INVITED REVIEW

Can Buckwheat Affect Health and Female Reproductive Functions?

Alexander V. SIROTKIN[1]

[1]Constantine the Philosopher University in Nitra, Nitra, Slovak Republic

Received April 9, 2024
Accepted August 29, 2024

Summary

The aim of the present narrative review is to summarise the existing knowledge concerning physiological and reproductive effects of buckwheat, its mechanisms of action on various targets, as well as outlines the direction of the further studies of this functional food plant. Search for literature was performed in agreement with the PRISMA criteria in Cochrane Library, Pubmed, Web of Science, SCOPUS databases between the year 1995 and 2023. Words used to search were buckwheat, review, fertility, ovarian and mechanisms. The current review of the available literature demonstrates the high nutritional value of buckwheat, as well as high contents and number of regulatory molecules in this functional food plant. These molecules can, via multiple signalling pathways, affect a wide spectrum of physiological processes and illnesses, which suggests a therapeutic value of buckwheat substances. Furthermore, recent reports demonstrate ability of buckwheat extract to directly affect basic ovarian cell functions (proliferation, apoptosis, viability, steroidogenesis). On the other hand, understanding the character and applicability of buckwheat influence on female reproductive processes requires further studies.

Keywords

Buckwheat • Nutrition • Health • Ovary • Signalling

Corresponding author

V. Sirotkin, Constantine the Philosopher University in Nitra, 949 74 Nitra, Slovak Republic. E-mail: asirotkin@ukf.sk

Introduction

Nutrition and food intake is considered as an important modifiable factor for health promotion and disease prevention and treatment. Understanding mechanism of action of natural regulators is important for characterization, prediction and control of physiological and pathological processes. One of the promising functional food and medicinal plant is buckwheat. Some publications summarized the information concerning chemical or medicinal characteristics of their plants [1-5]. On the other hand, they did not reflect some buckwheat constituents, as well as buckwheat action on reproductive processes. The present publication is the first review concerning physiological and reproductive effects of buckwheat, which summarizes the available data concerning mechanisms of action of this plant on various targets, as well as outlines the direction of the further studies of this functional food plant.

Materials and Methods

Search for literature was performed in agreement with the PRISMA (= preferred reporting items for systematic review) criteria [6]. To search the related articles, Cochrane Library, Pubmed, Web of Science, SCOPUS databases between the year 1995 and 2023 were used. In cases of repeated or conflicting informations or references, more recent sources have been preferred. Words used to search were buckwheat, review, fertility, ovarian and mechanisms. If the eligibility of some publications or their abstracts (due to lack of sufficient information concerning methods, results or their processing) was questionable, these details were verified by analysis of the full text and supplementary materials, as well as by the direct contact with the corresponding author.

PHYSIOLOGICAL RESEARCH • ISSN 1802-9973 (online)
Fax +420 241 062 164, e-mail: physres@fgu.cas.cz, www.biomed.cas.cz/physiolres

Results and Discussion

Provenance and properties

Buckwheat is an ancient pseudocereal crop under Polygonaceae family and genus *Fagopyrum*. The genus *Fagopyrum* (Polygonaceae), currently comprising 15 species of plants, includes three important buckwheat species: *Fagopyrum esculentum (F. esculentum)* Moench. (common buckwheat), *Fagopyrum tataricum (F. tataricum)* (L.) Gaertn. (tartary buckwheat) and *Fagopyrum dibotrys (F. dibotrys)* (D. Don) Hara. (perennial buckwheat), which have been well explored due to their long tradition of both edible and medicinal use [2].

Buckwheats have numerous ecological adaptabilities, so they can be cultivated in high altitude regions with low rainfall and temperature. The most popular and common is Tartary buckwheat originated from mountainous provinces of southern China, but now it is broadly cultivated in Asia, Europe, and the Americas. The world-leading buckwheat producing countries are China, Russia, France, Ukraine, Poland, the United States and Kazakhstan [7]. It is generally used as a cereal after removal of the husk (cereal grain) or milled for flour. Buckwheat flour is generally processed into other foods such as noodles, confectionery, bread, and the products of fermentation such as vinegar, and alcoholic spirits. The leaves are also used as leafy vegetables and can be dried to make teas and powder. Furthermore, buckwheat plants are cultivated for landscaping and for honey production [1, 8].

Buckwheat has high nutritional value: it contains several times more proteins, fat, fiber and vitamins than other popular grains - rice, wheat, maize and oat [7, 9, 10]. Buckwheat proteins are of high quality with a balanced essential amino acid composition characterized by abundant amounts of sulphur-rich amino acids [11]. The protein quality of buckwheat seeds varies between the tartary and common buckwheat types, but both are gluten-free and contain considerable amount of indispensable amino acids [12].

Buckwheat possesses high nutritional and health-promoting value due to its constituents. The Fagopyrum esculentum genome sequencing and transcriptome analysis detected or predicted 33-36.000 its genes encoding proteins, flavonoids and other biological active substances [9]. 178 bioactive compounds have been detected in buckwheat [10]. There are fatty acids, polysaccharides, proteins, and amino acids, iminosugars, dietary fiber, fagopyrins, resistant starch, vitamins, as well as triterpenoid saponins, flavinoids (i.e., rutin, quercetin, kaempherol) flavones (luteolin, vitexin, orientin, metabolites of quercetin), flavanones (hesperitins, naringenins), flavanols (catechins), anthocyanins (cyanidins) fagopyrins, isoflavones (genistein and others), stilbene resveratrol and many others. Buckwheat is also a good source of minerals (calcium, iron and zinc) [4, 5, 7, 9, 11, 13, 14]. The content of flavonoids in Tartary buckwheat grain and groats is much higher than in common buckwheat [4], The content of polyphenols, as well as the total antioxidant activity of buckwheat flour is increased during backing [14].

In damaged or milled grain under wet conditions, most of the rutin is degraded to quercetin by rutin-degrading enzymes (e.g., rutinosidase). From Tartary buckwheat varieties with low rutinosidase activity it is possible to prepare foods with high levels of rutin, with the initial levels preserved in the grain [13].

Physiological actions

Various buckwheat compounds have anti-oxidant, anti-tumor, anti-inflammatory, hepatoprotective, anti-bacterial, anti-fungal, anti-viral, anti-ulcer, anti-fatique, hypolipidemic, prebiotic, immunomodulatory, neuroprotective, cardioprotective, hypotensic, anti-diabetic, anti-atherosclerotic, anti-neoplastic, anti-thrombotic and anti-aging activities. They decrease blood glucose and cholesterol level indicating the applicability of buckwheat and its constituents for treatment of metabolic syndrome and related disorders [1, 3-5, 7, 15, 16]. Buckwheat constituents can suppress adipocyte differentiation and fat accumulation and therefore obesity and obesity-related disorders [4, 17]. For example, fermented buckwheat reduced mice body, epididimal and liver fat. Metagenomic analysis revealed that fermented buckwheat affected the mice metabolic pathways of primary bile acid biosynthesis, metabolism of pyrimidine lipid, glutathione metabolism, glycine, serine and threonine, amino sugar and nucleotide sugar metabolism, etc. Additionally, the fermented buckwheat regulated the mRNA levels of hepatic genes involved in hepatic lipid metabolism and bile acid homeostasis [18]. Buckwheat have protective action against ethanol-induced liver injury [4, 12]. In addition, buckwheat does not contain substantial amount of gluten, therefore it can prevent metabolic disorders induced by gluten [11, 12, 19]. Buckwheat constituents are prebiotics supporting and normalizing good microflora [1, 7, 12, 20] (see below).

On the other hand, it is important to note that these data concerning the health-promoting effect of buckwheat compounds were obtained during in-vitro experiments or few experiments performed on laboratory animals. Human studies showed only that buckwheat can be a good basis for functional food to mitigate the manifestation of gluten-related diseases such as celiac disease, non-celiac sensitivity and wheat allergy [19]. Furthermore, the few clinical trials demonstrated, that both acute and chronic administration of buckwheat to diabetic subjects modulated metabolic and cardiovascular markers [11].

Mechanisms of action

Due to a number of biologically active constituents with various properties and targets, the mechanisms of buckwheat action is not easy to formulate.

The drug target prediction, network analysis, and molecular docking simulation enabled to predict 97 putative target molecules, which can mediate buckwheat action on type II diabetes, hypertension and hyperlipidemia [15]. The experiments indicated involvement of some of these predicted targets in mediating buckwheat action on these and other illnesses. For example, the ability of buckwheat to suppress fat storage can be explained by its down-regulation of liver triglyceride accumulation, serum level of triglycerides, mRNA expression levels lipogenic enzyme genes, fatty acid synthase, acetyl-coenzyme a oxidase and stearyl-coenzyme a desaturase 1, transcription factors ChREBP (Carbohydrate-responsive element-binding protein) and SREBP1c (sterol regulatory element-binding protein 1) and transcripts of lipogenic genes in mices [21]. In addition, buckwheat extract inhibited lipid accumulation, triglyceride content, leptin production, and glycerol-3-phosphate dehydrogenase activity during adipocyte differentiation. This action was associated with down-regulation of the mRNA levels of genes involved in fatty acid synthesis, such as peroxisome proliferator-activated receptor-γ, CCAAT/enhancer binding protein-α, adipocyte protein 2, acetyl-CoA carboxylase (acetyl-coenzyme A carboxylase), fatty acid synthase, and stearoylcoenzyme A desaturase-1 [22, 23].

The anti-oxidant properties of 11 kinds of buckwheat substances, especially of rutin, tocopherols and quercetin [7, 14] indicate that their ability to neutralize reactive oxygen species and to prevent the oxidative stress-induced DNA damage and apoptosis can explain their anti-tumor, anti-inflammatory, anti-diabetic, anti-aging, neuro-, hepatic- and cardioprotective properties [3, 4, 7, 24].

The antioxidant properties of buckwheat molecules and their ability to suppress obesity and obesity-related disorders can be due to anti-inflammatory action of buckwheat. At least, buckwheat extract can suppress adipocyte inflammation reducing the mRNA levels of inflammatory mediators such as tumor necrosis factor-α, interleukin-6, monocyte chemoattractant protein 1, inducible nitric oxide synthase and nitric oxide production [23]. The anti-inflammatory action of buckwheat molecule quercetin-3-O-glucuronide can be explained by its accumulation and metabolization by macrophages and resulted suppression of their actions [16].

The prebiotic properties of buckwheat polysaccharides, fiber and phenols, especially rutin, quercetin could be responsible for some of its effect on lipid and carbohydrate metabolism and immune system regulated by gut microbiota [1, 7, 12, 20]. Buckwheat polypeptide glutaredoxin can promote lifespan via up-regulation of both antioxidant enzymes and of heat shock transcription factor [25]. The trypsin inhibitor isolated from buckwheat can suppress cancerogenesis via up-regulation of cancer cell nuclear apoptosis associated with DNA fragmentation and of cytoplasmic apoptosis associated with mitochondria dysfunctions manifested by release of cytochrome C from the mitochondria to the cytosol and activation of cytoplasmic caspase-3, -8 and -9 [26, 27], pro-apoptotic transcription factor p53 [28]. and changes in apoptosis regulators bcl-2 (B-cell lymphoma *2* protein) and FAS (FS-7-associated surface antigen) [29]. The other buckwheat molecules, flavonoids, have similar mechanism of action: they induce leukemia cell apoptosis via release of cytochrome C from mitochondria to the cytosol, as well as via upregulation of pro-apoptotic Fas (FS-7-associated surface antigen) expression on the cell surface, through a caspase-3-dependent mechanism in cytoplasm and via inactivation of nuclear transcription factor NF-kappaB (nuclear factor kappa-light-chain-enhancer of activated B cells) [30]. Furthermore, D-chiro-inositol, and other bioactive compound of tartary buckwheat, can prevent cardiovascular diseases and type II diabetes via prevention of mitochondrial dysfunctions as well [24]. In addition, it can prevent these illnesses via mitigation of endoplasmic reticulum stress, an inactivation of inflammation-associated interleukin 6 and Jun n-terminal kinase, which are considered triggers of endothelial dysfunction and lesion [24].

In adipocytes, buckwheat extract reduced cyclin-dependent kinase 2 and cyclin expression and increased p21 and p27 expression, thus causing cell cycle arrest at the G1/S phase [22]. The arrest of the cancer cell cycle and prevention of transition from G(0)/G(1) phase to S phase induced also the anti-cancer protein isolated from buckwheat [29].

Finally, buckwheat-containing food can prevent adipocyte differentiation and fat storage via inhibition of the expression of adipogenic transcription factor, peroxisome proliferator-activated receptor γ, and AMP-activated protein kinase [17].

These observations demonstrate the action of numerous buckwheats bioactive molecules via multiple intracellular signalling pathways. In some cases, the same intracellular pathway could mediate action of several buckwheat molecules on different processes. On the other hand, one buckwheat molecule can use different mediators of its action.

Effects on female reproductive processes

Effect on ovarian cell proliferation, apoptosis and viability

It can be postulated that fecundity depends on ovarian follicle development, which is in turn determined by follicular cell viability. The viability of cell population in turn depends on the proliferation: apoptosis rate. The available observations concerning character buckwheat on these processes in ovarian cells are contradictory. In some experiments, buckwheat extract reduced viability and accumulation of marker and promoter of proliferation PCNA (proliferating cell nuclear antigene), not influencing cytoplasmic/mitochondrial apoptosis marker bax (Bcl-2-associated X protein) [31, 32] in cultured porcine ovarian granulosa cells. In other experiments, this extract did not influence viability and this apoptosis marker, but PCNA accumulation was promoted [31]. In other similar experiments, buckwheat extract enhanced cell viability and accumulation of bax not influencing PCNA [33]. Although all cited data were obtained during experiments performed on the same model (primary porcine ovarian granulosa cells), the differences in the observed responses of cells to buckwheat extract could be caused by initial differences in reproductive state of animals – donors of granulosa cells.

Despite the variations in the observed effects of buckwheat, the performed in-vitro experiments demonstrated its direct action on ovarian cell proliferation, apoptosis, and viability.

Effect on ovarian cell hormone release

Inconclusive are also the reports concerning influence of buckwheat extract on steroid hormones' release by cultured porcine ovarian granulosa cells. In some experiments, the addition of buckwheat extract increased the release of progesterone, but not of estradiol [34]. Several experiments did not show buckwheat influence on progesterone release, but it reduced estradiol output [31, 32]. In other experiments, buckwheat extract affected neither progesterone nor estradiol release, but inhibited testosterone output [33]. These differences, like differences in buckwheat action on proliferation and apoptosis of cultured porcine granulosa cells mentioned above could be due to variability in initial reproductive state of animals, which is characterized by different release of steroid hormones and their response to upstream regulators [34,35].

Therefore, the performed studies on cultured porcine ovarian granulosa cells showed that buckwheat extract can directly influence basic ovarian cell functions – proliferation, apoptosis, viability and steroidogenesis, although the character of this influence varied among the experiments. Such variability in response of cultured porcine ovarian cells to buckwheat treatment could be due to variations in the initial state of ovarian cells used in experiments.

The functional interrelationships between buckwheat effects and their mechanisms remain to be elucidated. Nevertheless, it might be proposed that buckwheat could directly affect ovarian cells and therefore female reproductive processes via changes in release of steroid hormones – the known regulators of ovarian cell proliferation, apoptosis and ovarian folicullogenesis and fecundity [35].

Effect on ovarian cell response to environmental contaminants

The publications cited above demonstrated, that buckwheat extract can not only affect basic ovarian cell functions, but also prevent the adverse influence of some environmental contaminants on these cells. Xylene suppressed viability, accumulation of PCNA, bax and release of progesterone and estradiol by cultured porcine ovarian granulosa cells. Addition of buckwheat extract prevented the suppressive influence of xylene on four from five measured ovarian cell parameters (viability, PCNA, bax, and estradiol output) [31]. Buckwheat was able to modify the influence of another oil-related environmental contaminant – benzene on cultured porcine granulosa cells. Benzene reduced cell viability, as well as P and E release, but not PCNA and bax accumulation. Buckwheat addition induced the stimulatory influence of benzene on accumulation of proliferation marker PCNA [33]. As concerns other oil-related contaminant, toluene, buckwheat not mitigated, but promoted the toxic effect of this hydrocarbon on viability and induced the stimulatory action of toluene on proliferation and progesterone release by cultured granulosa cells [32]. Finally, buckwheat modified the influence of copper nanoparticles supported in titania on these cells. These nanoparticles increased cell viability, proliferation, apoptosis, and testosterone but not progesterone release, and reduced the 17β-estradiol output. Addition of buckwheat extract to culture medium mitigated the nanoparticles' effects on cell viability, PCNA and estradiol release [34].

Taken together, the available reports demonstrate the ability of buckwheat to directly affect ovarian cells, to change their basic functions (proliferation, apoptosis, viability, steroidogenesis), as well as to mitigate or prevent the influence of some environmental contaminants (xylene, benzene and copper nanoparticles, but not of toluene) on these functions. The possible targets of buckwheat and environmental contaminants listed above controlling female reproduction are summarized in Fig.1.

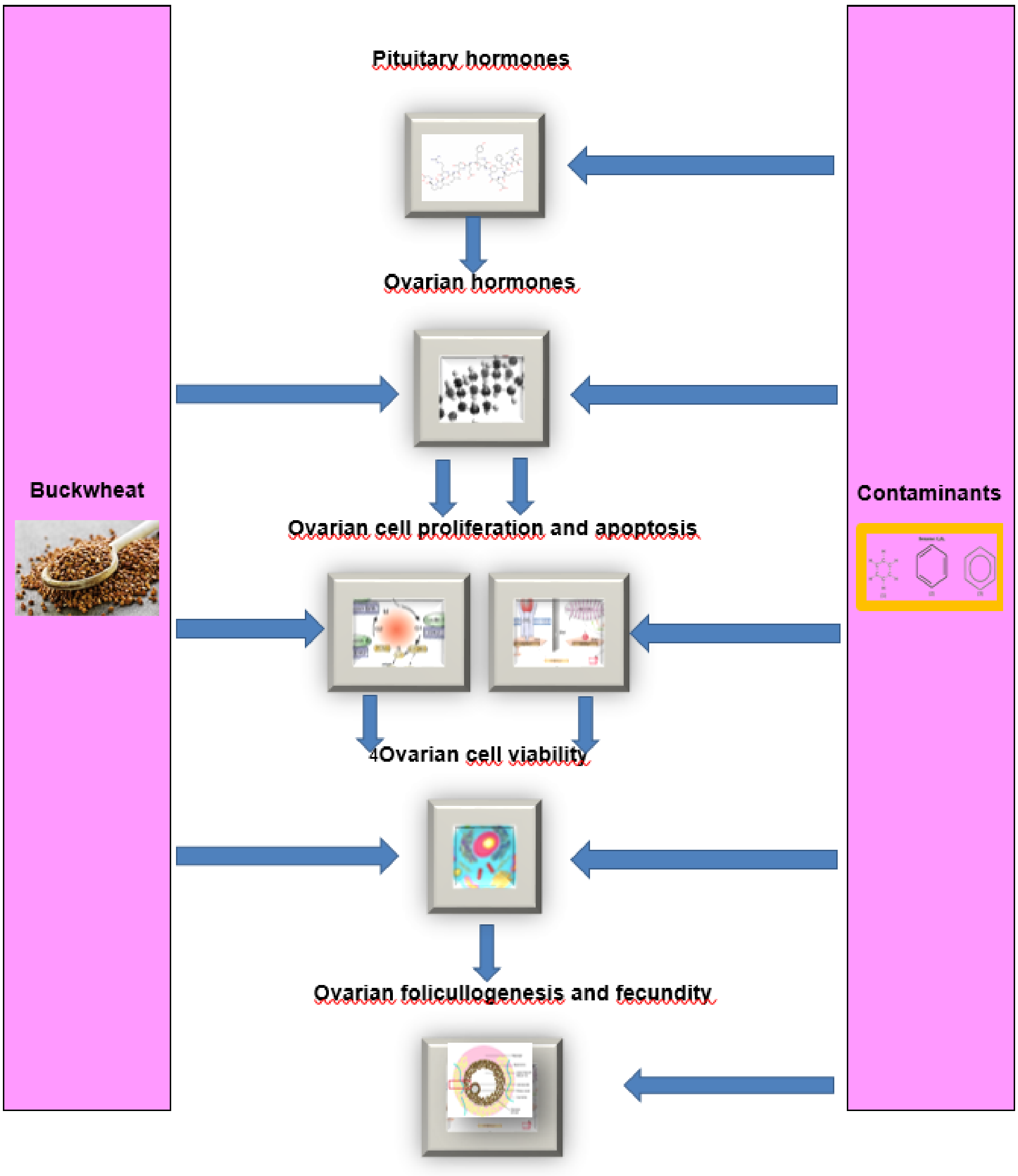

Fig. 1. The possible targets of buckwheat and environmental contaminants controlling female reproductive processes. For details see the main text.

Application in reproductive biology and medicine

If the suppressive action of buckwheat on ovarian functions occurs not only in-vitro, but also in vivo, the potential adverse influence of this plant on female reproduction is to be taken into account before medical application of buckwheat or its constituents or before overconsumption of buckwheat containing food.

On the other hand, the ability of buckwheat to prevent the influence of various harmful environmental contaminants on ovarian cells suggests its potential applicability as a novel natural protector of female reproductive system from contaminant action.

These applications of buckwheat and its molecules remain rather speculative as of yet; they could be validated by the corresponding in-vivo studies.

Conclusions and possible direction of future studies

The available literature demonstrates the high nutritional value of buckwheat, as well as the high contents and number of regulatory molecules in this functional food plant. These molecules can, via multiple signalling pathways, affect a wide spectrum of physiological processes and illnesses, which suggests a therapeutic value of buckwheat substances. Furthermore, recent reports demonstrate ability of buckwheat extract to affect directly basic ovarian cell functions (proliferation, apoptosis, viability, steroidogenesis).

On the other hand, the major data concerning therapeutic effects of buckwheat and its molecules were obtained in animal or in-vitro experiments. The described influence of buckwheat on metabolism, which influence on reproductive processes is accepted, as well as the changes in hormones release, proliferation, apoptosis and viability of animal ovarian cells or human non-ovarian cell lines (see above) treated by buckwheat and its constituents (see above) indicates potential usefulness of these treatment for control of human reproductive processes and medicine against human reproductive disorders. These studies suggested the potential applicability of buckwheat, but no clinical trials focused on reproductive effects of buckwheat on human reproductive processes have been performed yet. We believe, the present review could demonstrate the potential clinical value of such studies. Understanding the hierarchical functional interrelationships between the physiological effects and mediators of buckwheat action require further studies too. Influence of buckwheat on ovarian cells was demonstrated only in in-vitro experiment on one model (cultured porcine granulosa cells), whilst the obtained results are variable, sometimes contradictory and therefore inconclusive. Therefore, understanding the character and applicability of buckwheat influence on female reproductive processes requires further studies.

The buckwheat application could be promoted also by higher output of its biological active constituents. The genomic analysis and selection of this plant, as well as the improvement of processing of buckwheat-based food can increase the content of desirable molecules (for example, of proteins, rutin, quercetin, [9, 12, 13] in this food, to improve their bioavailability [16] and its physiological and medicinal benefits. Isolation [12, 36] or production of recombinant bioactive buckwheat molecules [25] could provide new drugs for prevention and treatment of various disorders.

Conflict of Interest

There is no conflict of interest.

Acknowledgements

The author expresses his gratitude to Prof. Abdel Halim Harrath for his kind help in preparation this manuscript. This work was supported by the Slovak Grant Agency of the Ministry of Education, Science and Sport and the Slovak Academy of Science (VEGA), project VEGA 1/0680/22.

Abbreviations

Acetyl-CoA carboxylase, acetyl-coenzyme A carboxylase; AMP-activated protein kinase, adenosine monophosphate-activated protein kinase; Bax, Bcl-2-associated X protein; bcl-2 - B-cell lymphoma *2* [protein] ChREBP - Carbohydrate-responsive element-binding protein; FAS, *F*S-7-*a*ssociated *s*urface antigen; mRNA, messenger RNA; NF-kappaB, (nuclear factor kappa-light-chain-enhancer of activated B cells; PCNA, proliferating cell nuclear antigene; SREBP1c, sterol regulatory element-binding protein 1 (SREBP-1)

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