ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Evaluation of Hypolipedimic Activity of Ethanol Precipitated Cress Seed and Flaxseed Mucilage in Wister Albino Rats.

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ABSTRACT

Gums and mucilage have attracted much attention for their function as dietary fiber which is expected to lower serum cholesterol, glucose and lipid peroxidation, thus hypolipidemic activity of ethanol precipitated cress seed mucilage (CSM) and flaxseed mucilage (FSM) in hyperlipidemic rats was evaluated. Fifty adult male Wister albino rats were adapted on a commercial solid diet and tap water for one week and then divided into 5 groups and fed on (i) a commercial solid diet (control), (ii) high fat diet (HFD), (iii) HFD with daily oral administration of standard lipid-lowering pharmaceutical drug (ATOR®), (iv) HFD with daily oral administration FSM (40 mg/kg), and (v) HFD with daily oral administration CSM solution (40 mg/kg) for four weeks. Rats fed on HFD induced significant elevations in serum glucose, triglycerides (TGs), total cholesterol and LDL-cholesterol as well as lipid peroxidation end products (malondialdehyde, MDA) levels when compared with control group. Oral administration of hyperlipidemic rats with ATOR10®, FSM or CSM reduced the serum triglycerides, total cholesterol, LDL-cholesterol and hepatic MDA as compared to HFD group. Inversely, treatment of hyperlipidemic rats with ATOR10®, FSM or CSM exhibited marked improvement in both serum HDL and hepatic total antioxidant capacity. However, CSM solution performed a stronger dislipidemic potential than that of FSM.

Keywords: Flaxseed mucilage, Cress seed mucilage, Hypolipidemic activity

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ISSN: 0975-8585

INTRODUCTION

Mucilage is physiological products formed in the cell and without injury to the plant [1]. It is mainly found in the seeds and other part of plants such as roots, leaves, barks and middle lamella (1, 3]. Mucilage, translucent amorphous substances, is mixed monosaccharides which many of them are combined with uronic acids or on hydrolysis yield a mixture of sugars and uronic acids [4].

Cress seed (*Lepidium sativum*) contain large amounts of mucilaginous constituents when soaked in water and a transparent gel forms around the whole seed [5]. The major sugars of cress seed mucilage are mannose, arabinose, galacturonic acid, fructose, glucuronic acid, galactose, rhamnose, and glucose [6]. Flaxseed (*Linum usitatissimum* L.) mucilage consists of a mixture of neutral and acidic polysaccharides. Neutral polysaccharides of mucilage composed mainly of arabinose, xylose and galactose residues, while acidic polysaccharides, containing galactose, rhamnose, and galacturonic acid residues [7]. The used of mucilage in food products increased due to their functional properties (viscosity, gelation, water binding) as well as to their bio-active role in prevention or treatment of certain diseases such as antihyperglycaemic properties [8]. In addition, they are used in pharmaceutical industries as film forming agents, emulsifiers, suspending agents, stabilizing agents, gelling agents and thickening agents, as well as coating agents in microcapsules including those used for protein delivery.

Natural gums and mucilage are biocompatible, low cost and easily and available as well as non toxic as compared to semi synthetic and synthetic excipients [9, 10]. Furthermore, mucilage may prevent or reduce the risk of various important diseases, such as diabetes, lupus nephritis, arteriosclerosis, and hormone-dependent types of cancer [11]. The mucilage from crude flaxseed exhibited strong antioxidant activity [12] and reduce the total cholesterol in the plasma and arterosclerotic lesions after the incorporation of flaxseed mucilage and α-linolenic acid into diet [13]. Cress seed mucilage exhibited antimicrobial and antifungal activity [14, 15] as well as reduce of plasma glucose, total cholesterol, triglycerides, LDL- cholesterol and increase in HDL-cholesterol when rats administrated with 20 mg cress seed mucilage/kg as compared to control group [16]. Therefore, the aim of this work was to evaluate the hypolipedimic activity of ethanol precipitated cress seed and flaxseed mucilage in adult male Wister albino rats.

MATERIALS AND METHODS

Materials

Flaxseeds (*Linum usitatissimum*) and cress seeds (*Lepidium sativum*) were purchased from local market, Cairo, Egypt; with moisture content of 6.64 and 6.84%, respectively. Adult male Wister albino rats (*Rattus norvegicus*) weighting 100-120 g were purchased from Animal House, National Research Center, Cairo, Egypt.

Methods

Flaxseed or cress seed mucilage extraction

Flaxseed or cress seed (100 g) were washed in water for 1 min to remove the surface dust, and then mixed with 900 ml distilled water. The seeds and water were then stirred for 5 h at a speed of 300 rpm/min, in a 60°C water bath, according to the method of Cui [17]. The extracted mucilage solution was filtered through 40-mesh screen and precipitated with two volumes of 95% ethanol. The mucilage was separated by centrifugation (Sigma 301, Western Germany) at 3000 xg for 10 min. The precipitated mucilage was then dried in a hot air oven at 60°C overnight. The average composition of flaxseed and cress seed mucilage were 3.76 and 10.30% for moisture, 12.17 and 13.27% for proteins, and 6.97 and 9.78% for ash, respectively.

Experimental design

After animals were kept one week, on a commercial solid diet and tap water under environmentally controlled conditions (25±1°C and 55±5% humidity) with free access to food and water, and a 12/12 h dark/light cycle before starting the experiment; animals were divided into five groups (10 animals each) as illustrated below. Hyperlipidemic rats model was induced via feeding animals on a high fat diet (Formula:

83.6% basis diet, 1% cholesterol, 0.2% pig bile salt, 0.2% propylthiouracil, 12% lard, 3% yolk powder) for a four weeks as described by Wang [18].

Group I : Healthy animals fed on a commercial solid diet and acting as control.
Group II : Healthy animals subjected to a high fat diet for four weeks and acting as hyperlipidemic group.
Group III : Hyperlipidemic animals subjected to daily oral administration of standard lipid-lowering pharmaceutical drug (ATOR®, Egyptian International Pharmaceutical Industries Co. including Atrovastatin 10 mg) in a dose of 10 mg/kg body weight for four weeks.
Group IV : Hyperlipidemic animals' subjected to daily oral administration of flaxseed mucilage solution in a dose of 40 mg/kg body weight [19] for four weeks.
Group V : Hyperlipidemic animals subjected to daily oral administration of cress seeds mucilage solution in a dose of 40 mg/kg body weight [19] for four weeks.

Blood sampling

At the end of each studied group, after 12 h of fasting animals and diether anesthesia, blood specimens (3-7 ml) were withdrawn from the retro-orbital plexus using capillary sterile heparinized glass tube (single withdrawal vacutainer needle) into open vacutainer collecting tubes [20]. Blood specimens were left to clot then centrifuged at 3000 rpm for 20 min using centrifuge (IEC centra-4R, International Equipment Co., USA). The sera were separated at once, divided into aliquots and stored at -20°C for biochemical measurements that could be completed as soon as possible. All the biochemical measurements were carried out using UV-Visible spectrophotometer (Schimadzu spectrophotometer 1201, Japan).

Serum biochemical parameters

Serum glucose level was estimated according to the enzymatic colorimetric method described by Trinder [21]. Serum triglycerides and total cholesterol were determined according to the photometric system described by Artiss & Zak [22]. Serum LDL- and HDL- cholesterol concentration was determined according to the CHOP-PAP method by photometric system described by Wieland & Seidel [23] and Lopes-Virella *et al*. [24], respectively. Serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities were determined according to colorimetric method described by Reitman & Frankel [25]. Urea and creatinine were determined according to Larsen [26] and Fawcett & Scott [27], respectivley.

Liver tissue sampling

At the end of blood collection, all animals were rapidly sacrificed and the liver of each animal was dissected and washed with saline, dried, weighted and subjected to homogenization in 50 mM phosphate buffer (ice cold) solution (pH 7.4) to give 20% homogenate (w/v) [28]. The homogenate was centrifuged at 9000 rpm for 20 min to remove the nuclear and mitochondrial fractions. The supernatant was stored also at -70°C till the determination of lipid peroxidation end product. All the biochemical measurements were carried out using UV-Visible spectrophotometer (Schimadzu spectrophotometer 1201, Japan)**.**

Liver lipid peroxidation

The supernatant was used in the determination of lipid peroxidation end product; malondialdehyde (MDA) level in biological materials as described by Luiz-Larnea *et al*. [29] was based on its reaction with thiobarbituric acid (TBA) which forms a pink complex that can be measured photometrically at 535 nm.

Liver total antioxidant capacity (TAC)

Liver total antioxidant capacity (TCA) was determined based on the method of Koracevic *et al.* [30] using reagent kits obtained from Bio-diagnostic Co., Dokki, Giza, Egypt. The TCA was performed by the reaction of antioxidants in the sample with a defined amount of exogenous provide hydrogen peroxide. The antioxidants in the sample eliminate a certain amount of the provided hydrogen peroxide. The residual was determined colorimetrically by an enzymatic reaction which involves the conversion of 3, 5, dichloro-2-hydroxy benzensulphonate to a color product.

ISSN: 0975-8585

Percentage of change A

Percentage of change (A) was calculated from the mean of control group according to the following equation:

$$\text{Percentage of change (A)} = [M_t\text{-}M_c / M_c] \times 100$$

Where: M_t, arithmetic mean of treated groups; M_c, arithmetic mean of control group.

Percentage of change B

Percentage of change (B) was calculated from the mean value of hyperlipidemic group according to the following equation:

$$\text{Percentage of change (B)} = [M_t\text{-}M_c / M_c] \times 100$$

Where: M_t, arithmetic mean of treated groups; M_c, arithmetic mean of hyperlipidemic group**.**

Statistical analysis

Data were expressed as means ±SE. Statistical analysis was performed using the GLM procedure with SAS [31] software. Analysis of variance (ANOVA) and Duncan's multiple comparison procedure were used to compare the means. A probability of $P \leq 0.05$ was used to establish statistical significance**.**

RESULTS AND DISCUSSION

Serum glucose

Table 1 shows the serum level of glucose and its change percentage of high-fat diet (HFD) fed rats, and HFD fed rats with pharmaceutical lipid lowering drug (ATOR10®), flaxseed mucilage (FSM) or cress seed mucilage (CSM) as compared to control diet fed rats (CT). Rats fed on HFD and HFD with ATOR10® recorded a significant elevation ($P < 0.05$) in serum glucose (9.1 and 8.7%, respectively) when compared with those fed on normal diet. There was no significant difference in level of glucose found in rats fed on HFD with FSM or CSM and those fed on normal diet ($P > 0.05$). On the other hand, the serum level of glucose and its percentage change in rats fed on HFD with FSM or CSM was lower than those fed on HFD only, the difference was no significant ($P > 0.05$). However, the value of serum glucose of rats fed on HFD with FSM or CSM solution was higher slightly ($P > 0.05$) as compared to that fed on normal diet. A similar observation was found by Kumar *et al.* [32] in rats fed on standard diet with 20 mg/kg. The decrease in glucose level was also in consistent with the finding of Rafieian-Kopaei *et al.* [33]. The possible reason for the hypoglycemic effect can be attributed to the reduction in the carbohydrate absorption from the gut [34]. The beneficial effect of FSM and CSM may be due to some of the bioactive compounds present in the mucilage, including L-arabinose, D-xylose, D-galactose, L-rhamnose, L-fucose, D-glucose, mannose, D-galacturonic acid, and 4-O-methyl-D-glucuronic acid that may facilitate insulin secretion.

Table 1: Serum glucose level of male albino rats fed on high-fat diet and high-fat diet with ATOR10®, flaxseed mucilage or cress seed mucilage as compared to normal diet fed rats

Animals groups	Serum glucose		
	(mg/dl)	A (%)	B (%)
CT	73.9^{B} ±1.78		
HFD	80.6^{A} ±3.16	9.1	
HFD-ATOR10®	80.3^{A} ±1.92	8.7	-0.4
HFD-FSM	75.9^{AB}±1.78	2.7	-5.8
HFD-CSM	76.8^{AB}±2.13	3.9	-4.7

Means (±SE, n=10) with the same letters in the same row are not significantly different at $P \leq 0.05$.
CT, control group; FSM, flaxseed mucilage solution; CSM, cress seed mucilage solution; HFD, high fat diet fed rats; ATOR10®, standard drug ATOR10®.

ISSN: 0975-8585

Serum lipid profile

Serum lipid profile of HFD fed rats and HFD with ATOR10®, FSM or CSM as compared to the rats fed on normal diet is illustrated in Tables 2 and 3. HFD induced significant elevations ($P < 0.05$) in triglycerides (TGs), total serum cholesterol and LDL-cholesterol levels as compared to the control group. The change of percentage was 31.3, 24.7 and 52.1%, for TGs, total serum cholesterol and LDL-cholesterol levels, respectively. Also, rats fed on HFD with FSM was higher significantly ($P < 0.05$) than those fed on normal diet. Compared to rats fed on HFD alone, ATOR10® and CSM oral administration following HFD feeding recorded a significant decrease ($P < 0.05$) in total cholesterol, LDL-cholesterol and TGs. In particular, when the ATOR10® and CSM were given with HFD, there were a -19.0 & -13.8%, -30.8 & -24.3% and -19.0 & -13.8% decrease in total cholesterol, LDL-cholesterol and TGs, respectively. Rats fed diet high in fat with ATOR10® and CSM were close to normal control (Table 2 & 3). A similar, but less marked, when the FSM was given with HFD, there was a -9.0, -10.1 and -17.8% decrease in in TGs total serum cholesterol and LDL-cholesterol levels. In contrast, a significant decrease was found in HDL-cholesterol in rats fed on HFD when compared to normal group ones. Animals ingested ATOR10 ®, FSM or CSM showed a significant elevation (14.1, 9.8 and 17.9%, respectively) in the serum HDL-cholesterol when all were compared to those fed on HFD; however the highest potential was awarded to the CSM and the lowest was awarded to FSM. Such an effect has been reported by other researchers such as Rafieian-Kopaei *et al.* [33]; Chen *et al.* [35] and Ma *et al.* (36). Amawi & Aljamal [35] found that the percentage change in plasma total cholesterol (22%), TGs (25%), LDL-cholesterol (23) significantly decreased, but HDL-cholesterol significantly increased (32%) when rats administrated with 20 mg CSM/kg 32% in comparison to control group Paschos *et al.* [38] and Pellizzon *et al.* [39] suggested that flaxseed gum has ability to lower blood cholesterol levels *in vitro* and *in vivo* studies in animal models.

Table 2: Serum total cholesterol and triglycerides of male albino rats fed on high-fat diet and high-fat diet with ATOR10®, flaxseed mucilage or cress seed mucilage as compared to normal diet fed rats

Animals groups	Total cholesterol			Triglycerides		
	(mg/dl)	A (%)	B (%)	(g/dl)	A (%)	B (%)
CT	93.0^{C} ±3.15			86.3^{A} ±4.07		
HFD	116.0^{A} ±3.94	24.7		113.3^{B} ±4.60	31.3	
HFD-ATOR10®	94.0^{BC} ±3.15	1.07	-19.0	89.4^{A} ±3.55	3.6	-21.1
HFD-FSM	104.3^{B} ±3.49	12.1	-10.1	103.1^{B} ±5.25	19.5	-9.0
HFD-CSM	100^{BC} ±3.34	7.5	-13.8	94.3^{A} ±4.14	8.08	-16.7

Means (±SE, n=10) with the same letters in the same row are not significantly different at $P \leq 0.05$.
CT, control group; FSM, flaxseed mucilage solution; CSM, cress seed mucilage solution; HFD, high fat diet fed rats; ATOR10®, standard drug ATOR10®.

Different mechanisms could be involved in the hypolipidaemic effect of mucilage. The hypocholesterolaemic effect of mucilage could be attributed to mucilage, soluble fiber, induce alterations in intestinal absorption, and lipoprotein metabolism as well as improvement both pancreatic hormone and bile acid secretions [19, 40]. Anderson *et al.* [41] also reported that soluble fibers characterized with high water-holding capacity, *e.g.,* pectin, gums and mucilage, exhibited more effective in lowering serum total and LDL-cholesterol in both normal and with hyperlipidaemia subjects**.** Hypolipidaemic effect of soluble fibers related to the water holding capacity, for example, guar gum which has higher water holding capacity showed a significant cholesterol-lowering effect whereas hydrolysed guar gum did not show any significant cholesterol-lowering effect in man [42, 43].

Table 3: Serum LDL- and HDL-cholesterol of male albino rats fed on high-fat diet and high-fat diet with ATOR10®, flaxseed mucilage or cress seed mucilage as compared to normal diet fed rats

Animals groups	LDL-Cholesterol			HDL-Cholesterol		
	(mg/dl)	A (%)	B (%)	(mg/dl)	A (%)	B (%)
CT	44.3^{C} ± 3.36			31.5^{A} ± 0.47		
HFD	67.4^{A} ± 4.25	52.1		25.6^{D} ± 0.39	-18.7	
HFD-ATOR10®	46.6^{CB} ± 3.69	5.2	-30.8	29.2^{BC} ± 0.44	-7.3	14.1
HFD-FSM	55.4^{B} ± 3.80	25.2	-17.8	28.1^{C} ± 0.42	-10.8	9.8
HFD-CSM	51.0^{CB} ± 3.62	15.1	-24.3	30.2^{AB} ± 0.46	-1.0	17.9

Means (±SE, n=10) with the same letters in the same row are not significantly different at P ≤ 0.05.
CT, control group; FSM, flaxseed mucilage solution; CSM, cress seed mucilage solution; HFD, high fat diet fed rats; ATOR10®, standard drug ATOR10®.

In addition, fermentation of fiber can lead to an enhanced production of short chain fatty acids (SCFA), which suppress cholesterol synthesis in liver and intestine [44, 45]. In addition, butyrate has been shown to reduce lipid transport by inhibiting microsomal triacylglycerol transfer protein in Caco-2 cells and triacylglycerol-rich lipoprotein output [44]. Another mechanism, Buhman *et al.* [47] suggested that the dietary fibers may be increased excretion of cholesterol and bile acids in feces. In this respect, an inverse linear relationship was found between plasma cholesterol concentration and fecal excretion of bile acids [48].

Liver functions

Data in Table 4 pointed that there was no significant difference in both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity (P > 0.05), as a liver functions, in all animals groups, even if AST activity were numerically lower in rats fed on HFD with ATOR10® than other groups. These results referring to the safety of both mucilages (FSM and CSM) as no hepatotoxicity signs were noticed. A similar observation was found by Datta *et al.* (49) in male and female rats fed on 0.5 –5.0 g CSM/kg body weight for 14 weeks. Boban *et al.* [19] found that analysis of serum AST and ALT did not show any significant difference among control and mucilage-fed animals, indicating that the liver function of these animals has not been affected.

Table 4: Activities of serum liver aminotransferase enzymes of male albino rats fed on high-fat diet and high-fat diet with ATOR10®, flaxseed mucilage or cress seed mucilage as compared to normal diet fed rats

Animals groups	ALT			AST		
	(IU/ml)	A (%)	B (%)	(IU/ml)	A (%)	B (%)
CT	33.4^{A} ± 0.53			31.4^{A} ± 1.69		
HFD	33.0^{A} ± 0.52	-1.2		35.2^{A} ± 1.90	12.1	
HFD-ATOR10®	32.9^{A} ± 0.53	-1.5	-0.3	29.7^{A} ± 1.59	-5.4	-15.6
HFD-FSM	32.4^{A} ± 0.51	-3.0	-1.5	33.3^{A} ± 1.79	-6.0	-5.4
HFD-CSM	33.9^{A} ± 0.53	1.5	2.4	33.1^{A} ± 1.78	0.0	-6.0

Means (±SE, n=10) with the same letters in the same row are not significantly different at P ≤ 0.05.
ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CT, control group; FSM, flaxseed mucilage solution; CSM, cress seed mucilage solution; HFD, high fat diet fed rats; ATOR10®, standard drug ATOR10®.

Kidney functions

Rats fed HFD only or those treated with ATOR10® or FSM after feeding on HFD illustrated a non-significant changes in the serum levels of kidney function parameters, urea and creatinin, when compare to either normal or HFD fed animals (Table 5). When rats treated with CSM after feeding on HFD, significant reduction was found in serum urea level (P > 0.05), compared with both those fed on HFD and normal diet. In particular, there were a -11.2 and -13.5% decrease in serum urea level of rats treated with CSM compared with both those fed on normal diet and HFD alone, respectively. This notion confirms the safety of both FSM and CSM or their non-nephrotoxic effect. This result goes hand in hand with McKoy *et al.* [50] and Chen *et al.* [35].

Table 5. Levels of serum urea and creatinin of male albino rats fed high-fat diet and high-fat diet with ATOR10®, flaxseed mucilage or cress seed mucilage as compared to normal diet fed rats

Animals groups	Urea			Creatinin		
	(mg/dl)	A (%)	B (%)	(mg/dl)	A (%)	B (%)
CT	30.3^{A} ± 0.89			0.85^{A} ± 0.04		
HFD	31.1^{A} ± 0.93	3.9		0.91^{A} ± 0.03	7.0	
HFD-ATOR10®	31.8^{A} ± 0.84	5.3	2.3	0.84^{A} ± 0.04	-1.1	-8.2
HFD-FSM	30.9^{A} ± 0.91	2.0	.0.6	0.87^{A} ± 0.04	2.3	-4.4
HFD-CSM	26.9^{B} ± 0.79	-11.2	-13.5	0.86^{A} ± 0.03	1.1	-5.5

Means (±SE, n=10) with the same letters in the same row are not significantly different at P ≤ 0.05.
ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CT, control group; FSM, flaxseed mucilage solution; CSM, cress seed mucilage solution; HFD, high fat diet fed rats; ATOR10®, standard drug ATOR10®

Liver lipid peroxidation and total antioxidant capacity

Table 6 shows the liver lipid peroxidation end product, malondialdehyde (MDA), and total antioxidant capacity (TAC) as well as their percentage change in male albino rats fed on high-fat diet and high-fat diet with ATOR10®, flaxseed mucilage or cress seed mucilage as compared to normal diet fed rats. Rats fed on HFD showed a significant elevation in the level of MDA matched with a significant decrease in the total antioxidant capacity (TAC) compared to normal group. The percentage change was 26.5 and -28.8% for MDA and TAC as compared to normal diet, respectively. Compared to rats fed on HFD, rats treated with either ATOR10®, FSM or CSM after feeding HFD revealed a significant decrease (-20.6, -8.7 & -15.5%, respectively) in the level of MDA ($P < 0.05$) accompanied with a significant enhancement (26.2 18.0 & 22.5%, respectively) in the TAC ($P < 0.05$). These data reflect that CSM is more potential than FSM in fighting the oxidative process and improving the whole anti-oxidative battery within the liver tissue. Also, these results confirmed the higher TAC of CSM than FSM solution against DPPH [51]. This finding is in consistent with that of Makni *et al.* [52]; Fan *et al.* [53] and Ma *et al.* [36].

Table 6: Level of hepatic lipid peroxidation and total antioxidant capacity of male albino rats fed on high-fat diet and high-fat diet with ATOR10®, flaxseed mucilage or cress seed mucilage as compared to normal diet fed rats

Animals groups	MDA			TAC		
	(µmol/g tissue)	A (%)	B (%)	(µmol/g tissue)	A (%)	B (%)
CT	$657^{A} \pm 27$			$1.56^{A} \pm 0.039$		
HFD	$831^{B} \pm 34$	26.5		$1.11^{C} \pm 0.029$	-28.8	
HFD-ATOR10®	$660^{A} \pm 27$	0.5	-20.6	$1.40^{B} \pm 0.035$	-10.3	26.2
HFD-FSM	$759^{A} \pm 31$	0.3	-8.7	$1.31^{B} \pm 0.033$	-16.0	18.0
HFD-CSM	$702^{A} \pm 29$	6.8	-15.5	$1.37^{B} \pm 0.034$	-12.2	22.5

Means (±SE, n=10) with the same letters in the same row are not significantly different at $P \leq 0.05$.
MDA, malondialdehyde; TAC, total antioxidant capacity; CT, control group; FSM, flaxseed mucilage solution; CSM, cress seed mucilage solution; HFD, high fat diet fed rats; ATOR10®, standard drug ATOR10®

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