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 minerals1,2, such as Se35. In Europe, buckwheat bread is gaining significance due to its nutritional properties, antioxidant capacity and the possibility of preparing gluten-free bread4. Recently, buckwheat herb was suggested as a functional food. Milled dried plants may be added as colorant to pasta and other products5. 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 published6. The authors reported five cases of new-onset polynuropathy with dyskinesia induced by composite tablets of black tea and Tartary buckwheat used as a hypoglycaemic food supplement. The diagnosed polynuropathy 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 batch6. 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, paraesthesia, 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 analyses6.

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 public7. However, numerous adverse effects have been found as a result of adulteration or contamination of herbal medicinal products, such as agranulocytosis, menigitis, organ failure, perinatal stroke and heavy metal poisoning8. Reports include neurological adverse effects such as paraesthesia and seizures9. Unfortunately, the data are largely anecdotal. Plant products may be susceptible to attack by pathogenic, often mycotoxicogenic, fungi with consequent increase of mycotoxins. Aspergillus flavus may produce aflatoxin B1 (AFB1), the most carcinogenic compound of fungal

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Clostridia are obligate anaerobes; second, the toxin is degraded with the lethal dose for an individual by the oral route being

difficulty of breath(16,17) and paraesthesia(18). The signs of botulism manifest as an expressionless face, dysphagia, dry mouth, short-

consumed without cooking pose a substantial risk: products(13). Chronic toxicity was found in daily doses of

zidine alkaloids, are a common cause of poisoning with herbal

genus

cardinal bacteria have been previously

references, as indicated in the milligrams of

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. flatus infection compared with F. esculentum(10).

Neuropathy described after taking buckwheat tablets(60) 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 pyrroli-

dizidine 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). Botulotxin 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(77). 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, short-

ness 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 Danshen root(19). Other than possible contaminants, adverse effects may also be due to plant metabo-

lites, 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(20). 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(24,25). This variabiliy indicates that rutin and nutrients are not equally distributed in the seed, and is attrib-

uted to specific seed morphology(26,27).

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 flavans otherwise consumed by at least 2-fold(28).

The composition and differential content of phenolic com-

pounds in seeds of common buckwheat were recently ana-

lysed(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) grans a preparative separation successfully purified five flavonoids: quercetin, kaempferol, quercitin 3-O-rutinoside-3′-O-β-glucopyranoside, rutin and kaempferol 3-rutinoside(29) (Fig. 2). Flavonoid metabo-

lism is related to responses to UVB radiation(30,31). Recently, a new Tartary buckwheat cultivar, ‘Manten-Kirani’, 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 irra-

diation(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 flavo-

noids, found in seeds, common buckwheat sprouts also contain vitexin, isovitexin and quercitin-3-O-robioside(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
## Table 1. In vitro tests of buckwheat activity and activity of its metabolites

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Test used</th>
<th>Main effect</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common buckwheat water extract</td>
<td>1 mg/ml</td>
<td>In vitro human digestion model and antioxidant activity of lipids in mouse brain</td>
<td>Increase in antioxidative activity</td>
<td>Hur et al. (54)</td>
</tr>
<tr>
<td>Quercetin, isoquercetin and rutin from Tartary buckwheat seeds and bran</td>
<td>12.5–100 μM</td>
<td>Cytotoxicity and antioxidant activity on human hepatoma cell line HepG2</td>
<td>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</td>
<td>Li et al. (55)</td>
</tr>
<tr>
<td>Methanol extracts of common and Tartary buckwheat</td>
<td>0–1 μM–rutin, 2.86 μM–quercetin</td>
<td>Induced DNA damage in human hepatoma cell line (HepG2), comet assay</td>
<td>Antigenotoxic effect</td>
<td>Vogrinič et al. (56)</td>
</tr>
<tr>
<td>70 % aqueous methanol extract of common buckwheat</td>
<td>0-4 to 20 mg buckwheat/ml</td>
<td>Radical-scavenging activity against DPPH free radical, TEAC and ORAC assay</td>
<td>Increase of antioxidant activities after 36 h of seed germination</td>
<td>Zhang et al. (57)</td>
</tr>
<tr>
<td>Ethanol extracts of Tartary and common buckwheat sprouts</td>
<td>2.5 mg/ml of sprouts</td>
<td>Radical-scavenging activity against DPPH free radical, ferrous ion-chelating capability, antioxidative capability on lecithin lipid micelles</td>
<td>Tartary buckwheat sprouts possess higher reducing power, free radical-scavenging activity, and superoxide anion-scavenging activity than common buckwheat sprouts</td>
<td>Lin et al. (58)</td>
</tr>
<tr>
<td>60 % aqueous ethanol extracts from Tartary buckwheat sprouts</td>
<td>Results expressed as μmol Trolox equivalents per g dry weight</td>
<td>Scavenge effects of DPPH, ABTS and superoxide free radicals</td>
<td>Elevated antioxidant activities during germination are related to increases in vitamin C, total flavonoids and rutin, but not vitamin E and quercetin</td>
<td>Zhou et al. (59)</td>
</tr>
<tr>
<td>Hot water rutin-free extract of Tartary buckwheat</td>
<td>Isolates from the acidic fraction (0.5 – 2.5 mg/ml)</td>
<td>Contractile experiment using Sprague – Dawley thoracic aorta rings contracted by phenylephrine</td>
<td>The acidic fraction of the extract elicited an endothelium-dependent vasorelaxation effect via NO/cGMP pathways (EC50 value of 0.25 mg/ml)</td>
<td>Matsui et al. (60)</td>
</tr>
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<td>The acidic fraction of the extract elicited an endothelium-dependent vasorelaxation effect via NO/cGMP pathways (EC50 value of 0.25 mg/ml)</td>
<td>Ushida et al. (61)</td>
</tr>
<tr>
<td>Buckwheat rutin isolate</td>
<td>0.8–8.8 mg/l rutin</td>
<td>Measurements of Ca2+, calcineurin and c-fos mRNA expression in cultured neonatal rat cardiomyocytes</td>
<td>Inhibition of angiotensin II-induced hypertrophy in cultured neonatal rat cardiomyocytes via Ca2+ promotion</td>
<td>Chu et al. (62)</td>
</tr>
<tr>
<td>Ethanol extract of buckwheat sprouts</td>
<td>10–500 μg extract/ml</td>
<td>Scavenge effects of DPPH, NO, serum peroxidation and chelating assays</td>
<td>Extract of buckwheat sprouts inhibited serum oxidation and possessed chelating activity. Inhibition of pro-inflammatory mediators IL-6 and TNF-α production in macrophages</td>
<td>Karki et al. (63)</td>
</tr>
<tr>
<td>Rutin</td>
<td>Rutin hydrate 1 μg/ml</td>
<td>HT22 cell viability test after treatment with 200 μM-ethanol Albumin–fructose glycation assay</td>
<td>Protection against ethanol neurotoxicity</td>
<td>Song et al. (64)</td>
</tr>
<tr>
<td>Ethanol extract of buckwheat and rutin</td>
<td>50–200 μg/ml extract or 40 μg/ml rutin</td>
<td>In vitro sucrase enzymic assay</td>
<td>Attenuation of protein glycation</td>
<td>Lee et al. (65)</td>
</tr>
<tr>
<td>Buckwheat bran extracts and rutin</td>
<td>100 μl of extract/500 ml of enzyme solution</td>
<td>In vitro human digestion model and antioxidant activity of lipids in mouse brain</td>
<td>Buckwheat bran extracts and not pure rutin inhibits sucrase activity</td>
<td>Hosaka et al. (66)</td>
</tr>
<tr>
<td>Rutin</td>
<td>0.1–10 μM</td>
<td>RIN-m5F rat insulinoma pancreatic β-cells, ATP detection assay and insulin secretion detection</td>
<td>Attenuate the induced glucotoxicity in β-cells by stimulating insulin receptor substrate 2 signalling</td>
<td>Cai &amp; Lin (67)</td>
</tr>
</tbody>
</table>

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); EC50, half maximal effective concentration.
### Table 2. Main published preclinical trials dealing with the effect of buckwheat and its metabolites on experimental animals

<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose</th>
<th>Model animal</th>
<th>Study population</th>
<th>Study design</th>
<th>Main outcome</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethanol extracts of Tarty and common buckwheat sprouts</td>
<td>2.5 mg/ml of sprouts</td>
<td>Syrian hamsters</td>
<td>Thirty-six animals</td>
<td>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</td>
<td>Buckwheat meals reduced total cholesterol level and serum TAG levels</td>
<td>Lin et al.(62)</td>
</tr>
<tr>
<td>Raw common buckwheat extract and germinated buckwheat extract</td>
<td>300–600 mg/kg</td>
<td>Spontaneously hypertensive rats and normotensive Wistar–Kyoto rats</td>
<td>Sixty animals</td>
<td>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</td>
<td>Reduced oxidative damage in aortic endothelial cells by lowering nitrotyrosine immunoactivity</td>
<td>Kim et al.(63)</td>
</tr>
<tr>
<td>Tarty and common buckwheat protein product</td>
<td>Buckwheat protein product (Tarty: 1710 mg quercetin/100 g), (common: 5.4 mg quercetin/100 g)</td>
<td>Male Sprague–Dawley rats and male ddY mice</td>
<td>Three groups of eight or nine rats, three groups of nine mice</td>
<td>Three groups of rats and mice were given experimental diets. Cholesterol and sodium cholate were added to the diets including casein, common or Tarty buckwheat protein extract</td>
<td>Reductions in serum cholesterol, in rats, enhanced excretion of faecal neutral sterols. Reduction in the lithogenic index</td>
<td>Tomotake et al.(68)</td>
</tr>
<tr>
<td>70% ethanol extracts of germinated common buckwheat seeds</td>
<td>100–200 mg germinated buckwheat extract/kg body weight daily</td>
<td>C57BL/6 male mice</td>
<td>Thirty animals</td>
<td>Control high-fat diet group and two germinated buckwheat extract-fed groups. 100 mg and 200 mg germinated buckwheat extract/kg body weight daily</td>
<td>Increased concentrations of serum HDL-cholesterol. Down-regulation of mRNA expressions of PPARs and C/EBPs in hepatocytes</td>
<td>Choi et al.(69)</td>
</tr>
<tr>
<td>Dry Tarty buckwheat sprouts, used in the production of pasta</td>
<td>5 g of pasta per rat per d (contained 30% of Tarty sprouts)</td>
<td>Spontaneously hypertensive rats</td>
<td>Twenty animals</td>
<td>Two strains of rats were randomly divided into two diet groups: durum wheat flour pasta and Tarty buckwheat sprouts</td>
<td>Higher plasma levels of vasoactivities, a lower level of the vasoconstrictor, and improved antioxidant capacity</td>
<td>Merendino et al.(71)</td>
</tr>
<tr>
<td>Tarty flour digested with pepsin, chymotrypsin and trypsin</td>
<td>100 mg of buckwheat digest per kg body weight</td>
<td>Spontaneously hypertensive rats</td>
<td>Ten animals</td>
<td>Two groups: one fed a diet with the Tarty buckwheat digest</td>
<td>Tarty buckwheat protein and not rutin exhibit angiotensin I-converting enzyme inhibition</td>
<td>Li et al.(75)</td>
</tr>
<tr>
<td>Common buckwheat flour and wheat germ</td>
<td>20% (w/w) of wheat germ and buckwheat flour relative to control diet</td>
<td>Female ICR/CD-1 mice</td>
<td>260 animals screened, eighty-eight used</td>
<td>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</td>
<td>Prematurely ageing mice that received cereal buckwheat showed improved parameters of innate and acquired immune responses</td>
<td>Alvarez et al.(70)</td>
</tr>
<tr>
<td>75% ethanol extracts from Tarty buckwheat</td>
<td>Extract contained 228.8 mg of rutin and 58.6 mg of quercetin</td>
<td>Male C57BL/6 mice and male Sprague–Dawley rats</td>
<td>Six groups of six rats and six groups of six mice</td>
<td>Increase of liver enzymes in serum was monitored in the ethanol- and carbon tetrachloride-induced animals. Antioxidant enzyme activities were also monitored</td>
<td>Hepatoprotection via promoting antioxidative and anti-inflammatory properties against oxidative liver damage</td>
<td>Lee et al.(82)</td>
</tr>
<tr>
<td>Common buckwheat protein extract</td>
<td>38.1% of the daily diet</td>
<td>Female Sprague–Dawley rats</td>
<td>Two groups of twenty animals</td>
<td>The 7,12-dimethylbenz anthracene-treated rats</td>
<td>Retardation of the development of mammary tumour in rats, correlated with lower serum oestradiol</td>
<td>Kayashita et al.(83)</td>
</tr>
<tr>
<td>Rutin and n-butanol extracted from Tarty buckwheat</td>
<td>100 mg/kg per d of rutin; 100–200 mg/kg per d of n-butanol</td>
<td>Male ICR mice</td>
<td>Five groups of five animals</td>
<td>The 7,12-dimethylbenz anthracene-treated rats examined for palpable mammary tumours and serum level of oestriadol was measured</td>
<td>Administration of buckwheat extracts alleviated induced cognitive impairments</td>
<td>Choi et al.(85)</td>
</tr>
<tr>
<td>Rutin</td>
<td>25–100 mg/kg per d</td>
<td>Male Wistar rats</td>
<td>Six groups of animals</td>
<td>Haloperidol-induced orofacial dyskinesia evaluated by behavioural tests (orofacial dyskinetic movements, stereotypic rearing, locomotor activity, percent retention)</td>
<td>Pretreatment with rutin reversed behavioural changes induced by haloperidol</td>
<td>Bishnoi et al.(87)</td>
</tr>
<tr>
<td>Ethanol extract of buckwheat, rutin and quercetin</td>
<td>Extract (100 μg/ml, 50 mg/kg), quercetin (6 μg/ml; 3 mg/kg), and rutin (23 μg/ml; 11.5 mg/kg)</td>
<td>C57BL/6 mice</td>
<td>Six groups of twelve animals</td>
<td>Oral glucose tolerance test and assay for blood glucose and insulin</td>
<td>Inhibited increases in blood glucose and insulin levels induced by fructose-rich diet</td>
<td>Lee et al.(89)</td>
</tr>
<tr>
<td>Buckwheat leaf and flower</td>
<td>5% buckwheat in the diet</td>
<td>Male Wistar rats</td>
<td>Forty animals in five groups</td>
<td>Rats fed a high-fat diet were analysed for weight gain, plasma lipid levels and differential plasma fatty acid concentration</td>
<td>Reduction of weight gain, plasma lipid concentrations and atherogenic index</td>
<td>Durendić-Brenesel et al.(90)</td>
</tr>
</tbody>
</table>

ICR, Imprinting Control Region.
Table 3. Main published clinical trials dealing with the effect of buckwheat consumption on human health

<table>
<thead>
<tr>
<th>Compound</th>
<th>Disorder</th>
<th>Main outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Buckwheat herb tea</td>
<td>Treatment of diabetes</td>
<td>105 children aged 2-12 years, nocturnal cough and sleep difficulties associated with upper respiratory tract infections</td>
</tr>
<tr>
<td>Cookies made of buckwheat honey,</td>
<td>Chronic venous insufficiency</td>
<td>60 patients, reducing mucosal symptoms (ocular, nasal and throat), decreased headache and tiredness</td>
</tr>
<tr>
<td>Tartary buckwheat</td>
<td>None</td>
<td>60 healthy subjects, double-blind cross-over study</td>
</tr>
<tr>
<td>Bread of buckwheat and wheat flour</td>
<td>Lower postprandial blood glucose and insulin response</td>
<td>10 patients, reducing mucosal symptoms (ocular, nasal and throat), decreased headache and tiredness</td>
</tr>
<tr>
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<td>None</td>
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</table>

Table 4. Flavonoids from common buckwheat seeds(29)

<table>
<thead>
<tr>
<th>Flavonoid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catechin</td>
</tr>
<tr>
<td>Epiafzelechin-epicatechin</td>
</tr>
<tr>
<td>Epicatechin</td>
</tr>
<tr>
<td>Isoorientin</td>
</tr>
<tr>
<td>Kaemperol-3-rutinoside</td>
</tr>
<tr>
<td>Kaemperol-hexoside</td>
</tr>
<tr>
<td>Orientin</td>
</tr>
<tr>
<td>Procyanidin B2 dimethylgallate</td>
</tr>
<tr>
<td>Procyanidin dimer (catechin-catechin)</td>
</tr>
<tr>
<td>Procyanidin dimon monogalate</td>
</tr>
<tr>
<td>Procyanidin tetramer isomer (four epicatechin units)</td>
</tr>
<tr>
<td>Procyanidin trimer 1</td>
</tr>
<tr>
<td>Procyanidin trimer 2 (three epicatechin units)</td>
</tr>
<tr>
<td>Procyanidin trimer 3</td>
</tr>
<tr>
<td>Quercetin-3-galactoside (hyperin)</td>
</tr>
<tr>
<td>Quercetin-3-glucoside (isoquercetin)</td>
</tr>
<tr>
<td>Quercetin-3-rhamnoside (quercitrin)</td>
</tr>
<tr>
<td>Quercetin-3-rutinoside (rutin)</td>
</tr>
<tr>
<td>Quercetin-hexoside gallate</td>
</tr>
</tbody>
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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(56).

With germination of buckwheat seeds, phenolic compounds, such as rutin, vextin, isovextin, 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
enrichment of the antioxidant activities of germinated buckwheat and may be used as a promising functional food. The highest total phenols in buckwheat sprouts of germinated soaked buckwheat seeds is at day 6 or day 8. Specifically, compared with buckwheat seeds, the sprouts contain relatively large amounts of rutin.

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. Treatment with raw common buckwheat extract and germinated buckwheat extract reduced oxidative damage in aortic endothelial cells by lowering nitrosyrosine immunoreactivity, which suggests an antihypertensive effect and may protect arterial endothelial cells from oxidative stress. 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.

CVD, hypertension and plasma cholesterol

Food rich in polyphenols possess cardiovascular protective properties, and antihypertensive properties. Specifically, buckwheat products reduce the serum levels of myeloperoxidase and cholesterol. 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. 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. Some earlier studies indicated reduced senile hyperlipidaemia, reduced blood pressure and reduction of weight; however, these studies were without control groups (for a review, see Wieslander & Norbäck).

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. A potent vasorelaxant effect was found in the (+)-osebeckic acid dimer, which was isolated from rutin-free Tartary buckwheat extract. Tartary buckwheat rutin-free extracts exert endothelium-dependent vasorelaxation action in isolated rat aorta rings, probably by NO/GMP signalling pathways. Buckwheat rutin exhibits an inhibitory effect on angiotensin II-induced hypertrophy in cultured neonatal rat cardiomyocytes via Ca2+ antagonism action, thus blocking the calcineurin-dependent signal pathway. 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.

Immune system and inflammation

Dietary supplementation with buckwheat flour appears to have a protective effect on immune cell functions in mice with premature senescence. 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.

Flavonoids including quercetin have shown viral inhibition properties such as antiviral activity against Herpes simplex virus, types 1 and 2. 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. However, it was not yet established if honey in general or buckwheat honey specifically was favourable for the relief of coughing.

Hune et al. 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.

Rutin has potential anti-inflammatory properties. 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. Extract of buckwheat and may be used as a promising functional food.

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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).
buckwheat sprouts was shown to inhibit pro-inflammatory mediators IL-6 and TNF-α production in macrophages(80). Extracts from Tartary buckwheat were shown to exert hepatoprotection 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 α-butyrol 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 α-butyrol fraction and rutin extracted from Tartary buckwheat(86).

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, α-chiro-inositol and myoinositol 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-inflammatory 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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