Potential health benefits of avenanthramides of oats

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Oats are known to be a healthy food for the heart due mainly to their high β-glucan content. In addition, they contain more than 20 unique polyphenols, avenanthramides, which have shown strong antioxidant activity in vitro and in vivo. The polyphenols of oats have also recently been shown to exhibit anti-inflammatory, antiproliferative, and anti-itching activity, which may provide additional protection against coronary heart disease, colon cancer, and skin irritation.

INTRODUCTION

Epidemiological evidence has indicated that a high intake of whole-grain foods is associated with a lower risk for coronary heart disease (CHD) and diabetes.[1–4] Whole-grain foods contain a significant amount of fiber, which is believed to be the major factor contributing to their beneficial effects on CHD and diabetes. Thus, several epidemiological studies have focused on the association of cereal fibers (representing whole-grain fiber) with the risks of CHD. An inverse relationship has been reported between the high intake of cereal fiber and the risk of myocardial infarction. Early meta-analysis of multiple, controlled studies has suggested that consumption of whole grains including wheat, rice, maize, and oats reduces the risk of CHD slightly better than even fruit or vegetables.[5] In addition to having dietary fiber, whole grain foods are a rich source of many nutrients, including complex carbohydrates, starch, oligosaccharides, minerals, vitamins, and phytochemicals.[1,6] The contribution of components of whole grains other than fiber and the mechanism by which whole-grain foods provide health benefits have not been clearly identified.

OAT CONSUMPTION AND HEART HEALTH

A recent comprehensive review of the literature by Kelly et al.[7] provided evidence that the beneficial effect of consuming whole grains on CHD in clinical intervention trials is mainly limited to whole-grain oats. The beneficial effect of consuming other whole grains remains to be elucidated by long-term, controlled clinical intervention trials.

Oats are unique among the whole grains. The consumption of oatmeal and oat bran, even for a short period of time, has been shown in most studies to reduce total plasma cholesterol and LDL-cholesterol levels, the main risk factors for CHD.[8] This is mainly attributed to β-glucan, the soluble fiber content of oats. β-glucan, the active component of the soluble fiber in oats, interferes with the reabsorption of bile acid in the gut and reduces cholesterol levels.[5] Due to this well-established effect of oats on the risk of CHD, the United States Food and Drug Administration in 1997 approved the heart-health-benefit claim on food labels of food containing soluble fiber from oats. In addition to its cholesterol-lowering effect, oats have been shown to improve endothelial function when consumed with supplements of vitamins C and E[9] and to reduce blood pressure.[10] Although the mechanisms of these effects are not known, it is plausible that the effects are mediated through increasing vessel wall endothelium production of nitric oxide (NO), which mediates relaxation of smooth muscle cells in the vascular wall.

Oats (*Avena sativa* L.), like all monocot cereal grains, contain relatively high levels of soluble fibers compared to other cereals; they also contain one-third more protein, nearly four times more fat, and have less starch.

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Importantly, oats contain a number of phytochemicals possessing a phenolic moiety[11] with free-radical scavenging capability and thus exhibit antioxidant properties in vitro.[12] Based on their chemical structure and biosynthetic pathways, these phytochemicals can be roughly divided into low-molecular-weight, readily soluble "free phenols" (such as tocopherols, tocotrienols, flavonoids, hydroxycinnamates, etc.), and bound phenols, or those covalently linked to complex high-molecular-weight and insoluble cell components (such as lignin, cell wall polysaccharides, structural and/or storage protein, etc.). The "free phenols" appear to represent readily absorbed sources of antioxidants in the human diet; however, insoluble "bound phenols" present different challenges for researchers attempting to evaluate their long-term efficacy, since they require further metabolism before absorption from the gastrointestinal tract.

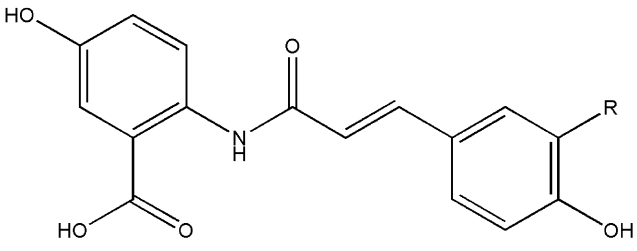
AVENANTHRAMIDES

Oats contain unique, low-molecular-weight, soluble phenolic compounds called avenanthramides (Avns),[13,14] which are not present in other cereal grains. These compounds are antipathogens (phytoalexins), which are produced by the plant in response to exposure to pathogens such as fungi.[15,16] Avns are conjugates of a phenylpropanoid with anthranilic acid or 5-hydroxy anthranilic acid. More than 20 different forms of Avns are present when extracted from oats, and the three major forms are A, B, and C (Figure 1).[17] Investigation of commercial processing of oats including steaming, autoclaving, and drum drying indicates that not all Avns are affected equally by processing.[18] Steaming and flaking moderately reduce the Avn-A content of dehulled oat groats, whereas Avn-C and -B are not affected by steaming. Autoclaving of oat grains and drum drying of steamed rolled oats significantly decrease the Avn content. However, the loss of Avns from drum drying of the whole meal made from autoclaved grains is less.

Antioxidant properties

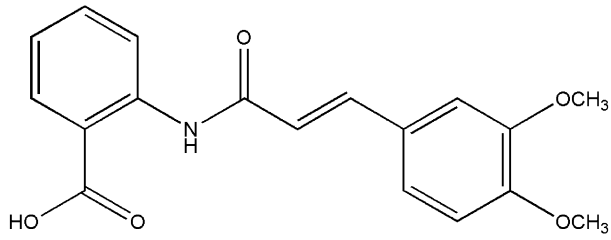
Avns extracted from oats and those synthetically prepared exhibit potent antioxidant properties in vitro and in vivo.[17,19–22] The antioxidant activity of Avns is 10–30 times greater than that of oats' other phenolic antioxidants such as vanillin and caffeic acid.[19] Avn-C, one of the three major Avns of oats, often comprises about one-third of the total concentration of Avns in oat grain (although the relative proportion of Avns is highly variable), and it has the highest antioxidant activity in vitro.[17] By far, these Avns constitute the major phenolic antioxidants present in the oat kernel.[23,24] They occur in relatively high concentrations in the whole grain (up to 300 ppm or 0.03%)[13,25] and in the oat kernel's outer regions (e.g., bran and subaleurone layers),[19] although they are not restricted to these plant tissues.[19,23]

The antioxidant activity of Avn-enriched extract of oats has been investigated in laboratory animals. Supplementing the diet of rats with Avn-enriched extract of oats at 100 mg/kg diet (providing about 20 mg Avns/kg bw) has been reported to increase superoxide dismutase (SOD) activity in skeletal muscle, liver, and kidneys, and to enhance glutathione peroxidase activity in heart and skeletal muscles.[26] Supplementation at 200 mg/kg diet, which provides about 40 mg Avns/kg bw in rats, attenuated the exercise-induced production of reactive oxygen species (ROS).[27]



Avenanthramide

Avenanthramide-a R = H
Avenanthramide-b R = OCH_3
Avenanthramide-c R = OH



Tranilast™

Figure 1 **Chemical structure of avenanthramides (Avns).** Avns are conjugates of a phenylpropanoid with anthranilic acid or 5-hydroxy anthranilic acid. Different forms of Avns are present when they are extracted from oats; the three major forms are A, B, and C. Tranilast [N-(3′,4′-dimethoxycinnamoyl)-anthranilic acid], a synthetic drug (Rizaban, Kissei Pharmaceutical Co, Japan) with structural similarity to the Avns.

Bioavailability

The bioavailability of Avns has been demonstrated in Golden Syrian hamsters.[22] Following oral administration of Avn-enriched extract of oats, the peak plasma concentration of Avns in hamster blood appeared after 40 min. Since most polyphenols exhibit antioxidant activity, their protective effect on vascular function and the prevention of atherosclerosis has been attributed to their protection of LDL oxidation. In this regard, Avn-enriched extract of oats combined with vitamin C, synergistically inhibited LDL oxidation in vitro.[22]

The bioavailability of Avns has also been reported in humans. In a randomized, placebo-controlled, crossover study, Chen et al.[21] reported that the peak plasma concentration of Avns appeared at about 2 h following intakes of 0.5 and 1 g of Avn-enriched extract of oats. The plasma concentrations of different forms of Avns were 40–110 nmol/L after intakes of 0.5 g and 90–370 nmol/L after doubling the dose to 1 g. Interestingly, consumption of Avn-enriched extract of oats significantly increased the plasma concentration of a reduced form of glutathione. These observations suggest that consumption of oat-derived Avns may increase the total antioxidant capacity in laboratory animals and humans.

Anti-inflammatory effects

In addition to demonstrating antioxidant activity, Avn compounds may interact with cellular components, not only through their antioxidant activity, but also through their interactions with the molecular and signaling pathways that govern cellular responses during inflammation. Using the human aortic endothelial cell (HAEC) culture system, the potentially beneficial health effects of oat Avns was found to be mediated via modulation of the cellular and molecular processes that are known to play an important role in the inflammation of arteries and the development of atherosclerosis. These unique oat polyphenols have been shown to inhibit vascular endothelial cell expression of adhesion molecules, including ICAM-1, VCAM-1, and E-selectin. Suppression of these adhesion molecules by Avns resulted in inhibition of monocyte adhesion to HAEC monolayers and reduced production of several inflammatory cytokines and chemokines, including IL-6, IL-8, and MCP-1,[28] the inflammatory components involved in fatty streak formation in arteries. The production of proinflammatory cytokines, chemokines, and adhesion molecules by endothelial cells has been shown to be regulated by redox-sensitive signal transduction involving nuclear transcription factor NF-κB.[29,30] The above-observed effects of Avns on HAEC and other cells are reported to be mediated through inhibition of NF-κB.[31] More recently, dihydroavenanthramide (DHAv), a synthetic analog of Avn, has been shown to protect pancreatic β-cells from damage[32] via inhibition of NF-κB. In a series of experiments, Guo et al.[31] determined that suppression of the expression of NF-κB activity by Avns is mediated via inhibition of the phosphorylation of IKK and IκB, and by suppression of proteasome activity in endothelial cells.

Antiproliferative effects

It is important to note that Tranilast [N-(3′,4′-dimethoxycinnamoyl)-anthranilic acid], a synthetic drug (Rizaban, Kissei Pharmaceutical Co, Japan) with structural similarity to the Avns (Figure 1), was originally developed and is currently used in Japan as an antihistamine. Later, it was discovered to have an antiproliferative effect on vascular smooth muscle cells (VSMCs), and in clinical trials it prevented restenosis after percutaneous transluminal coronary angioplasty.[33–37] Cell culture studies have also revealed that, like Tranilast, Avns inhibits proliferation of VSMCs,[38] a process that is known to be a major contributing factor to the development of atherosclerosis and restenosis after angioplasty.[39,40] Subsequently, Nie et al.[41] studied the molecular mechanism of Avns' inhibition of VSMC proliferation and showed that, through modulation of cell cycle regulatory proteins such as p53, p21*cip1*, p27*kip1*, cyclin-D1, and pRb, Avns inhibits cell cycle signaling at the G1 to S phase transition. It was reported that Avns and Avn-C (synthetically prepared) suppressed phosphorylation of pRb, whose hyperphosphorylation is a hallmark of the G1 to S transition in the cell cycle. This was accompanied by a decrease in cyclin D1 expression and an increase in cyclin-dependent kinase inhibitor p21*cip1* expression, without significant changes in p27*kip1* expression. Furthermore, Avn-C treatment increased the expression level and stability of p53 protein, which could account for the increase in p21*cip1* expression. In a recent set of studies, our research group examined the antiproliferative effects of Avns on several cancerous cell lines and found that Avn-enriched extracts of oats, Avn-C, and the methyl-ester derivative of Avn-C are more effective on colonic cancer cell lines, including Caco-2, HT29, LS174T, and HCT116, than on prostate or breast cancer cell lines.[42] While this is a preliminary observation, it provides additional insight into the mechanism by which consumption of oats, with their high fiber content and Avns, may reduce the risk of colon cancer.

Vasodilation effects

Another potentially interesting biological effect of Avns on the cardiovascular system would be their effect on nitric oxide (NO)-dependent vasodilation. Nie et al.[38]

reported that Avns increase NO production and endothelial NO synthase expression by both endothelial cells and VSMC. This effect of oat Avns might have contributed to the previously observed increase in flow-mediated vessel dilation and reduction of blood pressure in humans following consumption of oats and oatmeal in earlier studies.[9,10] The inhibitory effects of oat Avns on VSMC proliferation and on the increase of NO production are additional characteristics that potentially lend another CHD-related health benefit to oats, beyond their known effect of lowering blood cholesterol.

Anti-itch effects

For some time, oatmeal has been recognized as a remedy for the treatment of poison ivy, sunburn, eczema, and psoriasis. Oat colloidal extract containing Avns has also proved to have antihistamine and anti-irritation activity.[43] While the anti-itching property of oats and oatmeal has been known for centuries, a recent report provided molecular evidence for the mechanism by which oat Avns may exert their soothing effect on irritated skin. Sur et al.[44] reported that at concentrations as low as 1 ppb Avns inhibited NF-κB activation in keratinocytes and reduced release of IL-8, a proinflammatory cytokine. In addition, topical application of Avns at 1–3 ppm mitigated inflammation in murine models of contact hypersensitivity and neurogenic inflammation and reduced puritrogen-induced scratching in a mouse model of itching. These observations indicate that Avns of oats appear to mediate oats' anti-inflammatory and anti-irritant effects, and that they probably work through inhibition of histamine signaling. DHAvn, a synthetic derivative of Avn, which has been developed as a drug, reduces histamine-related skin disorders like itching, redness, and wheals.[45]

Cytoprotection effects

It was also reported that DHAvn increased resistance of RINm5F cells and pancreatic islets to cytokine-induced toxicity and decreased β-cell destruction and maintained normal insulin secretion capacity. In vivo, pretreatment of mice with DHAvn blocked the development of Type 1 diabetes induced by streptozotocin-treatment, probably by preserving functional β-cells in the pancreas.[32]

CONCLUSION

Taken together, current evidence suggests that consumption of foods containing oats is beneficial. Oats keep the heart healthy by lowering total and LDL cholesterol through β-glucan content and by suppressing inflammation, relaxing arteries, and inhibiting SMC proliferation; these effects are due to oats' unique polyphenol content, the avenanthramides, which potentially contribute to the reduction of CHD risk. In addition, the polyphenols of oats possess anti-inflammatory action and antiproliferative properties that, combined with oats' high fiber content, may contribute to the reduction of colon cancer risk. It also appears that oats' anti-irritation effect on skin, which has been recognized for centuries, is mediated, at least in part, by the presence of oat polyphenols. These findings suggest that oat avenanthramides and synthetic analogs provide a broad range of health benefits that complement the already known health benefits derived from oats. Thus, current evidence indicates that the regular incorporation of foods containing oats into the daily diet may reduce the risk of several diseases associated with inflammation.

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