REVIEW

Dietary oats and modulation of atherogenic pathways

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Received: October 20, 2011
Revised: November 30, 2011
Accepted: December 20, 2011

Consumption of oats has long been known to lower plasma total and low-density lipoprotein (LDL) cholesterol levels, an effect usually attributed to the soluble fibers β-glucans. On the basis of this cholesterol-lowering effect, oats are ascribed cardiovascular health-promoting properties. However, besides cholesterol levels, effects of oats on parameters relating to atherosclerosis development have not been extensively investigated. Since oxidation of lipoproteins and inflammation are characteristics of atherosclerosis in addition to lipid accumulation in the vessel wall, micronutrients in oats (phytochemicals) with antioxidative and anti-inflammatory properties may contribute to an atheroprotective action. Here, we summarize evidence on antiatherogenic properties of oats obtained from in vitro assays, animal experiments, and human studies. Possible effects involving anti-inflammatory and antioxidative actions, as well as preservation of endothelial function, are considered in addition to those related to reduction of plasma cholesterol. Since results of in vitro assays with isolated oat components are difficult to compare with effects of whole oats in humans and experimental animals, more observational studies with isolated oat components or fractions of oats are warranted. Also, there is a lack of epidemiological studies focusing on effects of oat intake on the cardiovascular disease panorama.

Keywords:
Atherosclerosis / Beta-glucans / Cardiovascular disease / Cholesterol / Inflammation

1 Introduction

There is convincing evidence that oats possess cholesterol-lowering properties, most often ascribed to its contents of soluble fibers, β-glucans [1–3]. On this basis oats are claimed to be useful in the prevention of cardiovascular disease. In 1997, the US Food and Drug Administration (FDA) endorsed claims that foods with soluble fiber from whole oats may reduce heart disease risk when eaten as part of a diet low in saturated fat [4], and in 2010, the European Food Safety Authority (EFSA) panel concluded that scientific evidence supports the two-step statement: "Oat beta-glucan has been shown to lower/reduce blood cholesterol. Blood cholesterol lowering may reduce the risk of (coronary) heart disease" [5]. Few attempts have however been made to directly address the potential of oats to reduce atherogenesis—the underlying cause of most cardiovascular disease events, such as stroke and myocardial infarction [6]. In view of the established effect of cholesterol-lowering therapy, e.g., using hydroxymethyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) on cardiovascular disease events [7], the cholesterol-lowering effect of oats is likely to be important in preventing disease. However, different cholesterol-lowering therapies, including diets, also have other effects that may influence atherosclerosis development. In particular, since inflammation and oxidation of lipoproteins are hallmarks of atherosclerosis, dietary micronutrients (organic chemicals and trace elements) in oats with anti-inflammatory and/or antioxidative properties may well contribute to an atheroprotective effect in addition to reduced levels of plasma lipids. The cholesterol-lowering effect of oats has previously been extensively reviewed [1–3, 8]. Here we aim to summarize work done to evaluate antiatherogenic effects of oats, and to pinpoint possible effects of oat components on atherogenic pathways.

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Abbreviations: CRP, C-reactive protein; **eNOS**, endothelial nitric oxide synthase; **GPx**, glutathione peroxidase; **GSH**, reduced glutathione; **GSSG**, oxidized glutathione; **HMG-CoA**, hydroxymethyl glutaryl coenzyme A; **ICAM-1**, intercellular adhesion molecule-1; **LDLr$^{-/-}$**, LDL-receptor deficient mice; **MCP-1**, monocyte chemoattractant protein-1; **MDA**, malondialdehyde; **NO**, nitric oxide; **oxLDL**, oxidized LDL; **SAA**, serum amyloid A; **SOD**, superoxide dismutase; **TNFα**, tumor necrosis factor α; **VCAM-1**, vascular cell adhesion molecule-1

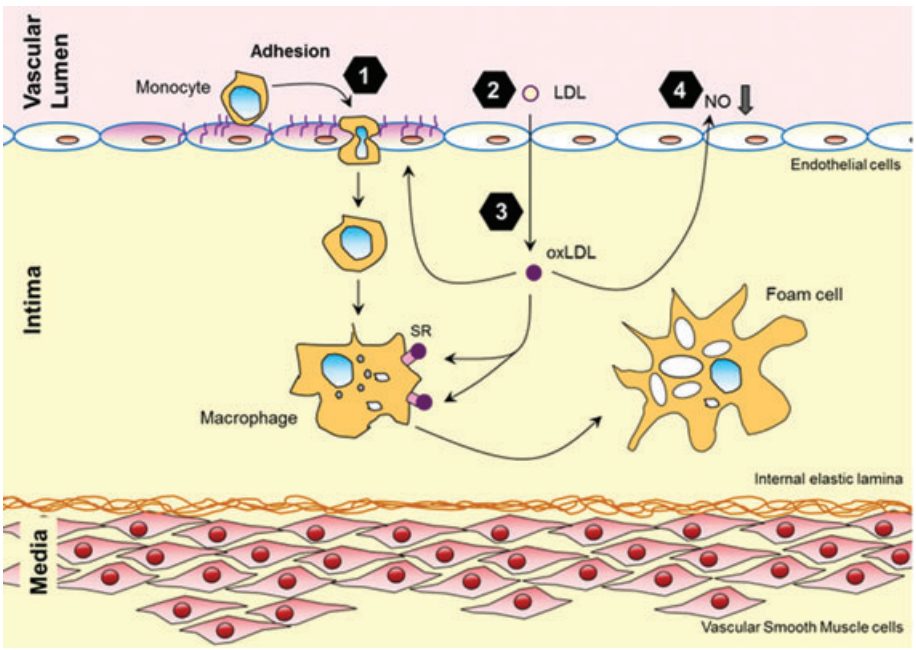
2 Overview of mechanisms causing atherosclerosis

Atherosclerosis is identified as an inflammatory disease associated with an immunological reaction against antigens mainly derived from modified low-density lipoprotein (LDL) particles retained in the subendothelial space of the blood vessel wall. Several different processes are involved, including oxidation of LDL, adhesion of monocytes and T-cells to the endothelial surface, migration of monocytes across the endothelium, maturation of monocytes to macrophages, and formation of foam cells via the ingestion of oxidized LDL (oxLDL) by macrophages [9]. This sequence of events is enhanced by factors causing increased endothelial permeability, increased expression of adhesion molecules on the endothelial surface, as well as increased retention and modification (such as oxidation) of LDL particles. Hence the presence of high local concentrations of LDL particles is essential, but oxidative stress and inflammatory reactions are integral components in the atherosclerotic process (summarized in Fig. 1). The atherosclerotic plaques arise from masses of lipid-laden foam cells, which are initially covered by migrating smooth muscle cells to form a fibrous cap ensheathing the lipid core and supporting a smooth endothelial surface (stable plaques). In advanced lesions there is an accumulation of cell debris, apoptopic and necrotic cells as well as cholesterol crystals in the plaque, and the fibrous cap surrounding this necrotic core is infiltrated by mast cells, activated T cells, and macrophages (vulnerable plaques). This may finally provoke rupture of the fibrous cap with ensuing thrombus formation and occlusion of the artery [10].

Molecular mediators such as the cytokines IL-6, IL-1, and tumor necrosis factor-α (TNFα) and the plasma acute-phase proteins C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen may serve as markers of inflammation for the prediction of future cardiovascular risk [11, 12].

Although elevated total and LDL cholesterol are well-recognized risk factors for cardiovascular disease, and their role in the atherosclerosis process is undisputable, the exact pathogenetic role of these plasma lipid disorders for the clinical outcome is still somewhat unclear. Significant positive effects (up to one-third reduction of coronary events) have been found in large studies evaluating statins, which lower LDL cholesterol levels by 20–60% [7], strongly suggesting that reduced LDL levels contribute to less coronary events. However, statins not only decrease LDL, but also increase high density lipoprotein levels, and there is much to indicate that they have additional effects associated with their specific mechanism of action, including improved endothelial function and anti-inflammatory effects [13].

The endothelium not only serves as a barrier between the blood stream and the surrounding tissue, but also actively participates in the regulation of vascular structure and function. The endothelium releases several vasoactive substances, including vasoconstrictors such as angiotensin II and endothelin-1 and vasodilators, primarily nitric oxide (NO) and prostacyclins. Dysfunction of the endothelium is generally associated with reduced vasodilatory action and is known to be an important mechanism behind hypertension and a risk factor for atherosclerosis [14]. Oxidative stress inhibits NO production and thus contributes to endothelial dysfunction as well as to inflammation by promoting LDL oxidation.



1. Anti-inflammatory effects
Oat polyphenols reduce the amount of adhesion molecules on the endothelial surface, resulting in less monocyte recruitment to the vascular wall.

2. Reduction of plasma cholesterol
The cholesterol-lowering effect of oats reduce the chance of LDL being trapped in the vascular wall.

3. Antioxidative capacity
Oat antioxidants prevent oxidation of LDL and scavenge other reactive oxygen species.

4. Maintained endothelial function
Oats may preserve nitric oxide production and thereby counteract endothelial dysfunction.

Figure 1. Simplified cartoon of the initial steps in atherosclerosis. Hypothetical protective effects of oats are indicated (1–4). OxLDL, oxidized LDL; NO, nitric oxide; SR, scavenger receptor.

An important component in the response to atherogenic stimuli is a phenotype shift, proliferation and migration of smooth muscle cells in the vascular wall. This can be regarded as a wound-healing response and is in principle a beneficial reaction by covering atherosclerotic lesions by a fibrous cap, stabilizing the lesion [9]. However, under certain circumstances excessive smooth muscle proliferation may compromise blood flow, as e.g. in restenosis following angioplastic therapy or grafting of coronary arteries. The role of smooth muscle cell reactions in various aspects of atherosclerosis and its complications is thus dependent on the pathophysiological context.

3 Characteristics of oats

Oats (*Avena sativa*) are rich in dietary fibers, and also contain relatively high levels of protein and unsaturated fat compared with other cereals [15–17]. Besides the nutritional value, the higher fat content make oats rich in lipid-soluble phytochemicals with antioxidative and possibly other physiologically active properties [18]. The fiber content of oats include cellulose, arabinoxylans, and the soluble fibers, mixed-linked (1→3),(1→4)-β-D-glucan [17]. The latter are usually referred to only as "β-glucans," and are considered to be mainly responsible for the cholesterol-lowering action of oats.

Various components in the oat grain protect its lipids from oxidation. Such antioxidative components include vitamin E (tocopherols and tocotrienols), phenolic compounds (such as the oat-specific polyphenols avenanthramides), phytic acids, sterols, and flavonoids [18]. The potential of plant antioxidants to scavenge free radicals and protect the plant from oxidation is transferred to the human body when oats or other antioxidant-rich foods are consumed [16]. For more detailed reviews on the specific oat antioxidants and how to extract them from oats, please see Peterson [18] and Ryan et al. [16]. Avenanthramides have been shown to be bioavailable in both human, hamster and rat [19–21]. Recently it was also found that they accumulate in liver, heart, and skeletal muscle tissue in rats, although only in the nanomolar range [21]. Some of the antioxidants in oats may be heat labile, but most of the antioxidative activity in oats is resistant to heat treatment, and is therefore likely to be present also in commercial oat products, which are usually heat treated to inactivate lipases and other enzymes [22]. From a health perspective, an advantage of oats compared to other cereals is that it is usually consumed as the whole grain.

Figure 1 summarizes how oats and oat components might modulate atherogenic pathways. In addition to their cholesterol-lowering and antioxidative properties, oat components also have the potential to exert anti-inflammatory effects and to beneficially affect endothelial function.

4 Potential modulation of atherogenic pathways by oats

4.1 Reduction of plasma cholesterol

Since elevated blood cholesterol is a well-recognized risk factor for cardiovascular disease [9] and oats since long are known to reduce cholesterol levels [1, 2, 23–30], the most obvious mechanism by which oats might prevent atherosclerosis is its cholesterol-lowering effect, which has been ascribed mainly to its contents of β-glucans. Several mechanisms have been proposed, including (i) binding of bile acids, thereby decreasing their uptake and increasing net excretion, (ii) increased viscosity of the small intestinal contents, producing an unstirred layer next to the intestinal wall that acts as a physical barrier to absorption of dietary cholesterol and reabsorption of bile acids [31]. Both mechanisms (i) and (ii) result in increased fecal excretion of bile acids (*i.e.*, reduced bile acid reabsorption). Since bile acid synthesis is highly regulated by feedback inhibition, the reduced levels of reabsorbed bile acids will stimulate hepatic bile acid synthesis. Cholesterol is a precursor for bile acid synthesis, so this contributes to increased hepatic uptake of circulating LDL particles and thereby to a reduced level of cholesterol in the circulation [32]. In a human ileostomy study, reduction of plasma cholesterol by oats correlated with increased bile acid synthesis, measured as serum levels of the metabolite 7α-hydroxy-4-cholesten-3-one, which is an indicator of cholesterol-7α-hydroxylase (CYP7A1) activity, the enzyme in the rate-limiting step in bile acid synthesis [32]. Intake of barley (another cereal containing high levels of β-glucans) increased hepatic CYP7A1 mRNA expression and activity in rats in correlation with reduced plasma cholesterol [33]. We have found increased mRNA levels of CYP7A1 in mice after oat bran intake, together with reduced plasma cholesterol (unpublished results). Other proposed mechanisms of action are that (iii) oat β-glucans reduce the rate of intestinal glucose absorption, causing lower insulin levels and reduced hepatic cholesterol synthesis [34], and that (iv) short-chain fatty acids (especially propionate) produced by bacterial fermentation of fibers inhibit hepatic cholesterol synthesis [35, 36]. The propionate hypothesis has however been questioned as being important for the reduced cholesterol levels [37, 38].

In addition to effects of β-glucans there are indications that other components in oats can contribute to the cholesterol-lowering effect: Liu et al. found that an avenanthramide extract reduced plasma levels of total cholesterol, LDL cholesterol, and triglycerides in humans [39]. They used an ethanol extract of oat bran, so besides avenanthramides the preparation may contain other ethanol soluble oat components. Nevertheless, the results open up the possibility that other components in oats, besides the β-glucans, contribute to the cholesterol-reducing effect. In this context it is also worth mentioning that to date no published study is available, neither human nor animal, which shows cholesterol-lowering

effects of pure oat β-glucans, since usually extracts or "β-glucan enriched" products with 20–70% β-glucans, or alternatively whole oats or oat bran, have been used.

Cholesterol is an essential component of biological membranes and is also the building block of bile acids, steroid hormones, and vitamin D. The intracellular cholesterol concentration is tightly regulated, but plasma cholesterol varies considerably due to genetic factors, diet, and environmental conditions [40]. When the circulating cholesterol load (carried by lipoproteins) exceeds tissue uptake, plasma cholesterol levels increase, mainly in the form of LDL particles. The main rationale for cholesterol reduction is the prevention of lipid incorporation into the vascular wall, and thus of atherosclerosis. Animal experiments indicate that effects of oats in preventing lipid incorporation into the vascular wall may be relatively greater than the effects in reducing plasma cholesterol [28, 41], suggesting that factors besides the reduction of plasma cholesterol might contribute to antiatherogenic effects of oats. Studies relating to effects of oats on inflammation and lipid oxidation as well as on endothelial function are discussed below and also summarized in Table 1.

4.2 Anti-inflammatory effects

In traditional medicine, oatmeal and oat extracts have been used as skin anti-itch agents, implying an anti-inflammatory effect, but the phytochemicals mediating the response have not been clearly identified. In recent years avenanthramides (polyphenols specific to oats) have been shown to have anti-inflammatory properties by inhibiting nuclear factor kappa B (NF-κB) signaling in keratinocytes, thus reducing the expression of many proinflammatory proteins [42]. When ingested as foods, oat phytochemicals with anti-inflammatory effects could possibly also contribute to less systemic and vascular inflammation and thus to a reduced progression of atherosclerosis.

To date, very few human intervention studies have addressed the effects of oats on systemic inflammation. Theuwissen et al. found no effects on the inflammatory marker CRP or the cytokines IL-6, IL-8, and TNF-α in serum from humans fed an oat β-glucan rich muesli [43]. Similarly, Queenan et al. found no reduction of CRP in blood by an oat bran concentrate [44]. In both of these studies there was however a significant reduction of LDL cholesterol. Moreover, in both cases an oat product with enriched β-glucan content was given to the subjects. It is possible that during the β-glucan enrichment process a major part of the oat lipids, and therefore also many of the oat polyphenolics, were removed from the original oat bran. Thus the amount of oat polyphenolics might be low in these preparations, and hence the expected effects on inflammation reduced. Therefore, evaluation of inflammation markers after intake of whole oats and/or lipid fraction(s) of oats is warranted.

In an experimental study on LDL-receptor deficient ($LDLr^{-/-}$) mice fed oat bran, we found reduced levels of the inflammation-related plasma proteins fibrinogen and soluble vascular cell adhesion molecule-1 (sVCAM-1), as well as reduced expression of the adhesion molecule VCAM-1 in the aortic wall [41]. Since high blood cholesterol levels *per se* can induce inflammatory responses [45], it is difficult to elucidate if the anti-inflammatory effects seen in this mouse study originates from specific anti-inflammatory agents or are a secondary effect of the reduction in plasma cholesterol produced by the oat bran. The results are nevertheless in accordance with cell studies of avenanthramides in vitro, where human endothelial cells showed less IL-1β-induced expression of VCAM-1, E-selectin, and intercellular adhesion molecule-1 (ICAM-1) in the presence of avenanthramides isolated from oats, with a concomitant reduction of monocyte attachment to the endothelial cells [46]. This study also showed reduced secretion of IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) when avenanthramides were added to the assay. It would be interesting to perform in vivo experiments with avenanthramides or the lipid phase of oats to investigate the anti-inflammatory properties of the isolated components and/or lipid soluble components, without any effects of β-glucans on plasma cholesterol. Such studies have been performed on rabbits fed isolated E-vitamin, which reduced the expression of ICAM-1 and VCAM-1 and concomitantly reduced the amounts of macrophages attached to the aortic wall [47].

Recruitment of monocytes/macrophages to the vascular wall is a prerequisite for atherosclerosis, but there are also reports that macrophages might emigrate from the plaque, a process associated with decreased plaque area [48, 49]. Some findings even suggest that increased activity of certain subsets of macrophages can reduce the development of the necrotic core of an atherosclerotic plaque by phagocytosis of apoptotic cells, a process known as "efferocytosis" [50]. In a mouse study with a β-glucan rich oat preparation (68% β-glucans) the oat preparation increased the number of macrophages and induced their phagocytic activity, in parallel with increased resistance to infecting agents [51]. It is thus possible that oat consumption might influence macrophage levels and activity in the atherosclerosis process, either negatively by stimulating foam cell formation, or positively by stimulating efferocytosis. Studies directly addressing this are however needed to support or discard these hypotheses.

4.3 Antioxidative capacity

Examples of oat components with potential antioxidative properties are phytic acid, tocopherols, polyphenolic compounds (such as avenanthramides), flavonoids, and possibly also polymeric lignins [16, 18]. They may exert their antioxidative action by scavenging reactive oxygen and nitrogen species and by chelating transition minerals. The oxygen scavenging effect is a defense system in the plant itself, but might also be beneficial in an animal consuming the plant [52]. Experiments in vitro have demonstrated that the lipid-soluble

Table 1. List of studies investigating possible atheroprotective effects of oats other than the hypocholesterolemic effect

Oat preparation/component	Type of study	Atheroprotective effect	Reference
		Effects on inflammation	
Avenanthramides (extracted from oats)	In vitro endothelial cells	VCAM-1 ↓, E-selectin↓, ICAM-1↓, IL-6↓, IL-8↓, MCP-1↓, monocyte attachment to cells↓	Liu et al., 2004 [46]
Oat bran	Mouse study	Aortic VCAM-1 ↓, plasma sVCAM-1↓, fibrinogen↓, IL-6↔, SAA↔	Andersson et al., 2010 [41]
β-glucan rich muesli	Human intervention study	Plasma CRP↔, IL-6↔, IL-8↔, TNFα↔	Theuwissen et al., 2009 [43]
β-glucan concentrate from oat bran	Human intervention study	Plasma CRP↔	Queenan et al., 2007 [44]
		Antioxidative capacity	
Ethanol and isopropanol extracts from oats	In vitro	LDL oxidation ↓, quenching of free radicals↑	Gray et al., 2002 [55]
Methanol extract from oats	In vitro	LDL oxidation ↓, quenching of free radicals↑	Handelman et al., 1999 [22]
Oat phenolics (including avenanthramides)	In vitro	LDL oxidation↓	Chen et al., 2004 [20]
Oat phenolics (including avenanthramides)	Hamster study	Ex vivo LDL oxidation ↔, ex vivo quenching of free radicals (with ORAC-assay)↔	Chen et al., 2004 [20]
Avenanthramides (synthetic)	Rat study	SOD activity↑, GPx activity↑	Ji et al., 2003 [57]
Avenanthramides (extracted from oats)	Human intervention study	Plasma GSH↑, GPx activity↔, MDA↔, ex vivo LDL oxidation ↔	Chen et al., 2007 [19]
Avenanthramide-rich extract	Human intervention study	Plasma GSH↑, SOD↑, MDA↓	Liu et al., 2011 [39]
Avenanthramide-rich extract	Mouse study (D-galactose induced oxidation)	Liver MDA↓, SOD activity↑, GPx activity↑	Ren et al., 2011 [58]
		Endothelial function/Blood pressure	
Avenanthramides (synthetic)	In vitro endothelial cells	eNOS expression↑	Nie et al., 2006 [62]
Oat bran	Mouse study	Aortic eNOS expression↑	Andersson et al., 2010 [41]
Oatmeal	Human meal study	Endothelial function↑	Katz et al., 2001, 2004 [63,64]
Whole oat cereal	Human intervention study	Systolic blood pressure↓, diastolic blood pressure↓	Keenan et al., 2002 [65]
Whole oat cereal	Human intervention study	Systolic blood pressure↓, diastolic blood pressure↔	Saltzman et al., 2001 [66]
		Antiproliferative effect	
Avenanthramides (synthetic)	In vitro smooth muscle cells	Cell proliferation↓	Nie et al., 2006 [62]
		Antiatherogenic effects	
Oat bran	Mouse study	Aortic arch lesions↓, descending aorta lesions↓	Andersson et al., 2010 [41]
Oat bran	Mouse study	Descending aorta lesions↔	Eussen et al., 2011 [72]
Oat bran	Hamster study	Aortic fatty streak↔	Wilson et al., 2002 [73]
β-glucan concentrate from oat bran	Hamster study	Aortic cholesterol ester content↓	Delaney et al., 2003 [28]

CRP, C-reactive protein; GPx, glutathione peroxidase; GSH, reduced glutathione; GSSG, oxidized glutathione; ICAM-1, intercellular adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; MDA, malondialdehyde; SAA, serum amyloid A; SOD, superoxide dismutase; TNFα, tumor necrosis factor α; VCAM-1, vascular cell adhesion molecule-1.

E-vitamins are incorporated into the lipoprotein particles very low density lipoproteins (VLDL) and LDL, providing effective antioxidant activity against oxidation of LDL [53]. One might speculate that this is true also for other lipid-soluble oat components, such as avenanthramides and other polyphenols.

There is a connection between oxidative stress and cardiovascular risk factors such as hypertension, diabetes, and obesity [54]. In the progression of an atherosclerotic lesion, the oxidized form of LDL is engulfed by macrophages in the intima of the blood vessel wall [9]. Dietary antioxidants therefore offer a potential limiting step for oxLDL accumulation in atherosclerotic lesions. Indeed, it has been demonstrated that both methanol, ethanol, and isopropanol extracts from oats, as well as isolated oat phenolics, reduce LDL oxidation in vitro [20, 22, 55]. However, when the same isolated phenolics were fed to hamsters and LDL withdrawn from the animals were Cu^{2+}-oxidized ex vivo, there was no reduction in oxidation [20]. Similarly, giving an oat-extracted avenanthramide-enriched mixture to humans did not reduce LDL oxidation ex vivo [19]. A possible explanation for this is that the phenolics were lost during the LDL isolation process preceding the ex vivo assay [20]. Another possible explanation is that the antioxidants were not absorbed in high enough concentrations to exert a detectable effect in the in vivo setting. It might also be difficult to compare antioxidative activities of oat-derived components due to the many different extraction techniques and solvents used to extract and fractionate the components [55, 56].

Besides exerting direct antioxidative effects there are indications that avenanthramides may have the ability to stimulate the body's own oxygen scavenging system. Superoxide dismutase (SOD) and glutathione peroxidase (GPx) are endogenous enzymes protecting the organism from oxidative damage [57]. Hepatic activities of both of these enzymes were increased in mice fed an avenanthramide-rich extract [58], and in rats fed synthetic avenanthramides [57]. Furthermore, serum levels of both SOD and GPx were also found to be reduced in humans after intake of an avenanthramide-rich extract, together with reduced serum levels of malondialdehyd (MDA, a biomarker of lipid peroxidation) [39]. Hepatic MDA levels were also reduced in mice fed an avenanthramide-rich extract [58]. Other examples of antioxidative effects of oat/oat components are elevated plasma levels of reduced glutathione (GSH, an endogenous antioxidant) in human subjects given an oat-extracted avenanthramide-enriched mixture [19], reduced oxidation susceptibility of muscle tissue in rabbits fed oats [59], and tissue-specific, antioxidative effects of synthetic avenanthramides after an exercise-induced oxidative stress in rats [57],

Not all literature data support an antioxidative effect of oats. In a human study, 12 weeks of oat consumption did not alter blood levels of biomarkers for oxidative stress (oxLDL, MDA, protein carbonyl, and glycosylated hemoglobin). The authors suggest that the study subjects had insufficiently elevated levels of markers of oxidative stress to reveal an effect of oats, or that alternatively the possible antioxidative components in oats were not present in high enough amounts [54].

4.4 Maintenance of endothelial function and blood pressure

The endothelial cells in the blood vessels are involved in the regulation of vasoconstriction and vasodilation, and hence also in the regulation of blood pressure. Certain postprandial conditions, such as insulin release, generation of oxygen-free radicals, and generation of triglyceride-rich lipoprotein particles, could contribute to endothelial dysfunction, resulting in vasoconstriction and higher blood pressure [60]. There are data in the literature suggesting that oats could influence at least two of the above conditions [34, 55] and thereby help maintaining endothelial function.

Generation of the vasodilating agent NO by endothelial NO synthase (eNOS) is known to protect against vascular complications [61]. Nie et al. demonstrated that avenanthramides increase the expression of eNOS on endothelial cells in vitro [62]. An increased expression of eNOS was also found in the aortic root of mice fed oat bran [41]. These results suggest that oat components, by affecting the expression of eNOS, could increase the production of NO and thereby help maintaining endothelial function.

In vivo evidence for an effect of oats on endothelial function in man is provided by ultrasound measurements of blood flow and arterial dilation following release of a brief occlusion of the brachial artery. Using this approach Katz et al. found that concomitant oat consumption tended to prevent the endothelial dysfunction provoked by a high fat meal in both healthy [63] and overweight, dyslipidemic adults [64]. There was also a tendency that long-term intake (6 weeks) of whole oat products increased the flow-mediated vasodilation postprandially after intake of a fatty test meal in overweight, dyslipidemic adults [64].

The impact of oat consumption on blood pressure has been investigated in human studies. In a pilot study by Keenan et al., both systolic and diastolic blood pressure was significantly reduced after whole oat cereal intake for 6 weeks (by 7.5 and 5.5 mmHg, respectively) [65], whereas only the systolic blood pressure was reduced in an extensive study by Saltzman et al. [66]. In hypertensive patients on medication it was found that after consumption of oat cereal meals the blood pressure medication could be reduced in 73% of the patients, compared with 42% in the control cereal group [67]. There have also been indications that obese persons benefit more from oat intake than lean persons with respect to the effect on blood pressure. Whereas both systolic and diastolic blood pressure was reduced after 12 weeks of oat consumption in subjects with a BMI$>$31.5, there was no change in blood pressure when subjects with a BMI$\leq$31.5 were included in the data [54].

It has been proposed that the reduced blood pressure after consumption of oats is accounted for by reduced postprandial

glucose and insulin levels, which would primarily be a β-glucan effect [54, 63]. Antioxidants such as phytoestrogens present in oats could however contribute to the beneficial effects [63], and in vitro studies on endothelial cells suggest that oat polyphenols can potentiate vasodilatory effects [62]. With the clinical and experimental studies performed so far it is not yet possible to discriminate effects on blood pressure originating from the β-glucan effect and those arising from other bioactive components in oats.

4.5 Antiproliferative effect

The smooth muscle cells are critical components of the vascular wall, both under normal and pathophysiological conditions. In addition to regulating vascular resistance, and thus blood pressure, in response to a multitude of signals they respond to inflammatory stimuli and vessel injury by modulating to a "synthetic" phenotype characterized by increased proliferation rate as well as migration and synthesis of extracellular matrix proteins [9]. As mentioned in Section 2, this response may help to stabilize atherosclerotic plaques but can also aggravate processes associated with narrowed vessel lumen. There is in vitro evidence indicating that avenanthramides inhibit the proliferation of vascular smooth muscle cells [62], although no in vivo data are yet available to our knowledge. However, Tranilast [N-(3′,4′-dimethoxycinnamoyl)-anthranilic acid], a synthetic drug structurally similar to avenanthramides [68], inhibits vascular smooth muscle cell proliferation [69]. When evaluating the effect of Tranilast on restenosis following arterial injury, there are however conflicting results in the literature [70, 71].

4.6 Antiatherogenic effects

To our knowledge there are only a handful of studies in the literature where atherosclerotic lesions have been directly addressed as endpoint for the effect of oats. In $LDL^{-/-}$ mice fed oat bran together with a high-fat diet, atherosclerotic lesions were reduced by 70% in the descending aorta and by 40% in the aortic arch. This was accompanied by reduced plasma total and LDL cholesterol levels, reduced inflammatory markers in both plasma and the blood vessel wall, and increased expression of eNOS in the blood vessel wall [41]. A similar trend was seen in a further study using a lower concentration of oat bran and a smaller number of animals [72]. Aortic fatty streak areas tended to be smaller in hamsters fed oat bran compared with wheat bran [73]. Furthermore, the contents of cholesterol esters in the aorta of hamsters fed an oat β-glucan concentrate (66% β-glucan) were significantly reduced compared with a negative control [28]. Even though large interindividual variation is typically seen in estimates of atherosclerotic lesions [74], these studies taken together clearly indicate that intake of oat bran is effective in reducing aortic lipid infiltration.

The above in vivo studies evaluated the effect of oat bran on atherosclerosis, and all showed reduced plasma cholesterol along with the reduction of atherosclerotic lesion area. It is therefore difficult to discriminate whether the antiatherogenic effect originates from the reduced plasma cholesterol alone, or if additional effects of other oat components contribute to the reduced atherogenesis. Effects of isolated oat components, such as avenanthramides, on atherosclerosis in in vivo models have rarely been investigated. Some studies have been performed with vitamin E, showing a reduced progression of atherosclerosis in $LDLr^{-/-}$ mice by suppressing oxidative and inflammatory events, and by increasing NO production [75]. Studies with oat polyphenols or lipid extracts are warranted to increase our understanding as to whether the antiatherogenic effects of oats originate only from reduced plasma cholesterol or if other components play a role, possibly due to their anti-inflammatory, antioxidative, and endothelial function-restoring effects discussed in previous sections.

When the expression of 71 genes involved in atherosclerosis metabolism was determined in peripheral blood mononuclear cells, no significant differences were found between humans fed oat β-glucan muesli and the negative control group [43]. This muesli was however a β-glucan concentrate, which possibly may have lost oat polyphenols during preparation. It would be interesting to do the same analysis after intake of whole oats, where all polyphenols are still present.

5 Concluding remarks

Patients that have survived a coronary artery event show a high incidence of relapse despite intensive statin treatment [76]. This fact demonstrates that once manifested, atherosclerotic disease is difficult to reverse. Instead, aims should be to reduce the accumulation of risk factors such as elevated LDL levels and high systemic inflammatory status in the general population, in order to forestall development and progression of the disease. In their goals for the promotion of cardiovascular health toward 2020 and beyond, the American Heart Association (AHA) argues that prevention aimed at the general public, outside the medical sector and in all age groups, will offer the possibility for substantial further gains in cardiovascular health [77]. Physical activity and promotion of healthy eating habits are central in this effort. Dietary components directly interfering with cholesterol homeostasis or systemic inflammation, such as those present in oats, are an additional tool for achieving this goal.

Consumption of whole grains has been correlated with reduced systemic inflammation and coronary artery disease [78, 79], but to our knowledge there are no epidemiological studies directly addressing oat consumption in relation to cardiovascular disease. The ultimate proof of efficacy of a treatment is a reduction in endpoints such as morbidity and

mortality, which requires execution of large clinical studies. While this is generally done in evaluations of new drug treatments, health benefits of dietary regimes have often been claimed on the basis of limited studies where biomarkers such as plasma total and LDL cholesterol rather than disease endpoints have been evaluated. There is therefore a need for direct evidence relating to the effect of these products on the disease itself [25]. Epidemiological studies evaluating effects of oat intake on cardiovascular disease are thus warranted to substantiate the health benefits inferred from the presently available experimental and human studies. An important question is if individual oat components are able to themselves reduce low-grade vascular inflammation, reactive oxygen species (ROS) production and endothelial dysfunction in excess of the effects possibly associated with lower plasma cholesterol, since cholesterol levels are correlated with the grade of inflammation [45]. In vitro assays where pure avenanthramides reduce VCAM-1 on endothelial cells indicate a direct effect of the polyphenols [46]. However, in vivo studies comparing the effects of different isolated oat components, or alternatively different fractions of oats, would be helpful to evaluate the physiological significance of such effects. This is of relevance, because presently nearly all focus is on the β-glucan contents, and a few products enriched in β-glucans have been introduced on the market. It would be important to know if the procedures used to increase the β-glucan contents preserve also other potentially valuable bioactive components. Also, by focusing on the reduction of plasma cholesterol by β-glucans we might overlook atheroprotective effects of other oat components. In experimental studies of processed oat products, it is important that the macronutrient composition of the product is clearly stated, ideally including also the contents of avenanthramides, tocols, and phenolic acids.

When effects of isolated bioactive components are evaluated in vitro they are usually administered in a rather high concentration, not always physiologically relevant to the ingestion of whole oat foods. With respect to anti-inflammatory, antioxidative, and endothelial effects of oat components it is worth questioning if high enough concentrations of the bioactive components are absorbed from the foods and present in the circulation. For example, the concentrations used for in vitro experiments with avenanthramides have been in the range of 20–50 μmol/L [46,62], which are high compared with reported values of 0.1–0.4 μmol/L in the blood after bioavailability tests performed in hamsters and humans [19,20]. However, since both in human and animal studies most atherogenic pathways have been found to be modulated by whole oats, there are reasons to believe that effects demonstrated with isolated compounds in vitro act in concert to exert beneficial health effects in vivo.

In the early 1970s, Trowell formulated a hypothesis that intake of whole-grain foods protects against coronary heart disease [80]. Subsequent work, including large epidemiological studies, has supported this hypothesis, while interestingly showing less consistent effects of cereal fiber alone [81, 82]. Of the different whole-grain sources, oats have a special interest because of their potent effects and the ease of consuming them as whole grains. However, no epidemiological or prospective interventional studies have yet specifically addressed the potential of oats to protect against cardiovascular disease. The action of various oat components on the atherogenic pathways reviewed here suggest that several different oat components besides β-glucans may confer an atheroprotective effect of possible significance for cardiovascular health.

Original work by the authors is supported by the Functional Food Science Centre of Lund University, the cross-disciplinary food research programme TvärLivs, and the Swedish Science Council.

The authors have declared no conflict of interest.

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