(Hard Copy)
E-ISSN : 2456-1045

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RESEARCH JOURNAL

VOLUME - 47 | ISSUE - 1

ADVANCE RESEARCH JOURNAL OF MULTIDISCIPLINARY DISCOVERIES

MARCH 2020

INTERNATIONAL JOURNAL FOUNDATION
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The Hypercholesterolemia activity of common (*Fagopyrum esculentum*) buckwheat

ORIGINAL RESEARCH ARTICLE

ISSN : 2456-1045 (Online)
ICV Impact Value: 72.30
GIF- Impact Factor: 5.188
IPI Impact Factor: 3.54
Publishing Copyright @ International Journal Foundation
Article Code: MDS-V47-I1-C4-MAR-2020
Category : MEDICAL SCIENCE
Volume : 47.0 (MARCH-2020)
Issue: 1(One)
Chapter : 4 (Four)
Page : 17-24
Journal URL: www.journalresearchijf.com
Paper Received: 28.04.2020
Paper Accepted: 09.05.2020
Date of Publication: 25-05-2020

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CITATION OF THE ARTICLE

Raghavendra Rao M.V; Verma M.K; Khan A.A; Ponnusamy K; Rao S; Leon T.C; Bhat S; Igman P; Mathai D. (2020) The Hypercholesterolemia activity of common (*Fagopyrum esculentum*) buckwheat; *Advance Research Journal of Multidisciplinary Discoveries;* 47(2) pp. 17-24

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ABSTRACT

Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality across the globe, accounting for approximately one-third of all deaths. [1] High blood pressure, elevated total cholesterol and low density lipoprotein cholesterol (LDL-cholesterol), and low levels of high density lipoprotein cholesterol (HDL-cholesterol) concentrations are clinically considered as major CVD risk factors [2]. There are increasing epidemiological studies suggesting that diets rich in whole grains are linked to a lower risk of CVD and mortality. In recent years, there has been an increasing interest in the use buckwheat for its nutritional value and its effects on the cardiovascular system. Common buckwheat and Tartary buckwheat are among the top nine species with agriculture significance and are the most widely grown species in the world [3]. Buckwheat is a plant used for many purposes, such as consumed as a food and used in the treatment of diseases. It is a good source of many vitamins and minerals and has balanced nutritional value. Because of its nutrient content and many positive effects on human health, buckwheat has become a functional food, recently. Main effects of buckwheat on human health are its hypotensive, hypoglycemic, hypocholesterolemic, neuroprotective and antioxidant effects. Thus, it is considered an alternative food component in dietary treatment for chronic and metabolic diseases, such as diabetes, hypertension and celiac disease. Also, its rich nutrient content supports daily diet and provides a better eating profile. As a result, buckwheat is accepted as a functional food, suggested to improve human health and is used in the treatment of diseases.

Besides the high starch content of energy source, it is rich in nutritionally valuable protein with a well-balanced amino acid profile, dietary fiber, lipids and minerals (manganese, copper, magnesium, iron, phosphorus), along with other health-promoting components such as phenolic compounds and sterols, which have attracted growing attention to buckwheat as a potential functional food [4]. The aim of this review is to explain some positive affects of buckwheat on human health [5] The body needs both HDL (high-density lipoprotein) and LDL cholesterol. LDL cholesterol is the basis for hormone production. Cholesterol undergoes a chemical conversion into the hormone pregnenolone followed by many other steps where it becomes testosterone and finally estradiol (estrogen). Without enough cholesterol, you would likely suffer multiple hormone deficiencies. Note: a more broad explanation of the importance of cholesterol. Cholesterol is a lipophilic molecule that contributes to many functions of the cell as well a precursor molecule. Cholesterol is an important component of the cell membrane with the role of maintaining the structural makeup and modulates the fluidity of the membrane. Is the precursor for the endogenous synthesis of vitamin D, steroid hormones (aldosterone, cortisol, and androgens in the adrenal cortex) and sex hormones (testosterone, estrogens, and progesterone in the gonads). [6] Cholesterol is also part of bile salts, needed for the facilitated absorption of fat-soluble vitamins (Vitamins A, D, E, and K) and fats from the diet. Cholesterol is transported through the blood with triglycerides inside lipoprotein particles (Chilomicrones, HDL, LDL, VLDL, IDL) [7]. HDL cholesterol is responsible for seeking out excess LDL cholesterol and taking it away from the arteries. If you have high LDL cholesterol levels, you are at an increased risk of developing atherosclerosis – hardening of the arteries due to clogging (plaque) from LDL cholesterol.

Lipoproteins core structure is made up of cholesterol esters and triglicerides, and the outer hydrophilic membrane of phospholipids, apoproteins, and free cholesterol; this allows the structure to move around the body and to be transported to cells that require them. LDL particles are thought to act as a major transporter of cholesterol, at least two-thirds of circulating cholesterol resides in LDL, to the peripheral tissues. Conversely, HDL molecules are thought to do the opposite, taking the excess cholesterol and return it into the liver for excretion. Clinically, high LDL and low HDL increase the risk for CVDs such as atherosclerosis vascular diseases [8], [9]. GH treatment reduces plasma LDL cholesterol by inducing LDL clearance. In humans, LDLR expression is a prerequisite for this effect, whereas it is not related to stimulation of bile acid synthesis [10].

High density lipoprotein removes tissue cholesterol and helps its transport. Cholesterol ester present in HDL cholesterol is transferred and incorporated in to VLDL and LDL cholesterol. Hence high HDL-cholesterol level reflects protective action on the animals because of its scavenging action. According to the NHLBI, your risk for heart disease and other health problems, such as diabetes, increases if you have an HDL cholesterol level of 40 milligrams per deciliter (mg/dL) or less for men and 50 mg/dL or less for women. The institute recommends that total daily cholesterol intake be less than 200 mg/dL, and that LDL cholesterol be less than 100 mg/dL. The association of high cholesterol and triglicerides in blood increases the risk for CVD. Observational studies on population have demonstrated that high levels of LDL cholesterol and apolipoprotein B (apoB) 100, are directly associated with risk for atherosclerotic cardiovascular events (ASCVE). Infiltration and the retention of apoB in the vascular wall initiates an inflammatory response and the promotion and development of atherosclerosis. An unresolved inflammation of the artery wall results of vulnerable [11], [12].

An unresolved of the wall vessel inflammation results in necrotic cell death leading to an increased smooth muscle cell death, decreased extracellular matrix production, and collagen degradation by the protease of the macrophages. The rupture of the weak thinning fibrous cap will promote the formation of thrombus and eventually resulting in the clinical ischemic ASCVE [13]. Atherosclerotic plaque can break free from arterial walls or rupture and cause blood clots that can impede blood flow to the brain or heart. The result from this would be a stroke or heart attack. High fat content in diet increased blood cholesterol in rabbits. Along with high fat diet if some spices are also ingested, they are likely to influence blood cholesterol levels. This hike in blood cholesterol level is important in the development of atherosclerosis. Cholesterol is present not only in the free form in the blood but remarkable amount of cholesterol is transported as a component of different lipoproteins.

KEYWORDS: Cardiovascular diseases, lipoprotein cholesterol, buckwheat, lipoprotein particles, Atherosclerotic plaque

I. INTRODUCTION

Buckwheat is introduced into the diet as an alternative crop of renewed interest due to its nutritive and health- promoting value. Experiments with animal models have demonstrated that buckwheat flour may alleviate diabetes, obesity, hypertension, and hypercholesterolemia [14] "Bad" saturated fat and trans fat raise the dangerous low-density lipoprotein (LDL) cholesterol that can lead to plaque buildup in the arteries. "Good" unsaturated fat helps lower LDL cholesterol and raise beneficial high-density lipoprotein (HDL) cholesterol, which can remove LDL cholesterol and help keep arteries clear [15] According to the lipid hypothesis, elevated levels of cholesterol in the blood lead to atherosclerosis which may increase the risk of heart attack, stroke, and peripheral artery disease. Since higher blood LDL – especially higher LDL concentrations and smaller LDL particle size – contributes to this process more than the cholesterol content of the HDL particles [16] LDL particles are often termed "bad cholesterol". High concentrations of functional HDL, which can remove cholesterol from cells and atheromas, offer protection and are commonly referred to as "good cholesterol". These balances are mostly genetically determined, but can be changed by body composition, medications, diet, and other factors. [17], [18].

A 2007 study demonstrated that blood total cholesterol levels have an exponential effect on cardiovascular and total mortality, with the association more pronounced in younger subjects. Because cardiovascular disease is relatively rare in the younger population, the impact of high cholesterol on health is larger in older people. [19] Elevated levels of the lipoprotein fractions, LDL, IDL and VLDL, rather than the total cholesterol level, correlate with the extent and progress of atherosclerosis [20] Conversely, the total cholesterol can be within normal limits, yet be made up primarily of small LDL and small HDL particles, under which conditions atheroma growth rates are high. A *post hoc* analysis of the IDEAL and the EPIC prospective studies found an association between high levels of HDL cholesterol (adjusted for apolipoprotein A-I and apolipoprotein B) and increased risk of cardiovascular disease, casting doubt on the cardio protective role of "good cholesterol [21], [22] . One in 250 adults can have a genetic mutation for the LDL cholesterol receptor that causes them to have familial hypercholerolemia. Inherited high cholesterol can also include genetic mutations in the PCSK9 gene and the gene for Apolipoprotein B [23] cardiovascular disease is one of the leading causes of death and disability in the world. Atherosclerosis, characterized by lipid accumulation and chronic inflammation in the vessel wall, is the main feature of cardiovascular disease. Although the amounts of fruits and vegetables present in the diets vary by country, diets, worldwide, contain large amounts of spices; this may have positive or negative effects on the initiation and development of atherosclerosis. Mutations of the protein convertase subtilisin-like/Kevin type 9 (PCSK9) are associated with hypercholesterolemia with increase risk of CVD or hypocholesterolemia, with a decrease risk of CVD. Patients harboring gain-of-function PCSK9 mutations will suffer from familial autosomal dominant hypercholesterolemia, with elevated LDL-C plasma concentrations. PCSK9 has become a promising therapeutically target. [24]

The author explains the potential protective effects of specific nutrients from spices, such as pepper, ginger, garlic, onion, cinnamon and chili, in atherosclerosis and atherosclerotic cardiovascular disease [12] Cardiovascular disease (CVD) is one of the leading causes of death worldwide, which may include coronary artery disease, acute myocardial infarction, peripheral arterial disease and stroke. The prevalence of CVD is estimated to increase from 36.9% to 40.5% from 2010 to 2030 in the United States, and the associated medical cost will increase by 200% [13]. Previous research has shown that Tartary buckwheat flour is capable of reducing plasma cholesterol [14] A multi-centre clinical trial in Spain showed that the intake of a Mediterranean diet with extra-virgin olive oil or nuts lowered the risk of CVD events compared to a conventional low-fat diet in participants who had a high CVD risk [15] Compared with that of wheat and rice flours, supplementation of Tartary buckwheat flour into diet led to greater neutral sterol excretion and lesser mRNA of intestinal Niemann-Pick C1 Like 1 (NPC1L1) and acyl-CoA: cholesterol acyltransferase 2 (ACAT2). It was therefore concluded that Tartary buckwheat flour was hypocholesterolemic via inhibition of cholesterol absorption, most likely mediated by down-regulation of intestinal NPC1L1 and ACAT2. [25].

Around 80% of garlic, which is native to Central Asia, is cultivated in China. Garlic is essential in Middle Eastern and Asian cooking. In folk medicine, garlic is used to treat conditions of the digestive system and respiratory system, as well as the flu. It also offers antioxidative effects in rat models However, a systemic review indicated that there is insufficient evidence to support the effects of garlic on cardiovascular mortality and morbidity in hypertensive patients [26] Garlic repressed neointima formation and the accumulation of cholesterol, triglycerides and phospholipids in cholesterol-fed rabbits [27] Hypertension, hyperlipidemia, and diabetes are important precursors of cardiovascular disease. Here, we evaluated the antihypertensive, antihyperlipidemic, and antidiabetic potential of five types of sprouts in fructose-loaded spontaneously hypertensive rats (SHRs). Powdered sprouts (PSs) were produced from mung bean, broccoli, radish, and buckwheat sprouts and germinated soybeans by lyophilization [28].

Buckwheat (BW) is a gluten-free pseudo-cereal, that belongs to the Polygonaceae family. BW grain is a highly nutritional food component that has been shown to provide a wide range of beneficial effects. Health benefits attributed to BW include plasma cholesterol level reduction, neuroprotection, anticancer, anti-inflammatory, antidiabetic effects, and improvement of hypertension conditions. In addition, BW has been reported to possess prebiotic and antioxidant activities [29] Fagopyrum esculentum Moench. A lot of research has be conducted in the functionalities and properties of buckwheat proteins, flavonoids, flavones, phytosterols, thiamin-binding proteins, and other rare compounds in buckwheat seeds. Buckwheat proteins have unique amino acid composition with special biological activities of cholesterol-lowering effects. [30]

Animal models of atherosclerosis

An ideal animal model of atherosclerosis resembles human anatomy and pathophysiology and has the potential to be used in medical and pharmaceutical research to obtain results that can be extrapolated to human medicine. Moreover, it must be easy to acquire, can be maintained at a reasonable cost, is easy to handle and shares the topography of the lesions with humans. In a meta-analysis review have shown that nineteen animal studies only four of then showed a significant decrease of body weight following buckwheat consumption and one showed an increased of body weight in comparison to control. Three out of seven showed a significant reduction of glucose concentration, with the remaining showed that the glucose levels were unaffected with buckwheat consumption. Lastly twenty-one animal studies all reported a significant reduction of total cholesterol and five with a significant reduction of LDL cholesterol. Twenty studies reported a decrease in serum concentrations of triglycerides [31]. In general, animal models of atherosclerosis are based on accelerated plaque formation due to a cholesterol-rich/Western-type diet, manipulation of genes involved in the cholesterol metabolism, and the introduction of additional risk factors for atherosclerosis. Mouse and rabbit models have been mostly used, followed by pigs and non-human primates. Each of these models has its advantages and limitations. [32]

Cholesterol rich western type diet (Hypercholesterolemia)

The effect in rabbits of giving isonitrogenous purified diets containing casein, ovalbumin, fish protein, milk-whey protein and soya-bean protein were compared. The diets were balanced for cholesterol and for the amount and type of fat. When incorporated into low-cholesterol diets (0.08 g cholesterol/kg), casein, ovalbumin and soya-bean protein produced similar levels of serum cholesterol. With a high background of dietary cholesterol (1.5 g/kg), serum cholesterol concentrations increased with soya-bean protein, whey protein, casein and fish protein, in that order. Thus, the hypercholesterolaemic effect of casein in carefully balanced diets was only seen against a high-cholesterol background. The development of Hypercholesterolaemia produced by giving fish protein was different from that produced by casein. First, less cholesterol accumulated in the very-low-density-lipoprotein fractions and more in the lipoproteins of higher density with fish protein than with casein. [33]

Cholesterol low Indigenous *Diet (Hypocholesterolaemia)*

Buckwheat grain has well-balanced nutritional value, whereas its digestibility is relatively low. This review summarizes recent advances in studies on the hypolipidemic activity of buckwheat. The most remarkable function is a powerful hypocholesterolemic activity of buckwheat protein in rats, which is far stronger than that of soy protein. The cholesterol-lowering effect is mediated by mechanisms involving higher excretion of fecal sterols and lower digestibility of buckwheat protein. The insoluble fraction of buckwheat protein associates with cholesterol and reduces micelle cholesterol uptake in caco-2 cells. Furthermore, consumption of buckwheat protein suppresses cholesterol-induced gallstones and body fat in rodents. Buckwheat sprouts also have hypolipidemic activity in rats or type 2 diabetic mice. Tartary buckwheat bran extract reduced the serum level of total cholesterol and triglyceride in hyperlipidemic rats. The consumption of buckwheat seed reduced low-density lipoprotein cholesterol in the pastureland Mongolian population. [34] Cholesterol rich western type diet are said to be hypercholesterolic agents and therefore useful for development of experimental atherosclerosis.

Buckwheat therapeutically tried to high cholesterol levels in patients. Hence in the evaluation of total diet induced blood cholesterol level, It is important to study the effect of hypercholesterosis and hypo cholesterosis agents given together simultaneously. Since 1000BC, buckwheat has been cultivated globally, but mainly in Russia and China as a traditional food. In recent years, changes to the traditional diets in China, have shown a dramatic decrease in the amount of whole grains that may be a contributory factor of the rise of CVD mortality in the country. [35]- [37]

II. MATERIALS AND METHODS

Rabbits were divided in to three groups. Each group consists of five numbers of rabbits. Control group was fed with cholesterol 0.5 g/Kg.per day). Test group without protection, was given Cholesterol rich

western type diet (0.5g/Kg/per day) and cholesterol. While test group with protection received Buckwheat (0.5g/Kg/per day) besides cholesterol and cholesterol rich western type diet. In addition all the groups of rabbits are given common calorigenic diet. One month later, blood samples were taken from the animals of these groups. Their total cholesterol (Zak's method 1957) and HDL cholesterol Barstein and Samaille 1960) were determined. [38]

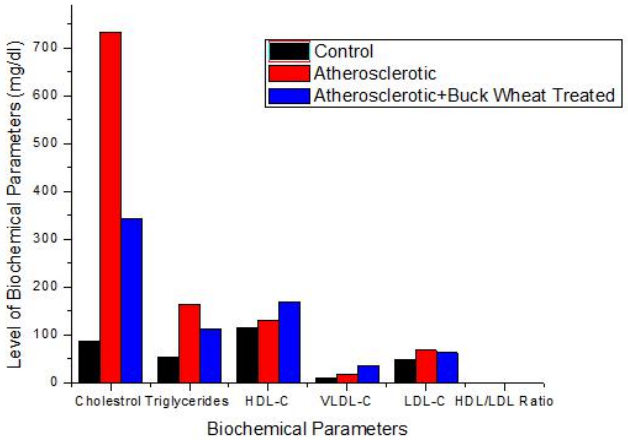
III. RESULTS

In a controlled study using three set of experiment the effect of Buckwheat on biochemical parameters are shown in table 1 and interpretation in figure 1. As result shown in table 1 group 2 and group 3 reported a significant change in biochemical parameters compare to control study. The level of HDL (129.82±12.80 to 167.50±13.45 mg/dl) and VLDL (17.65±6.71 to 34.54±7.40 mg/dl) increased in group 2 and group 3 compare to control study. Further study also reports a significant reduction in cholesterol (733±211 to 342±125 mg/dl) and triglycerides level (164.30±12.70 to 113±9.75 mg/dl) in group 2 and group 3 compare to control study. The plasma level of LDL-C reported reduced in group 3 over group 2 where animal were fed with Buckwheat (group 2). The LDL/HDL ratio was also determined and reported a mild change in group 3 and group 2 compare to control study.

Table 1. Levels of serum cholesterol, LDL-C, VLDL-C, HDL-C and LDL/HDL ratio in normal and experimental animals. Values are expressed as (mg/dl) mean ±SD. For statistical evaluation of significant variations, Group I was compared with Group II; and Group II was compared with Group III. Statistical significant alterations were statistically significant at **p<001., and ***p<0.001.

No	Parameters	Group 1 Control	Group 2 Atherosclerotic	Group 3 Atherosclerotic+Buck Wheat Treated
1	Cholesterol	86±27	733±211***	342±125***
2	Triglycerides	50.63±6.16	164.30±12.70** *	113±9.75***
3	HDL-C	115.70±32.40	129.82±12.80**	167.50±13.45** *
4	VLDL-C	10.14±1.24	17.65±6.71***	34.54±7.40***
5	LDL-C	47.81±7.07	67.34±6.47***	62.64±5.72**
6	LDL/HDL ratio	0.41± 0.21	0.51±0.50**	0.37±0.42***

Figure 1. Levels of serum cholesterol, LDL-C, VLDL-C, HDL-C and LDL/HDL ratio in normal and experimental animals



IV. DISCUSSION

High fat diet alone is the causative factor for the raise in total cholesterol level, is the chief observations in the present study in contrast to the earlier observations made by the other group. [39] The present study correlates the study of Nan Yang et al (2014) [25]. Thirty-six male hamsters were divided into four groups fed either the control or one of three experimental diets containing 24% respective flour, for a period of 6 weeks. Results showed that Tartary buckwheat flour but no wheat and rice flours reduced plasma total cholesterol (TC) and non-high-density lipoprotein cholesterol (non-HDL) as well as hepatic cholesterol concentrations [40]-[42] Further raise in blood cholesterol by inclusion of cholesterol rich western type diet, is addition to high fat diet is found that Cholesterol rich western type diet induced atherosclerosis by reducing HDL cholesterol significantly and thereby making the animals more vulnerable. Buckwheat diet is more effective in counteracting the hypercholesterolemia effect of high fat diet. While Cholesterol rich western type diet feeding made animals susceptible by reducing their HDL cholesterol level, the Buckwheat diet significantly neutralized this action of cholesterol rich western type diet and confers a protective umbrella [43]-[44].

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