that the ethanol extract of buckwheat and rutin attenuates protein glycation to lower the generation of advanced glycation endproducts through the suppression of fructosamine and α-dicarbonyl compounds; hence it may be used as a protection agent in diabetic patients[88]. The ethanol extract of buckwheat, rutin and quercetin improved glucose uptake via promoting Akt phosphorylation and preventing PPARγ degradation in a hepatocyte cell line[89]. Buckwheat bran extracts and not pure rutin inhibit sucrase activity *in vitro*, which may have a beneficial effect on diabetes[90]. Similarly, it seems that buckwheat concentrate has insulin-mimetic effects on select protein phosphorylation events in rat hepatoma cells; however, D-chiro-inositol and myo-inositol are not probably active components responsible for the observed effects[91]. Rutin was found to attenuate the induced glucotoxicity in β-cells by stimulating insulin receptor substrate 2 signalling in rat pancreatic β-cells. The intrinsic protective effects of rutin in preserving insulin signalling may lead to novel strategies for the prevention of type 2 diabetes[92].

In healthy subjects consuming bread with buckwheat and wheat flour, lower postprandial blood glucose and insulin response were measured, compared with a group eating wheat bread[93]. Proanthocyanidins in buckwheat flour can reduce salivary nitrite to NO in the stomach. This may improve the activity of the stomach, helping the digestion of ingested foods[94]. Proanthocyanidins from persimmon inhibit oxidative stress and the digestive enzymes related to diabetes, such as α-amylase and α-glucosidase[95].

Buckwheat leaf and flower food supplementation apparently reduces weight gain, plasma lipid concentrations and atherogenic index in rats fed a high-fat diet; buckwheat products are thus suggested for the potential prevention and curing of hyperlipidaemia[96].

Summary

Numerous reports have shown the potential health benefits of consuming buckwheat, which may be in the form of food, dietary supplements, home remedies or possibly pharmaceutical drugs. There are reports of the antioxidative activity of buckwheat; on the other hand, both cytotoxic and anti-genotoxic effects have been shown. Reduction of hyperlipidaemia, reduction of blood pressure and improved weight regulation have been suggested. Consuming buckwheat may have beneficial effect on diabetes. Rutin was also suggested to have potential therapeutic applications for the treatment of Alzheimer's disease. It can be concluded that the literature indicates that buckwheat is safe to consume and may have various beneficial effects on human health.

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