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Review Article

# Barley: A Potentially Beneficial Health Cereal

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## Abstract

Barley is the cereal that contains the highest amount of beta-glucans (β-glucans), which provides multiple health benefits. However, its consumption within the diet is limited, since the nutritional properties that this cereal provides are unknown. A high consumption of β-glucans significantly decreases the risk of developing chronic-degenerative diseases such as metabolic syndrome. Likewise, the consumption of barley improves glycaemia and insulin sensitivity in non-diabetic and diabetic people because it is rich in phenolic acids, flavonoids, lignans, tocols, phytosterols and folate. Its high fibre content helps overweight and obese individuals to significantly improve weight loss. A higher intake of foods containing barley positively impacts various gastrointestinal disorders, in addition to helping the regulation of the immune system. The recommended intake of barley soluble fibre is 6g daily. The high concentration of β-glucans and phytochemicals in this cereal could be largely responsible for its health benefits. This document reviews the available information on clinical studies related to barley and its potential to combat chronic degenerative diseases

***Keywords:*** *Cereal; Dietary Fibre; Functional foods; Nutrition; Beta-glucans*

## Abbreviations

BG: beta-glucans (β-glucans); TNF: Tumour Necrosis Factor; LPS: Lipopolysaccharide; TLR: Toll-like Receptors; NLR: Node-like Receptors; AMP: Adenosine Monophosphate; SCFA: Short Chain Fatty Acids; MAO-B: Monoamino Oxidase B; PBS: PBS Phosphate Buffered Saline; BA: Bile Acids; HDL: High Density Lipoprotein; LDL: Low Density Lipoprotein; AMPK: Protein Kinase Activated by AMP; BS: Barley Sprout; HMGCR: Hydroxy-3-Methylglutaryl-CoA Reductase; FDA: Food and Drug Administration; EFSA: European Food Safety Agency; EG: Experimental Group; CG: Control Group; HMW: High Molecular Weight; LMW: Low Molecular Weight; HBG: High in Betaglucans; LBG: Low in Betaglucans; HP: High in Prevotella; HPB: High in Prevotella and Bacteriodes; cAMP: Cyclic Monophosphate Adenosine; NO: Nitric Oxide; EV: Vascular Endothelium; TRP: Tyrosinase Related Protein; g: Grams; Kg: Kilograms.

## Introduction

The consumption of dietary fibre has become the fundamental pillar of a healthy diet to treat different chronic-degenerative diseases, such as obesity, diabetes and cardiovascular diseases. In addition to having a direct impact on lipids, blood pressure, blood glucose control and an improved immune system. [1]. However, most people consume less than half of the recommended level of daily dietary fibre. This is due to suboptimal intake and lack of knowledge on the type of foods that contain it.

One of the main sources of dietary fibre are cereals, as they provide a large amount of β-glucans that contribute to maintaining and improving our health [2,3]. The β-glucans are linear homopolysaccharides of glucose linked through β- (1 → 3) and β- (1 → 4) bonds. They are easily obtained from cereal grains by dry milling, followed by a sieving process and solvent extractions. The highest proportion of β-glucans is found in barley [4] (Table 1).

During 2016, Russia was the country with the highest production of barley in the world, with 12.7% of its total production. Germany followed with 7.6%, France with 7.3%, Ukraine with 6.7% and Australia with 6.4% [5]. In Mexico, the main states that pro-

duce barley are Guanajuato, Hidalgo, Tlaxcala, Puebla and Mexico, which together contribute 859 thousand tons, that represent 89% of the national volume [6]. The food industry uses barley ß-glucans to produce breads [7,8] and pasta [9] because they improve the consistency of the food, retaining moisture and replacing the use of sugar [10].

| Cereals | gr of β-glucans (100 gr of cereals) |
|---|---|
| Barley | 2-20g [4] |
| Oat | 3-8g |
| Sorghum | 1.1-6.2g |
| Rye | 1.3-2.7g |
| Corn | 0.8-1.7g |
| Wheat | 0.5-1.0g |
| Rice | 0.13gr |

**Table 1**: Grams of β-glucans in cereals.

Barley brings multiple benefits to the body, containing B Vitamins, folic acid, choline and vitamin K, in addition to being a good source of potassium, magnesium and phosphorus, but its greatest benefit is its richness in trace elements: iron, sulphur, copper, zinc, manganese, chromium, selenium, iodine and molybdenum. In addition, it contains lysine (limiting amino acid in wheat and corn), which plays a central role in the absorption of calcium, in the construction of muscle mass and in the recovery of surgical interventions or sports injuries [11] (Figure 1).

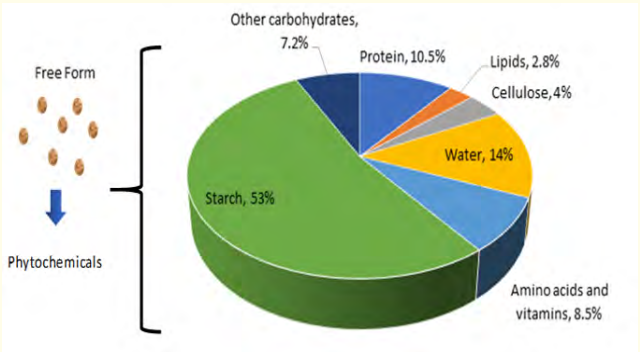


**Figure 1:** Composition of Barley grain.

Since there is limited data on the consumption of foods made from this cereal and taking into account the positive impact of barley on different bodies and systems, we have conducted a review, in order to illustrate the importance of its consumption.

## Food application of soy products

In 1818, the Spanish botanist Claudio Boutelou categorised barley into eight groups, the most used today is the barley *Hordeum vulgare* L. [12] This type of barley is a plant that belongs to the grass family, its leaves are narrow, light green and it has a shell that protects the pericarp, the endosperm and the germ, its shell is formed by the lemma and the palea. According to Wang, 70% is used for animal feed, 20% is used as a source of malt and other uses in the industry and another 5% for food in general (Wang, 2005) [13].

Barley contains a large amount of β-glucans, located in the cell walls of the endosperm, the development of which is dependent on geoclimatic conditions. The content of β-glucan is regulated by the enzyme β-glucan-endohydrolase (1→ 3, 1→ 4), also known as licheninase or 1→ 3, 1→ 4 β-glucanase, the function of which is to promote the degradation of the endosperm cell wall during germination. These β-glucans are classified as soluble dietary fibre, since they are not digestible in the small intestine of the human body because there are no pancreatic or intestinal enzymes capable of degrading them [14] (Table 2).

| Name | Glycosidic Link |
|---|---|
| Cellulose | β-1,4 |
| Curdian | β-1,3 |
| Laminarin | β-1,3 y β-1, |
| Chrysolamin | β-1,3 |
| Lentinan | β-1,6: β-1,3 |
| Lichenin | β-1,3 y β-1,4 |
| Pleuran | β-1,3 y β-1,6 |
| Zymosan | β-1,3 |

**Table 2**: Beta-glucan and the type of O-glycosidic bond.

In recent decades, interest in the role of β-glucans in health has been increasing. Of all dietary fibres, these are the most widely studied in terms of the positive impact on the health of the foods that contain them. In addition, no adverse effects have been reported when adding β-glucans to food. It is worth noting that barley contains gluten, so it is not suitable to use this cereal for people with celiac disease [15].

## Barley and Immune System

There are few studies that have acknowledged the effect of barley on the immune system. Pruimboom described the effect of β-glucans on non-specific immune responses, in particular the

stimulation of macrophages and neutrophils. It is also mentioned that all functions of macrophages improve after the ingestion of β-glucans [16]. It should be noted that the most known immunomodulatory effect has been that of lentinan; which is a β-glucan with a glycosidic linkage β-1-3: β-1. Kerékgyártó C., *et al.* studied the effect of lentinan on the antitumor cytotoxicity and secretion of peritoneal macrophages of TNF in mice under *In vivo* and *In vitro* conditions. In their study it was found that this β-glucan has an effect on primary macrophages and RAW264 cell lines by increasing cytotoxic activity and inflammatory cytokines [17].

β-glucans balance the immune system, which is predominantly driven by humoral resistance regulated by Th2 helper cells, moving more towards a response regulated by the Th1 helper cells, in particular towards a cellular immune response, which increases resistance to bacterial and parasitic infections [18,19]. Blaszczyk., *et al.* investigated the transcriptomic profile in peripheral blood of rats with LPS-induced enteritis, which were fed a diet supplemented with barley β-glucans. They observed several genes expressed in the groups supplemented with β-glucans that encoded proteins belonging to the TLR and NLR signalling pathways, as well as to the prostaglandin synthesis and regulation pathways. These results show the protective effect exerted by β-glucans in the inflammatory state induced by LPS [20,21].

Few studies show the effect of β-glucans on the immune system and even fewer that discuss the specific effect of barley. This is why more clinical trials are required to obtain more evidence to support the previously described results and demonstrate their potential in the regulation of this system and the use of barley as an essential food in a diet for immunological diseases.

## Barley and Digestive System

Barley has a direct effect on the formation of viscous gels in the gastrointestinal tract, delaying gastric emptying and interfering with the activity of pancreatic enzymes, improving the digestion process and absorption of cholesterol and glucose [22,23]. Its consumption helps to regulate blood insulin levels and to reduce the glycaemic index of foods, directly impacting the prevention of diseases such as obesity, diabetes mellitus, colon cancer and cardiovascular diseases [24-26].

Velikonja., *et al.* conducted a randomized, double-blind, placebo-controlled clinical trial involving 43 volunteers at high risk of developing metabolic syndrome. During their study participants consumed experimental barley bread containing 6g of β-glucans or bread similar to barley without the same amount of β-glucans for 4 weeks. After the dietary intervention, total plasma cholesterol decreased in the test group (-0.26 ± 0.54, p = 0.019), but not in the control group. The composition of short-chain fatty acids (SCFA) in faeces changed significantly with the increase in propionic acid in the group that consumed barley bread (43.2%, p = 0.045) and with the decrease in acetic acid in the control group (41.8. %, p = 0.011) [27] (Table 3).

Junki Miyamoto conducted a study with mice, in which he showed that a diet high in barley β-glucans decreases glucose, weight and appetite as they increased the levels of plasma peptide YY and glucagon-like peptide-1. Likewise, modifications were found in the composition of the microbiota. It should be noted that the effects of barley on the gastrointestinal tract have not been properly examined. It is necessary to carry out intervention studies that show the modifications that this cereal causes within the gut microbiota when consumed frequently [28] (Table 3).

## Barley and Hordenine

Barley possesses a phenylethylamine alkaloid called Hordenine, known as N, N-dimethyl-4-hydroxyphenylethylamine, or C10H15NO. It is a phenethylamine alkaloid found in several plants such as cactus and bitter orange.[29] Lovett., *et al.* demonstrated that hordenine is biosynthesized by the gradual N-methylation of tyramine, which is first converted to N-methyltyramine, and then methylated into hordenine [29].

Mann., *et al.* through laboratory culture of barley seeds, showed that hordenine concentrations reach their maximum within 3 to 9 days of germination and decrease slowly until only traces remain after 1 month in the roots of the barley [30]. It has been reported that hordenine has several effects, including the inhibition of monoamine oxidase B (MAO-B) [31], stimulation of gastrin release in rats, antibacterial and antibiotic properties [32]. Likewise, Hordenine exerts a positive effect on our mood and feeling of happiness, as it stimulates dopaminergic receptors and weight loss, according to the study conducted by Yokoo Y., *et al.* [33].

In the study by Sang-Cheol Kim., *et al*. the effects of hordenine on melanogenesis and its mechanism in human melanocytes were investigated. A culture of the human epidermal melanocytes was carried out at 37°C in a humidified atmosphere with 5% CO2 and 95% air. Human melanocytes were incubated with hordenine (0.5-100 μM), un-germinated barley and germinated barley extract (0-100 μg/ml) for 5 days. This revealed that the hordenine contained in the barley had an inhibitory effect on melanin, and on other

| Reference | Study Design | Country | Disease | Subjects | Duration | Type of product | Dose of Barley | CHOL | Glucose | Weight | Wrist | Short Chain Fatty Acids (SCFA) | Microbiota | Bile Acids | Insulin Sensitivity / Gut Hormones | Other Results |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Ana Velikonja,et al. (2018) (27)** | Randomised, controlled, parallel, double-blind | Republic of Slovenia | Metabolic Syndrome | n=43 | 4 Weeks | Barley bread with or withouth β-glucans | 6 gr. | **EG**=−0.26 ± 0.54 p=0.019 | | **EG**:−0.89 ± 1.32 (p= 0.002), GC:-0,96±1,76 (p=0.038) | EG:- 0,43 ± 0,72 (p=0.005) | **EG**: propionic acid 43,2% (p=0.045), **CG**: acetic acid 41.8% (p=0.011) | **EG**: ↓ Clostridioum leptum cells | | | |
| **Thandapilly et al. (2018) (46)** | Phase IV Randomised controlled, crossover trial. | Canada | Hypercholesterolemia | n=30 | 5 Weeks | Barley β-glucans | **Group A**:3 g (HMW) **Group B:** *5 (LMW) **Group C**:3 g LMW | | | | | | | ↑ Lithocholic acid (LCA) excretion (P <0.001) when consuming 3 g of barley HMW β-glucan per day. | | |
| **Sandberg J, et al . (2018) (47)** | Randomised crontrolled crossover study | Sweden | Metabolic disorders or food allergies. | n=99 | 3 days | Barley bread and wheat bread. | 85% barley grains (Finax) and 15% white wheat flour. | | ↓ Blood glucose response | | | | | | **HP Group** : ↑Plasma peptide YY (PYY), **HPB Group**: ↑ glucagon peptide 1 (GLP-1 and GLP-2). | |
| **Sang-Cheol Kim.,et al. (2013) (29)** | Experimental study | Republic of Korea | Melanogenesis in human melanocytes | *** | 2 weeks | Barley germination | | | | | | | | | | ↓ Melanin and the MITF protein, tyrosinase, TRYP-1 and TRYP-2. ↓ cAMP production |
| **Anthony R. Bird., et al. (2008) (51)** | Comparative study, Randomised crossover design. | Australia | Bowel | n=17 | 4 weeks | Bread, cookies, muffins. | 45, 32 y 21 g/d | | | | | ↑ 57% fecal SCFA | ↑ 33% | | | |
| **Hiroshi Ashigai., et al .(2018) (49)** | Randomised, controlled, parallel, double-blind | Japan | Circulatory System | n= 48 Humans n= 30 Rats | *** | Roasted barley extract in Japanese beverage | 100 gr- 250 gr | | | | | | | | | ↑ Blood flow in rat tail. ↑ NO in endothelium ↑ Skin temperature |
| **Junki Miyamoto., et al . (2018) (28)** | Experimental study | Japan | Metabolism | n= 13 mice | 12 weeks | Barley Flour | 20% barley flour that contained high levels of BG. * HBG; 2% BG * LBG; 0.6% BG | | ↓ Mice with HBG diet | ↓ Mice with HBG diet | | | Mice with diet HBG and LBG: ↑ Actinobacteria (Bifidobacterium). ↑ Fecal acetate (Propionate and butyrate) | | ↑ Peptide YY (PYY) ↑ Glucagon peptide 1 (GLP-1) | |
| **Teixeira C., et al .(2018) (48)** | Experimental Study | Sweden | Microbiota and metabolic functions. | n= 56 | 12 days | Malt products and barley extracts | 96 y 527 g kg -1 | | | | | | ↑ Acetic acid, butyric acid and propionic acid ↑ Lactobacillus, blautia, allobaculum, Ruminococcaceae (15% vs <7%, p <0.05) | | | |
| **Ghaffarzadegan T., et al . (2018) (52)** | Experimental study | Sweden | Bile acids | Rats | 25 days | Barley flour | 13 to 80 g / kg | | | | | | | ↑ BA in low-fat diets with more betaglucans. (P <0.05) ↑ BA in groups with diets rich in fat (p <0.05) | | |
| **Mikkelsen MS., et al. (2017) (50)** | Experimental study | Denmark | Hypercholesterolemia | Rats | 7 weeks | Barley Beta glucans. | 100 kg/d to 530 kg/d | | | | | ↑ fecal SCFA. | ↑Bifidobacterium. ↓Bacteroides / Prevotella y Lactobacillus. | | | |
| **Choi JS., et al. (2010) (38)** | Experimental study | Korea | Fatty liver disease and insulin resistance | Mice | 12 days | Barley Beta glucans. | 2 or 4% of BG | ↑ Expression of cholesterol 7α-hydroxylase gene | 4% BG improves glucose tolerance | | | ↓ Fatty acid synthase | | ↓ Liver lipids | ↓ Insuline resitance index and Glucose-dependent insulinotropic polypeptide. | |

**Table 3:** Effects of barley intake on Cholesterol, Glucose, Weight, Short Chain Fatty Acids, Microbiota, Bile acids, Insuline Sensitivity, Gut Hormones and other results in randomized controlled clinical trials and experimental studies.

EG: Experimental Group , CG: Control Group, HMW: High Molecular Weight, LMW: Low Molecular Weight, HBG: High in Beta-glucans , LBG: Low in Beta-glucans , HP: High in Prevotella , HPB: High in Prevotella and Bacteriodes , cAMP: Cyclic adenosine monophosphate, BA: Bile Acid , TRYP: tyrosinase related protein , NO: Nitric Oxide, g: Grams, g/d: Grams per día, Kg: Kilograms , --- : Not found.

components that are directly related to melanogenesis. Suggesting that hordenine may be an effective inhibitor of hyperpigmentation [29].

## Barley and liver

The liver is the organ responsible for synthesizing cholesterol and is essential for the formation of bile acids (BA), steroid hormones and vitamin D, it is involved in the regulation of metabolism and energy expenditure. Cholesterol enters the body through food of animal origin, binds to LDL and enters cells through endocytosis [34]. Bile acids are efficiently reabsorbed from the intestine into the liver and only 5-20% of these bile acids are excreted through the faeces. When larger amounts of bile acids are lost, a certain amount of these must be produced in the liver [35] to lower the level of cholesterol in the blood. The structure of insoluble dietary fibre contained in barley allows it to bind bile acids and lower cholesterol levels (Figure 2).

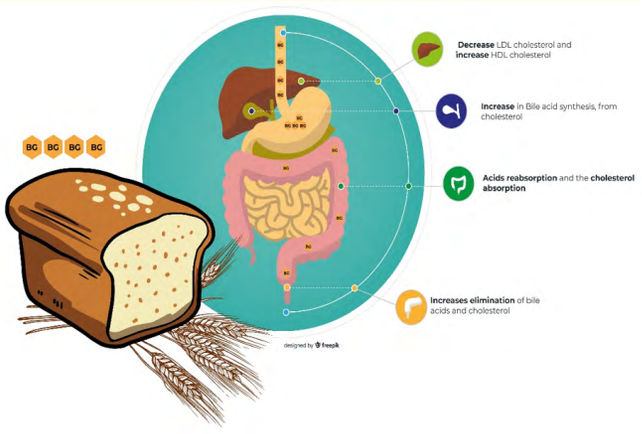


**Figure 2:** Effect of B-glucans from barley in liver, gallbladder, bile ducts and colon.

Shen Y., *et al*. demonstrated the effect of polyphenols extracted from black barley *In vitro* and *In vivo* in mice given 600 mg/kg of body weight, showing a significant decrease in total cholesterol, low density lipoprotein cholesterol and the index of atherosclerosis, in addition to markedly high the high-density lipoprotein cholesterol levels ($p = <0.05$). Additionally, in their study they demonstrate the potential antioxidant effect of barley, as the polyphenols extracted from this cereal have a strong superoxide radical, a hydroxyl radical and a radical uptake activity of 2,2-diphenyl-1-picrylhydrazyl, with power ferric reducing antioxidant and moderate activity of ion chelation [36].

A potential target for dietary interventions in metabolic disorders is AMP-activated protein kinase (AMPK), which is the cellular sensor of energy metabolism and regulates the metabolism of cholesterol, glucose and hepatic lipid metabolism. Ji Hae Lee., *et al*. investigated the mechanism of barley shoot extract (BS), on the metabolism of cholesterol and glucose. In their study the mice were administered BS extract orally (4.8 mg/kg/day). After 12 weeks of feeding, the liver and adipose tissues were obtained, as well as the plasma. The BS extract reduced intracellular cholesterol concentrations and plasma cholesterol concentrations in the mice by activating AMPK and the subsequent inhibition of HMGCR phosphorylation. The activation of AMPK with BS reduced the concentrations of fasting glucose, hepatic triglycerides and in the prevention of developing fatty liver in mice [37].

It has been shown that the consumption of a diet high in barley prevents insulin resistance, as mentioned by Choi JS., *et al*. They investigated the mechanism of the effects of barley β-glucans in three groups of mice that were fed high-fat diets containing 0, 2 or 4% barley β-glucans, for 12 weeks. The groups with 2% β-glucans and 4% β-glucans had significantly lower body weights compared to the 0% β-glucans group. The group with 4% β-glucans showed better glucose tolerance and lower levels of insulin resistance index and insulin-dependent glucose-dependent polypeptide. Diet consumption of β-glucans decreased the content of hepatic lipids, showed a decrease in fatty acid synthase and an increase in the expression levels of the cholesterol alpha-hydroxylase gene. The consumption of barley β-glucans increases hepatic insulin signalling by decreasing serine phosphorylation of insulin receptor substrate 1 and Akt activation, and decreased levels of glucose-6-phosphatase and phosphoenolpyruvate carboxykinase mRNA levels [38] (Table 3).

## Barley and Cardiovascular System

The three leading causes of death for both men and women in Mexico are heart disease, diabetes mellitus and malignant tumours [39]. Only coronary heart disease, stroke and hypertension affect more than 80 million people. Although cardiovascular diseases are the most frequent cause of death, it is probably the most modifiable, since 82% is attributed to lifestyle practices such as diet, physical activity and 19 to 60% is attributed to the dietary patterns [40]. Prospective cohort studies documented that high levels of fibre intake, especially the consumption of grains such as barley, are associated with a decrease in the prevalence of cardiovascular diseases by up to 29% [41].

The dietary fibre of barley contributes significantly to health; however, there is sufficient evidence that the phytochemicals contained in this cereal also play important roles in preventing the development of cardiovascular diseases [33]. Lee., *et al*. reported that barley shoot extract containing polyphenols regulated the AMP-activated protein kinase. Barley shoot extract containing 19.65 mg/g of the total polyphenol concentration reduced the total and free intracellular cholesterol concentrations of a 24% to 18% respectively [37].

Another of the main risk factors for the development of cardiovascular diseases is hypercholesterolemia. Among the treatments accepted for this pathology are statins [42,43]. However, there is a need to identify lipid-lowering agents such as β-glucans contained in barley which, in combination with statins, help to potentiate the effect of the drugs. Kashif Ghafoor showed an economic and easily reproducible method for the recovery of phenolic compounds from barley seeds, to obtain the maximum amount of phenolic and

improve the antioxidant properties, allowing its later use in nutraceuticals and functional foods, contributing with the existing drugs for diseases that directly affect the heart [44-47].

According to the Food and Drug Administration (FDA), the European Food Safety Agency (EFSA) and various authors, the daily consumption of 3 g of β-glucans in barley (1 → 3) and (1 → 4) can reduce cholesterol levels and the risk of cardiovascular disease [48-50]. Even with these evidences, few clinical studies have been conducted regarding barley and its relationship with cardiovascular diseases. Although the level of barley intake is associated w a reduced risk of cardiovascular disease and a lipid-lowering effect [51,52]. Controlled clinical trials are required to provide guidelir for the use of barley in the prevention and treatment of differe pathologies.

## Conclusion

Barley is a cereal with the potential to benefit various systems that make up the human body. The β-glucans and phytochemica which contain barley, have anti-inflammatory, antioxidant activ and help regulate the immune system. It can also lower LDL chol terol, while increasing HDL cholesterol levels. However, since stu ies on the effects of barley on health are limited, it is worthwhile continue researching the efficacy, safety and underlying molecu mechanisms of barley in humans, promoting the use of barley a Functional food and coadjuvant in the treatment of different chro ic-degenerative diseases. Currently products made with barley are not easily accessible for the Mexican population, coupled with the lack of information about this cereal makes it difficult to recommend its consumption in a diet. In Mexico, we are initiating clini projects with daily consumer products such as bread, tamales and tortillas made from barley with the aim of increasing the consun tion of this cereal and, at the same time, obtaining the benefits brings to health.

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## Conflict of Interest

There is no conflict of interest

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