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REVIEW ARTICLE

Avenanthramides of Oats: Medicinal Importance and Future Perspectives

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ABSTRACT

Avenanthramides (Avns) are polyphenols found exclusively in oats. Consumption of oats has been linked with a decreased risk of several important diseases such as cancer, diabetes and cardiovascular diseases. Avns possess an array of bioactivities including anti-inflammation, antiproliferation, antioxidation, antipruritic, and vasodilator activities. Recently, Avns have been found to be bioavailable in humans and have reported to modulate different signaling pathways associated with cancer, diabetes, inflammation, and cardiovascular diseases. We document all updated and relevant literature about the medicinal benefits of Avns. These findings suggest that these polyphenols can be a potential therapeutic candidate for the treatment of several diseases. This review summarizes the updated literature on the Avns and their future prospects in the prevention of various diseases.

Key words: Avenanthramide, nutraceuticals, oats, polyphenols

INTRODUCTION

Oats produce unique soluble polyphenolic amides known as avenanthramides (Avns). Around 40 Avns which consist of anthranilic acid and hydroxycinnamic acid derivatives have been identified and classified based on their structure.[1-6] Avns are low molecular weight phytoalexins found in leaves, seeds during germination, predominantly in bran and subaleurone layer of oat groats.[1,7-9] These polyphenolic compounds are produced in response to the infection/inoculation by an incompatible race of crown rust fungus (*Puccinia coronata f sp. Avenae*) or when oat leaves are treated with various elicitors (e.g., chitin fragments, a host-specific toxin, heavy metal ions, victorin C, Ca ionophore, etc.).[10] Therefore, Avns are a group of secondary metabolites produced by oats for its defense. Their production can be increased by biotic and abiotic factors such as on fungal infection (*P. coronata* in oat leaves) and are relatively stable at pH 4–6.[1,2] Avns are more stable to ultraviolet (UV) light and pH than phenolic acids.[11] Structurally, Avns are divided into two groups; Group 1 and Group 2. Group 1 has amides of different cinnamic acids and Group 2 has cinnamic acids with 5-hydroxy-anthranilic acid. The major forms of Avns are Avns-A, Avns-B, and Avns-C among all reported Avns. These major forms of Avns come under Group 2.[8,9,12,13] Avns have similar structures to the synthetic drug, a well-known antihistamine compound tranilast (N-[3',4'-dimethoxycinnamoyl] anthranilic acid) used in allergy and autoimmune disorders [Figure 1].[14-17] Among all Avns, Avns-C has the highest antioxidant property, maximum heat stability during commercial processing, and present in relatively high concentration in oats (up to 300 ppm).[9,12,13,18] Avn-B biosynthesizes and metabolizes more actively than Avn-A. Commercial processing analysis of Avn indicates that Avn-B and Avn-C remain unaffected by steaming process whereas Avn-A gets reduced.[19,20] Avns are bioavailable to the blood circulation. When given by oral ingestion in the rat, it reaches peripheral tissues and accumulates in hepatic, cardiac, and skeletal muscle tissue differentially. Avns' bioavailability has also been observed in humans and golden hamsters with retention time approximately 2 h and 40 min.[10,21-23] Various *in vitro* and *in vivo* studies suggest a protective role of Avns against several chronic diseases such as cardiovascular diseases, cancer, and diabetes. Avns have anti-inflammatory, antifibrotic, antipruritics, antiatherogenic, and vasodilator properties.[23-25] Eudes *et al*. recently demonstrated sustainable biological production of two valuable Avns, i.e., Avn-D and Avn-F, from glucose by *Escherichia coli*.[26] They identified a molecular pathway for microbial production of Avns, which has several advantages such as fewer requirements for toxic chemicals and natural sources, simple extraction, and consistent quality production. Considering a wide range of therapeutic applications of Avns and the fact that these are chemically synthesized or extracted from food source, i.e., oats, this approach seems promising, eco-friendly alternative method of Avns bioproduction. In a recent study conducted on mice and human microbiota, Avns get metabolized and produce bioactive metabolites by mice and the human microbiota.[27]

This review highlights the importance of Avns in various diseases such as atherosclerotic plaque formation, inflammations, diabetes, skin disorders, and cancer and the future prospects of using these secondary metabolites as therapeutic agent.

MATERIALS AND METHODS

All the information of this review was obtained by the comprehensive literature study. Literature search was done using the electronic

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databases including Medline/PubMed, Scopus, ScienceDirect, and Google Scholar.

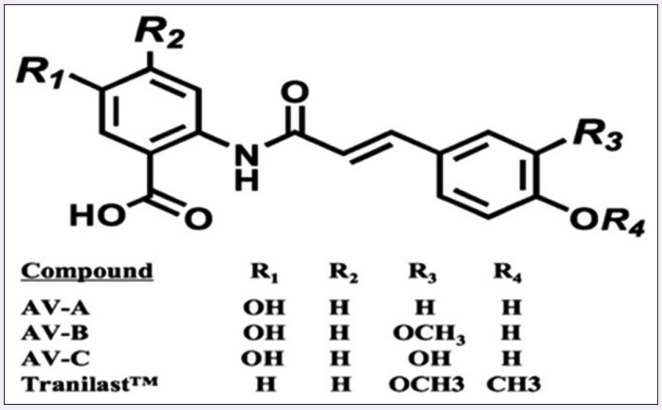
AVENANTHRAMIDES AS ANTICANCER AGENT

Chemoprevention by natural products or their analogs is of great interest and considered as a promising, inexpensive, and readily applicable approach to the cancer control and management. A synthetic analog of naturally occurring Avns is dihydro-avenanthramide (DHAvD). DHAvD suppresses activation of nuclear factor-kappa B (NF-κB) which in turn regulates the expression of matrix metalloprotease (MMP-9).[28] MMP-9 promotes invasiveness of MCF-7 breast cancer cells.[28] Further, a study was conducted by Lee *et al*. to assess the effect of DHAvD on invasion of breast cancer cells (MCF-7 cells) and to elucidate the molecular mechanisms involved in this activity. In this study, MMP-9 expression and subsequent mitogen-activated protein kinase (MAPK)/NF-κB and MAPK/activator protein (AP-1) pathway were induced by treating MCF-7 with the 12-O tetradecanoyl phorbol-13-acetate (TPA). DHAvD inhibited the TPA-triggered invasion potential of MCF-7 cells and strongly blocked the MAPK/NF-κB and MAPK/AP-1 signaling pathways in MCF-7 breast cancer cells, suggesting that DHAvD may be a potential candidate for preventing breast tumor invasion and metastasis *in vivo*.[28,29] β-catenin is a key mediator of Wnt pathway. In the aberrantly activated Wnt pathway, erratic stabilization of β-catenin is a crucial step in several human cancers including colorectal cancers, cervical cancer, almost half of prostate cancers, and around one-third of melanoma.[30] Therefore, attenuation of Wnt/β-catenin signaling pathway is considered as a promising target for cancer therapy. In this regard, Avns could be a potential chemopreventive agent as they are reported to modulate aberrantly activated Wnt/β-catenin signaling pathway in cervical cancer cells. Avns-A modulates upstream steps of β-catenin-mediated transcriptional activation of Wnt target gene, cMyc, and suppresses proliferation of human cervical cancer cells.[30,31] Avns and its methylated form (CH3-Avns-C) inhibit the proliferation of several human colon cancer cell lines. The inhibitory effect of Avns on these cells is independent of cyclooxygenase-2 expression and prostaglandin (PGE-2) production.[32] In another recently conducted study, Wang *et al*. reported that even the Avn 2c and its metabolites DHAvD-C (M6) cause apoptosis of human colon cancer cells (HCT-116). DHAvD-C shows the highest inhibitory potential among the six tested compounds (2c, avenanthramide-C, DH-2c, DHAvD-C, DH-2f, DHAvD-B, caffeic acid, 5-hydroxyanthranilic acid, and 2f, avenanthramide-B) in terms of triggering apoptosis in human colon cancer cells.[27] Avns also promote apoptosis alone and in combination with vitexin-2-o-xyloside in highly resistant malignant cell lines, CaCo-2 colon cancer cells and HepG2 liver cancer cells.[33]

Taken together, these studies suggest that Avns can exert their anticancer effects by modulating different cell signaling pathways and activating cell death signals and thereby inhibiting cancer development or progression [Figure 2].

Avenanthramides as antioxidant

Antioxidants are substances which protect cells from the oxidative damage and thereby help in preventing or alleviating several chronic diseases caused by reactive oxygen species (ROS) generation. Several preliminary studies reported significant antioxidant activity in the oat extracts.[34-36] However, the specific component in the extract responsible for this activity was not known. Dimberg *et al.* reported for the first time about the antioxidant activity of Avn. Their group isolated two Avns A1 and A2 and reported a significantly higher antioxidative potential of these Avns than the other simple phenolics. However, this antioxidative potential was lower than that of α-tocopherol.[37] In another study, three most abundant Avns, Bf, Bp, and Bc, were synthesized and purified, and their antioxidant activity was measured in *in vitro* systems. All Avns showed antioxidant activity in both the assays. The order of antioxidant activity was found as Avn-C > Avn B > Avn-A.[9,36-38] These oat phenolics also inhibit the calcium led oxidation of low-density lipoprotein (LDL) in a dose-dependent fashion. Moreover, Avns also show synergistic interaction with vitamin C, suggesting that Avns may act synergistically with other antioxidative compounds. During rigorous exercise, individuals are more susceptible to increased exposure to ROS.[39] Avns have now become an interesting and novel dietary supplement because of its antioxidant potential. The antioxidant potential of oat's extract containing Avns has been studied in rats. Avns supplementation does not have a direct effect on ROS production in most of the tissues. However, the dietary addition of Avns could decrease the ROS production and related lipid peroxidation caused by strenuous exercise, suggesting its effect on selected tissues. The antioxidant effects of Avns could be related to its effect on the antioxidant enzymes of the tissues such as superoxide dismutase (SOD) and glutathione (GSH) peroxidase activities. However, the precise molecular mechanism is not yet explored.[37] Similar type of another study was conducted to investigate whether dietary supplementation of Avns would attenuate muscle oxidative damage induced by lengthening contraction of the skeletal muscle (23). The results showed that Avns at the given dietary dose had no significant antioxidant response. Inhibitory effect of Avns on ROS generation indicates that it may attenuate specific pathways of ROS production.[23] The antioxidant nature of Avn A, B, and C and



Compound	R_1	R_2	R_3	R_4
AV-A	OH	H	H	H
AV-B	OH	H	OCH_3	H
AV-C	OH	H	OH	H
Tranilast™	H	H	OCH3	CH3

Figure 1: Chemical structure of avenanthramide and tranilast (a well-known anti-histamine), its analog (Chen, *et al*., 2007; Sur *et al*., 2008; Lee-Manion *et al*., 2009)

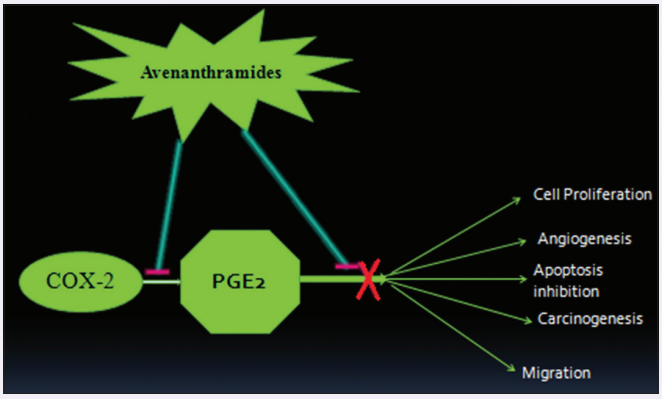


Figure 2: Avenanthramide inhibiting cyclooxygenase-2 enzymatic activity and prostaglandins production which further helps against various chronic conditions shown

its pharmacokinetics studies have been performed in healthy adults in a randomized, placebo-controlled trial. Placebo or 0.5 or 1 g Avn-enriched mixture (AEM) of the oats was given to the subjects, plasma samples were collected after 10 h, and then the concentration was measured. The bioavailability of Avns-A was reported to be 4-fold higher than that of Avns-B (at 0.5 g AEM dose), suggesting that oat Avns have good bioavailability and increase in antioxidant capacity in healthy adults.[23] In another study, the antioxidant and antigenotoxic actions of synthetic form of Avns were observed using 2,2-diphenylpicrylhydrazyl (DPPH) assay and ferric reducing antioxidant potential assay, and the most reactive Avns were found to be 2c in comparison to 2p and 2f. The antigenotoxic activity was determined using the comet assay with hydrogen peroxide-stressed human adenocarcinoma colon cells (HT-29 cells). The results confirmed the DNA damage preventing role of Avns. Avns-2c had the maximum protective effect at a very low concentration (0.9 μmol/L). The trend of antigenotoxic effect and antioxidant potential was similar (2c >2p. 2f). However, these effects were not significant.[16] Further, the aromatic substitution in the aromatic rings of 15 Avns and its effect on the structure-antioxidant activities were evaluated using DPPH assay. The important findings of this study were that compared with α-tocopherol, the Avns protected linoleic acid from oxidation slowly but for a longer duration.[41,42] The antioxidant capacity of Avns was also observed on human serum in a randomized trial with oats-derived Avns capsules or placebo for 1 month. The levels of serum SOD and reduced GSH hormone was found to be significantly increased along with a decreased in the total cholesterol, triglyceride, and LDL cholesterol levels.[43] Moreover, it is suggested that Avns can be used in the food industry to prevent the oxidative reaction of unsaturated fatty acids.[17] Moreover, Avn-rich extract is also reported to show the antioxidant activity against the D-galactose-triggered oxidative stress.[44] All these findings suggest that Avns can serve as a potential dietary antioxidant supplement; however, its tissue-specific effects need to be further investigated.

Avenanthramides in inflammation

Avns not only act as anti-oxidant but also inhibit pro-inflammatory processes. It is a well-known fact that the inflammatory processes have a significant role in different diseases and in this process; vascular endothelium and immune cells along with several pro-inflammatory immune mediators participate. The anti-inflammatory activity of Avns has been reported on human aortic endothelial cells (HAECs). Supplementation of partially purified AEM to HAECs decreased the production of pro-inflammatory cytokines (interleukin [IL]-6, IL-8, and MCP-1) which bring the immune cells to the site of stimulation.[45] Furthermore, these unique oat polyphenols inhibit vascular endothelial cell expression of adhesion molecules, including ICAM-1, VCAM-1, and E-selectin.[45] Later, when this study was carried out using the synthetic form of Avns (Avns-c and CH3-Avns-c) having higher potencies, it was found that the suppression of these pro-inflammatory cytokines was done through the inhibition of NF-κB activation and this activity is mediated by inhibiting phosphorylation of inhibition kappa B (IκB) kinase (IKK) and IκB as well as by reducing proteasome activity. NF-κB belongs to the family of eukaryotic transcription factors, which regulates the transcription of the genes associated with the inflammatory pathways. However, Avns do not directly inhibit binding of NF-κB to DNA rather inhibit it indirectly. Moreover, the methyl derivative of Avns-c has more potent anti-inflammatory activity than other Avns.[46] Avns are found in oats at the concentration of approximately 300 ppm and exert their anti-inflammatory activity in the skin also.

Avns attenuates the phosphorylation of p65 subunit of NF-κB and thereby promotes the inhibition of nuclear factor kappa B-α (IκB-α) in keratinocytes at a very low concentration (1 ppb). Moreover, in *in vitro* studies, Avns treatment inhibits the tumor necrosis factor-α (TNF-α)-triggered NF-κB luciferase activity which further leads to the reduction in the release of IL-8. The effect of topical use of Avns is so profound that even a dose of 1–3 ppm, Avns reduce neurogenic inflammation substantially in murine models with contact hypersensitivity and neurogenic inflammation.[15] High levels of dietary intake of Avns significantly reduce the systemic inflammatory response in postmenopausal women as indicated by lowered neutrophil respiratory burst activity and plasma C-reactive protein levels. Avns supplementation attenuates plasma IL-1 β levels and suppresses mononuclear cell NF-κB activation. The encouraging results of these studies indicate that the dietary supplementation of Avns at the standardized optimum dose could be very helpful in reducing inflammation caused by strenuous exercise.[47]

AVENANTHRAMIDES IN DERMATOLOGY

Oatmeal has long been used in the treatment of different types of dermatologic disorders. Colloidal oatmeal has been found quite effective in the treatment of atopic dermatitis, drug-induced rash, psoriasis, and other related conditions. In recent years, several *in vitro* and *in vivo* studies conducted to elucidate the different mechanisms of action of naturally derived colloidal oatmeal have revealed the anti-inflammatory and antihistamine activity of colloidal oatmeal. It is noteworthy that Avns are responsible for many of these effects. Avns are reported to have protective effects in various dermatological complications such as atopic dermatitis sunburn, allergic, or contact dermatitis.[15] These complications are characterized by the abnormal functioning epidermal barrier, itching, inflammation of skin, and higher levels of the molecules which promote inflammatory pathways such as IL-8, TNF-α, and arachidonic acid.[48] Avns possess anti-inflammatory and anti-itching effect (antipruritics).[15] The anti-inflammatory effects of Avns have been demonstrated in human keratinocytes. Avns suppress the activity of NF-κB transcription factor in TNF-α-treated human keratinocytes. NF-κB is one of the very crucial regulatory transcription factors. Avns abrogate the inflammatory effect induced by the TNF-α in the human keratinocytes as it reduces the IL-8 production, indicating that the anti-inflammatory action of the Avns is exerted through the NF-κB pathway. The effect of the Avns on contact hypersensitivity, neurogenic inflammation, and itching has also been studied in the mouse model. Avns reduce oxazolone-induced contact hypersensitivity (in a dose-dependent manner), resiniferatoxin-stimulated neuronal inflammation, and compound 48/80-induced histamine-mediated itch. It causes a substantial reduction in substance P-induced histamine release from mast cells.[49] Another study explained that as compared to flavonoids, amino acids, lipids, and saponins. Avns-enriched fraction of oats strongly reduces UV-induced erythema within 20 h after its skin application. Further *in vitro* studies confirmed that highly purified Avns significantly suppress histamine and protect skin from erythema.[50] DHAvD (synthetic analog of Avns) is useful in preventing UV light-induced skin photoaging as it inhibits UVB-caused ROS generation in fibroblasts and suppresses UVB-induced phosphorylation of MAPKs, activation of NF-κB, and AP-1.[51] To sum up, Avns modulate nerve responses and has beneficial effect against dermatological disorders. In addition to this, Avns may also prevent the chances of secondary inflammation due to the disrupted barrier function of the skin (atopic dermatitis and eczema) by controlling sensory nerve response to the site of itching and subsequent scratching.

AVENANTHRAMIDES IN CARDIOVASCULAR DISEASES

Atherosclerosis is the leading cause of death worldwide. It is a coronary heart disease in which inflammatory mediators cause recruitment of

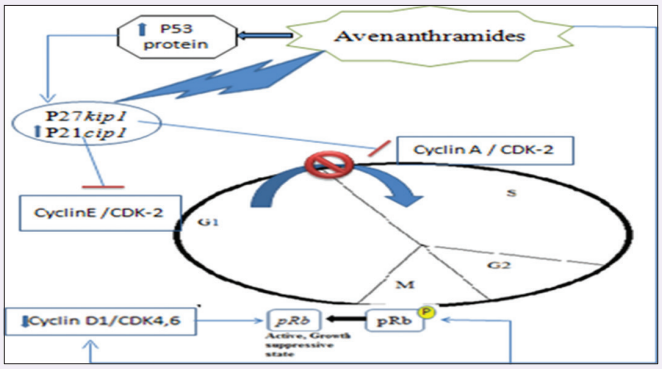


Figure 3: Antiproliferative mechanism involved in inhibition of vascular smooth muscle cell proliferation: Avenanthramide suppresses phosphorylation of retinoblastoma protein by decreasing cyclin-D1 expression and increasing cyclin-dependent kinase inhibitors p21Cip1 expression without significant modifications in p27kip1 production. Avenanthramides are also responsible for increase in expression level and stability of p53 protein which further increases p21cip1 expression

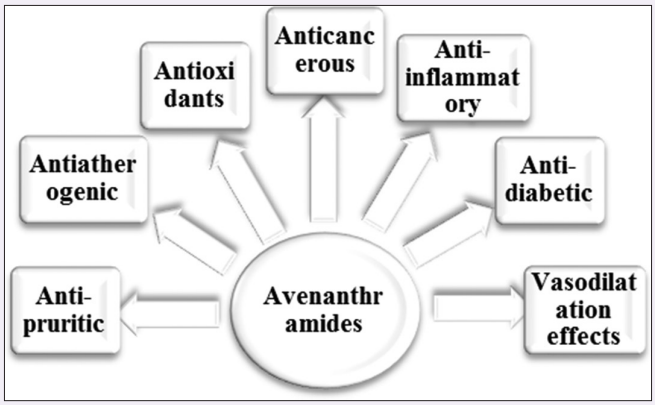


Figure 4: Versatile nature of avenanthramide

leukocytes to the vascular endothelium followed by plaque formation and thickening of the arterial walls.[45,46,52,53] Consumption of oats and oats' products has been linked to reduce the risk of cardiovascular disease.[13,19,40,54-58] A number of pro-inflammatory mediators (such as ICAM1, VCAM1, MCP-1, and IL-6) activate the proliferation and migration to the intimal layer of the endothelium which finally lead to accumulation of lipids and plaque formation in atherosclerosis.[51] NF-κB plays a crucial role in this process as it is associated with the expression of these proinflammatory molecules. Therefore, NF-κB is a key candidate for regulatory control. The first study on the antiatherogenic potential of Avns was performed on HAEC monolayers by examining the effects of AEM on interactions between the immune mediators and the endothelial cells as the interaction between these two is mainly responsible for the progression of atherosclerosis. HAEC, pretreated with AEM, significantly suppressed the expression of IL-1β induced expression of adhesion molecules, chemokines, and cytokines. To mimic the *in vivo* inflammatory conditions in the HAECs, the cells were treated with IL-1β; a key pro-inflammatory cytokine to observe the cell adhesion. Pretreatment of activated HAECs with different dosage of AEM inhibited the cell adherence in a dose-dependent manner. Moreover, AEM also inhibited the IL-1β-induced expression of adhesion molecules (ICAM1, VCAM1, and E-selectin) in a concentration-dependent manner. These adhesion molecules assist in the migration of leukocytes to the endothelium and plaque formation.[44] The impaired nitric oxide (NO) production and vascular smooth muscle cells (VSMCs) proliferation are the two important conditions that lead to the development of atherosclerosis. Therefore, in this regard, Nie *et al.*, 2006a[53] conducted a study to observe the effect of synthetic Avns-2c on the proliferation of SMC and NO production by SMC and HAECs. The proliferation of SMC was induced by fetal bovine serum. The results demonstrated that synthetically prepared Avns-2c treatment inhibited the cell proliferation in a concentration-dependent manner.[51] Avns-2c treatment also led to more than twofold increase in the expression of endothelial NO synthase mRNA and the production of NO increased significantly in both VSMCs and HAECs, indicating that the Avns may prevent atherosclerosis by inhibiting SMC proliferation and subsequent increase in NO production.[51] The same group further continued their work to determine the molecular mechanisms by which Avns-c inhibits the progression of cell cycle on rat embryonic aortic SMC line A10. Treatment of A10 cells with Avns-2c decreased the number of cells shift from G1 to S phase suggesting it may trigger the G1/S cell cycle checkpoint since, hyperphosphorylation of retinoblastoma protein (pRb) is a marker of cell cycle progression from G1 to S phase, Avns2c treatment decreased the phosphorylation of pRb [Figure 3]. The study concluded that Avns-2c treatment arrests SMC proliferation at G1 phase.[52] Further, to determine whether the inhibitory effect of Avns on the expression of pro-inflammatory immune mediators is related to NF-kB-dependent transcription, Guo *et al.* continued their previous work on HAECs. The HAECs were treated with Avns of oats (AVnsO) and synthetically prepared Avns (Avns C and CH3-AvnsC). AvnsO decreased the IL-1β-stimulated activity of the NF-κB p50 in a dose-dependent fashion in HAECs by inhibiting the DNA binding of NF-κB p50. Similar results were obtained with synthetically prepared methylated form of Avns C (CH3-Avns). This led to the inhibition of IL-1beta- and TNF alpha-stimulated NF-kappa B activation and significant reduction in the secretion of MCP-1, IL-6, and IL-8 by HAEC. This inhibitory effect of Avns on activation of NF-κB is mediated by inhibiting the phosphorylation of IKK and IκB as well as by reducing the proteasome activity. However, the Avns inhibition on NF-κB activity was not in direct manner rather in an indirect way. All the Avns, AvnsO, Avns-C, and CH3-Avns-c also inhibited the NF-kB-dependent reporter gene expression induced by TNFR-associated factor-2 (TRAF2), TRAF6, and NF-kB-inducing kinase. Among all the Avns, the CH3-Avns-C had the highest potency to inhibit the pro-inflammatory cytokines.[45]

AVENANTHRAMIDES AS ANTIDIABETIC COMPOUND

A synthetic analog to naturally occurring Avns, DHAvD is reported to protect pancreatic β-cells from cytokines and streptozotocin toxicity in mice models.[54] Type 1 diabetes is an auto-immune disorder in which the immune system is activated to destroy the insulin-producing β-cells in the pancreas. Pro-inflammatory cytokines are reported to (such as, IL-1 β, TNF-α, and IFN-γ) trigger β-cells death and subsequent insulin deficiency in *in vitro* and *in vivo* model.[55] In a study conducted by Lv *et al.*, they observed the effect of DHAvD on cytokine (IL-1 β and IFN-γ)-induced or streptozotocin-induced β-cell damage. They found that the pretreatment of rat pancreatic β-cells (RINm5F cells) or isolated pancreatic islets with IL-1β and IFN-γ induces β-cell damage which is mediated by NF-κB-dependent signaling pathway. DHAvD protects β-cell from this damage by suppressing NO production. Further, they assessed the ability of DHAvD to protect against streptozotocin (a compound having preferential toxicity toward pancreatic β-cells)-mediated type 1 diabetes and observed that prior injection with DHAvD maintained the normal level of blood glucose and insulin besides blocking the

STZ-stimulated islet destruction and maintaining the number of islet cells. Moreover, pretreatment with DHAvD before injection with STZ suppressed NF-κB activation, indicating that NF-κB activation may be a key determinant in the STZ-triggered islet destruction in the mouse model. This study suggests that these alkaloid phenolic compounds can maintain normal level of plasma glucose and insulin secretion and hence prevent chronic disease such as type 1 diabetes.[59,60] The encouraging results of Lv *et al.* on pancreatic β-cells suggest that the potential role of Avns in diabetes needs to be further explored.

CONCLUSION AND FUTURE PROSPECTS

Natural-based therapies play an important role in handling several diseases such as inflammatory and cardiovascular diseases, diabetes, obesity, and cancer. Natural products with their large molecular diversity and unique biological functionality without any apparent side effect remain a primary choice of drug development for cancer and several other diseases. In cancer, normal cell growth, differentiation, and behavior are lost, and there occurs alteration in the regulation of cell cycle. Thus, any significant changes of cell cycle-specific proteins by Avns can potentially affect and block the continuous proliferation of tumorigenic cells. A considerable amount of evidence indicates that Avns interfere at various stages of cancer progression through modulation of different cellular processes such as by inhibiting irregular Wnt-signaling pathway, MAPK pathway, and cyclooxygenase-2 enzymes activity, stabilizing P53 protein, and regulating pRb phosphorylation. This alkaloid can affect the overall process of tumorigenesis by various mechanisms and their effects are tissue/organ-specific and dose-dependent. Taken together, these finding suggests that Avns may serve as potential therapeutic agent in cancer and regular consumption of Avns-rich oats could have preventive and curative benefits in many chronic and age-related diseases. It has been demonstrated that these unique oats metabolite suppress inflammation, block smooth muscles proliferation, and relax blood vessels and therefore can be considered as potential candidates for preventing inflammatory diseases. Further, these soluble polyphenols have been recognized for antipruritic effects on dermis for centuries. In addition, these alkaloids of oats possess antidiabetic properties. Interestingly, Avns exhibit a significant role not only in cardiovascular protection but also in improving cognitive ability by vasodilating cerebral arteries. To sum up, Avns play a versatile role and could be of enormous health benefits in preventing several diseases [Figure 4].

The current emphasis should be on precise identification of the molecular mechanism of action of Avns. Moreover, future studies should also explore the synergistic effect of Avns with other natural compounds so as to develop a more effective and less toxic therapy for the above-mentioned diseases. It is a fact that most of the world's population is unable to afford modern medicine. In addition to the cost issue, in most of the diseases, drug resistance is another area of concern. The modern synthetic drugs also exhibit side effects/toxicities to other systems of the body. Because of Avns' pharmacological safety, these can be used alone or along with current chemotherapeutic agents to enhance therapeutic effects and minimize chemotherapy-induced toxicity. Therefore, it is a fact that regular consumption of oat-enriched Avns in diets is beneficial not only for cancer and heart-related disease but also for several other diseases. The future studies should be focussed on elucidation of the precise molecular pathways modulated by Avns so that it can be used as a future therapeutic agent for several diseases including one of the most devastating diseases to modern society like cancer. The natural compounds have innate affinity for the cellular receptors. It is suggested that a comprehensive evaluation of various pharmacological parameters of Avns followed by controlled clinical trials could be a boon which would improve the availability of Avns as future drug at an affordable cost with more effective and less toxic therapy for several chronic diseases.

The purpose of this study is to concise all the available information about AvnsO for future research. These studies suggest that more research is required to explore Avns' full therapeutic potential.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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