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MINI-REVIEW ARTICLE

Bioactivity of Marine Natural Product Xyloketals

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Dedicated to Prof. Tarun Kumar Sarkar to celebrate his 70th birthday.

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Abstract: Oceans can play a major role in supplying life-saving medicines to the world. Although considerable progress has been made in finding new medicines from marine sources, great efforts are still necessary to examine such molecules for clinical applications. Xyloketals are an important group of natural products with various powerful and prominent bioactivities such as inhibition of acetylcholine esterase, antioxidant activity, inhibition of L-calcium channels, radical-scavenging behavior, suppression of cell proliferation, reduction of neonatal hypoxic-ischemic brain injury, *etc*. This review describes the isolation and structural characterization of all xyloketal natural products giving major emphasis on their bioactivity.

Keywords: Bioactive molecules, natural products, xyloketals, marine compounds, drug development, acetylcholine.

1. INTRODUCTION

Natural products play an important role in the development of new drug molecules. Around 40% of the world's best-selling drugs come from natural products directly or indirectly. The natural product may be used directly into the new drug ingredient in some cases. Moreover, the natural product is largely deemed to be a starting point for the development of drugs. Medicinal chemists may routinely modify the compound to enhance its efficacy, selectivity, and pharmacokinetic properties as a drug. In that scenario, a natural product derivative would eventually be developed. The sea occupies 70.8% of the earth and has plenty of life. Because of their diverse living environment and lengthy evolutionary history, these marine organisms are likely to have a special biochemical system and genetic background. The marine ecosystem is now a major source of medicines to be found from natural products. As for example, cod-liver oil, is rich in vitamins A and D, and it was possibly the first widely commercialized marine natural products [1-4].

In 1984, arabinofuranosyl-adenine (Ara-A) was extracted from the gorgonian Eunicella cavolini and used successfully in the clinic for antitumor and antiviral therapy. The biodiversity of the marine environment has given rise to many interesting molecules. Furthermore, marine substances have strong biological functions, such as analgesic, antiallergic, antiviral, anticancer, anti-inflammatory, and immunomodulatory. As marine microorganism research increases, a growing number of new bioactive and structurally different metabolites are extracted from marine fungi. The reason behind choosing the marine-fungi for developing multiple metabolites is that these species experience the extreme high-pressure marine environment with low nutrients, low temperature, high salt content and lack of light, which is vastly different from the environments on the surface of the earth. Therefore, it is feasible for marine fungi to produce special secondary metabolites to survive in this environment. Marine-derived fungi have been identified to be active and potential sources of valuable anticancer, antibacterial, anti-inflammatory and antiviral drug candidates and thus interest in this area is increasing day-by-day. Hundreds of structurally distinct and biologically active compounds from marine fungi have been identified as of now. The purpose of writing this review is to give a good overview of the biological activities of xyloketal natural products, which are found to be possible drug candidates for the treatment of various diseases.

2. ISOLATION AND STRUCTURAL ELUCIDATION OF THE XYLOKETAL NATURAL PRODUCTS

In 2001, the isolation and characterization of five structurally similar natural products, namely xyloketal A(**1**), B(**2**), C(**3**), D(**4**), and E(**5**), was reported by Lin and coworkers [5]. Such natural products have been collected from the south china sea coastal populations of mangrove fungus Xylaria sp. 2508. These fungi were collected from seeds of an angiosperm tree. Xiaobo *et al*. reported a better isolation technique later [6]. Also, Lin *et al*. recently reported the isolation and structural clarification of xyloketal F(**6**) and G(**7**), two other representatives of these natural product relatives [7, 8]. They also described the isolation of another metabolite later called xyloketal H(**8**) from the fungus *Xylaria* sp 2508. NMR spectroscopy and mass spectrometry clarified the structure of xyloketal H(**8**) [9]. Xyloketal H did not show activity against Hep-2 cell line and gram-positive bacteria *S. aureus* in standard disk assays (200μg/disk). Through detailed spectro-

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scopic studies along with X-ray crystallography, the molecular structures and comparative stereochemistries of these natural products have been elucidated. The complete stereochemistries of xyloketal A (**1**), D(**4**), F(**6**) and G(**7**) are established by examining their Circular Dichroism(CD) spectra. Analogy established the absolute stereochemistry of the remaining members of this class of naturally occurring molecules. All xyloketal molecules have similar 5,6-bicyclic acetal moieties bonded to an aromatic nucleus. It has been observed that the stereochemistries of ring junctions are cis-fused in all cases and the bicyclic acetals are aligned with the methyl groups at the C-5 position of five-membered rings. Xyloketal A(**1**) has a special molecular structure with C_3-symmetry that fuses three bicyclic acetal moieties. It was known that Xyloketal B(**2**) and the minor C_2-symmetric molecule, xyloketal C(**3**), have two bicyclic acetal moieties. Xyloketal D(**4**) and the xyloketal G(**7**) are equivalent regioisomers containing one bicyclic acetal moiety. Xyloketal C(**3**) is comparatively unstable compared to xyloketal B(**2**), a natural regioisomeric product and is isomerized to provide the latter in solution. It is logical to assume that unfavorable dipole interactions constrained xyloketal B(**2**). The isolation and elucidation of the structure of xyloketal E (**5**), a sibling of xyloketal B(**2**), indicates that (4R)-2, 4 dimethyl-4,5-dihydrofuran is a common biogenic antecedent of all these natural products. This natural product is probably formed by a direct substitution reaction of the electron-rich aromatic ring of xyloketal B(**2**) on protonation of the aforementioned dihydrofuran antecedent. In addition, acid-catalyzed condensation of xyloketal B (**2**) with formaldehyde furnished the xyloketal F(**6**). From the same mangrove fungus Xylaria sp 2508, Xu *et al*. found three new metabolites that were present in low quantities and their structures could not be elucidated [10]. Subsequently, fermentation of the fungus in a large scale produces xyloketal J (**10**) along with two other metabolites containing a known substituted dihydro benzofuran moiety. Xyloketal J (**10**) was obtained as colorless, blocky crystals. Xu *et al*. also tested the antibacterial activities of these three metabolites, but they showed no effect against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Sarcina lutea at 50 μg/mL. They could not perform further bioactivity studies due to the low yields of these compounds. Note that after the identification of xyloketal H(**8**) by Lin *et al*., another congener of the xyloketal family was isolated by Yin *et al*. and named as xyloketal H [11]. Later, in order to stop the confusion, compound **9** was named as xyloketal I [12]. The unique structural diversity and promising biological activity of xyloketal natural products attracted the chemical community for their synthesis. Both racemic and some asymmetric synthesis of Xyloketal A-H was reported by various groups using different synthetic strategies [13-23].

3. BIOACTIVITY OF XYLOKETALS

3.1. Inhibition of Acetylcholine Esterase

The initial biological analysis of xyloketals revealed that xyloketal A, B, C, and D (Fig. **1**) were shown to inhibit acetylcholine esterase [24] with IC_{50} values 29.9, 137.4, 109.3 and 425.6 μmol/L respectively [25]. Acetylcholine(ACh) is the most abundant neurotransmitter in the human body and is necessary for cholinergic communication in the cerebrum. In the metabolic saponification of the activated neurotransmitter acetylcholine to inactive choline within the human nervous system, the enzyme acetylcholine esterase (AChE) plays a crucial role. Patients with neurological disorders such as Alzheimer's disease have been found to have a lower level of acetylcholine in their brain tissue. Inhibiting acetylcholine esterase is the most commonly used medical technique for the treatment of Alzheimer's disease [26]. The acetylcholine esterase inhibitor (AChEI) is a biochemical or a drug molecule that inhibits the action of acetylcholinesterase enzyme-catalyzed saponification of acetylcholine, cumulating acetylcholine's rate and period of action. Alzheimer's, Lewy body dementia, and Parkinson's disease are treated with AChEI. AChEIs are primarily used for these neurodegenerative conditions to combat mental dementia symptoms like memory and learning deficits. Thus, for the treatment of such neurological diseases, xyloketal A, B, C, and D are possible lead molecules in drug discovery.

3.2. Antioxidant Action

Oxidative stress plays a vital role in the pathogenesis of several heart diseases. Xyloketal B easily enters into the cell membranes because of its small molecular weight and strong liposolubility. By decreasing the Ang II-induced HUVEC toxicity and the dissimulation of NADPH oxidase function in zebrafish embryos, xyloketal B is a strong natural HO-1 inducer and xyloketal B instigated HO-1 articulation plays a vital function in the antioxidant operation of the natural molecule [27]. Stimulation of the pathways Nrf-2 and PI3 K/Akt and Erk is mainly responsible for the xyloketal B-prompted HO-1 articulation. Additionally, xyloketal B can directly scavenge DPPH free radicals and protect mitochondria from oxidative stress. Thus, xyloketal B has a strong ability to handle oxidative stress-related diseases as a possible drug candidate.

3.3. Inhibition of L-Calcium Channel

Abundant findings published in recent years have shown that in some pathological conditions such as hypertension and atherosclerosis, vascular function is affected. Hypertension is a persistent heart disease correlated with an altered equilibrium in the vasodilator and vasoconstrictor receptors and coronary tissue modifications in the proportion of biological effort. Calcium channel inhibitors are various drug molecules that disrupt calcium ion (Ca^{2+}) movement through calcium channels. Subsequent biological tests found that at concentrations of 0.03 μmol/L, xyloketal A, B, and F block L-calcium channels by 21, 12, and 50% respectively [28]. L-type calcium channels are responsible for controlling the transport of calcium ions in and out of the skeletal, cardiac muscle and the secretion of aldosterone into the adrenal cortex's endocrine cells. Because the large quantity of these channels is found in the cardiac muscle and the calcium ion motion is directly associated with the contraction of the cardiac muscle, as a consequence, calcium channel antagonists are used in patients with hypertension to reduce blood pressure. Hence, xyloketal A, B, and F are considered to be possible drug candidates for the treatment of various cardiovascular diseases.

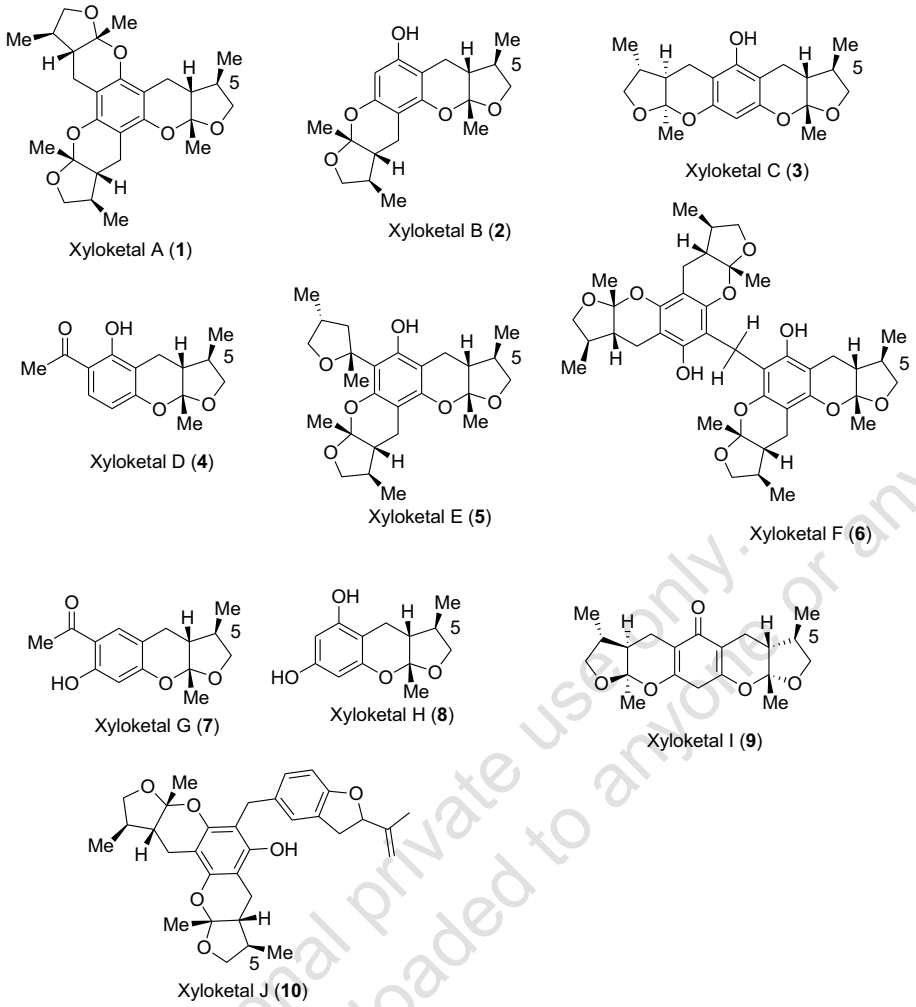

Fig. (1). Structures of Xyloketal A (**1**), B (**2**), C (**3**), D (**4**), E (**5**), F (**6**), G (**7**), H (**8**), I (**9**) and J (**10**).

3.4. Radical-Scavenging Action

Free radicals and other reactive oxygen species (ROS) have inevitable side products in biological redox reactions and emphasize significant roles in health disorder and cell damage. The choice of appropriate antioxidants to scavenge free radicals has therefore triggered keen interest. The antioxidant nature can describe its neuroprotective role and the defensive function of the mitochondria. Using absorption spectrometry, Xu *et al*. stated that a variety of synthetic xyloketals and associated chromans display radical scavenging activities of 2,2-diphenyl-1-picrylhydrazyl (DPPH) and 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) [29]. Results in their research showed that most of the xyloketals have strong radical scavenging properties, although among them, natural product xyloketal B showed substantial antioxidant activity towards DPPH and ABTS.

3.5. Protective Effects Against MPP+ -Induced Neurotoxicity

Lu *et al*. studied the neuroprotective role of the xyloketal B in Caenorhabditis elegans and PC12 cells, response to MPP+ -induced neurotoxicity [30]. Neuro-deterioration viability and DA were tested by distinguishing expression of the green fluorescent protein (GFP) in DA neurons in C. elegans. Cell injury to PC12 was assessed using MTT and nuclear morphology. They assessed the reactive oxygen species (ROS) within the potential of the cell and the mitochondrial membrane along with total GSH. The studies uncovered that xyloketal B protected toward MPP+ in the case of C elegans induced a decrease in viability and a dose-dependent of DA neurodegeneration. In addition to xyloketal B, Li *et al*. prepared 39 divergent xyloketal derivatives [31]. All 40 synthetic compounds are tested for *in vivo* neuroprotective activity by breathing burst assays and prolonged assays of longevity. Some of the molecules exhibit strong neuroprotective activity, and some of the compounds containing benzopyrano pyran ring system display antioxidant activity.

3.6. Depletion of Oxygen-Glucose Deprivation (OGD)-Induced Cell Injury

Oxygen-Glucose Deprivation (OGD) in the PC12 cell line has been used in the development of potential neuroprotective agents as a strong and responsive ischemic stroke model *in vitro*. Firstly, PC12 cells are subjected to a small length of OGD (ischemia), after which they are exposed to model cerebral ischemia-reperfusion injury during re-oxygenation and reappearance of standard culture medium

(reperfusion). This design should therefore, superiorly reproduce the pathological stroke conditions. Xyloketal B can defend PC12 cells against concentration-dependent OGD-induced cell damage and can, therefore, be a successful stroke therapeutic agent [32].

3.7. Depletion of Neonatal Hypoxic-Ischemic Brain Injury

It is usually found that sensorimotor impairment is induced by neonatal hypoxic-ischemic encephalopathy owing to neurodegeneration and brain injury [33-35]. In their research, Xiao *et al*. examined the reaction of xyloketal B and mechanistic pathway to oxygen-glucose deprivation-induced nerve cell death in the critical cortical culture of the mouse and to *in vivo* neonatal mice's hypoxic-ischemic cerebral injury [36]. They found a reduction in neuronal cell death caused by anoxia *in vitro* in the presence of xyloketal B. In fact, xyloketal B facilitated the animals for efficient cognitive rehabilitation following hypoxic-ischemic affront. In comparison, xyloketal B significantly decreased the intake of calcium, decreased the amount of TUNEL-positive cells, decreased the amounts of cleaved caspase-3 and Bax proteins, and increased the Bcl-2 protein portion after hypoxic-ischemic injury. Their findings show that xyloketal B is effective in hypoxia-ischemia models and thus has the potential to act as a lead compound for hypoxic-ischemic brain injury therapy.

3.8. Reduction of Atherosclerotic Plaque Formation and Endothelial Dysfunction

Atherosclerosis is presently the leading cause of death among cardiovascular diseases worldwide [37]. Endothelial dysfunction is an initial key incident involving atherogenesis [38] and was viewed as a standard link in the vascular system of all cardiovascular risk factors, including dyslipidemia [39], hyperhomocysteinemia [40], hypertension [41], diabetes [42], and smoking [43]. Vascular endothelium protection is well established as a therapeutic strategy for clinical prevention and atherosclerosis treatment. For therapeutic inhibition of the progression of atherosclerotic plaque and other cardiovascular diseases, clinical drugs and novel compounds with beneficial effects on endothelial dysfunction are thus of great promise. Two basic endothelium roles correlated with enhancing injury in atherosusceptible areas consist of maintaining the vascular penetrability barrier and ensuring the bioavailability of nitric oxide (NO) [44]. The reason behind the loss of NO bioavailability is mainly due to reduced NO production and further accumulation of species of reactive oxygen (ROS) and is a cardinal component of endothelial dysfunction during atherosclerosis development [45]. The area of interest for medicinal use is the quest for compounds that improve NO bioavailability and eNOS activity. In their study, Zhao *et al*. observed [46] that the dose-dependent addition of xyloketal B decreased the atherosclerotic plaque area both in the aortic sinus and throughout the aorta throughout apoE-/-mice given a high-fat diet. In particular, xyloketal B significantly reduced vascular oxidative stress intensities as well as restoring damaged epithelium quality and NO-dependent artery vasorelaxation in mice vascular hardening. In cultured human umbilical vein endothelial cells (HUVECs), xyloketal B significantly changed the phosphorylation levels of intensity of endothelial nitric oxide synthase (eNOS) and Akt without altering the overall eNOS and Akt expression. Hence their analysis reveals that xyloketal B has a strong *in vivo* anti-atherosclerotic effect due to its antioxidant properties and possible endothelial function enhancement to some degree. The control of phosphorylation of the Akt/eNOS pathway may be attributed to the protective effects of xyloketal B on endothelial cells and will require further research. Since xyloketal B is very stable and has low molecular weight and strong liposolubility, it can be absorbed easily when intragastrically administered and therefore has tremendous potential to develop new drugs against cardiovascular diseases correlated with endothelial dysfunction.

3.9. Suppression of Glioblastoma Cell Proliferation and Migration

The most well-known and aggressive form of brain tumors, glioblastoma, has horribly propagative and invasive characteristics. The need to seek a new and specific drug molecule is important as the existing methodologies have limited clinical effects for the treatment of glioblastoma disease. Chen *et al*. used a U251 cell line of glioblastoma in their analysis first to investigate the impacts of on cell viability, proliferation, and migration of xyloketal B, and further to explore the underlying molecular mechanisms and signaling pathways [47]. Many methods such as MTT analysis, colony development, wound healing, western blot, and patch clamp *etc*. have been used in these studies. They find that xyloketal B reduced cell viability, proliferation, and U251 cell migration. Using wound healing assay they have examined the cell migration. The results show that the treatment of xyloketal B at a concentration 300μm largely inhibits the U251 cell migration. They also discovered that, xyloketal B decreased the signals of pAkt and p-ERK1/2 protein. Therefore, the marine natural product xyloketal B has been identified to be a possible drug molecule for the treatment of glioblastoma, but further research especially *in vivo* studies, is essential before its use. The study shows that the inhibition property of xyloketal B on cell proliferation is time and concentration-dependent. Moreover, xyloketal B at a concentration of less than 300μm mainly shows the inhibitive effect of cell proliferation, instead of the production of cytotoxic effect on the U251 cell.

3.10. Anti-Stress and Anti-Ageing

Ageing is a dynamic and common process that slowly threatens the homeostasis network, which ultimately leads to organism deterioration and even death. Delay in aging ensures the expansion of lifespan as well as healthspan. Previous studies have shown that xyloketal B and its metabolites, a collection of marine novel ketone compounds, have a special antioxidative impact on endothelial and oxidative neuronal injuries. Pang *et al.* explored the impact of xyloketal derivatives on the expanding lifespan and healthspan of Caenorhabditis elegans [48]. The results revealed that most of the selected xyloketals were able to protect Caenorhabditis elegans from heat stress and increase worm lifespan. Altogether, their study showed that xyloketals had good prospects and applications for diseases related to longevity and aging.

3.11. Anti-Hypertensive Effect

Hypertension is a major risk factor that makes patients prone to cardiovascular disorders and has high morbidity and mortality rates. Emerging data show increases in the pathogenesis of hypertension in systemic oxidative stress and vascular inflammation. Endothelial dysfunction, which occurs as the impaired bioactivity of nitric oxide (NO), is an important early occurrence correlated with the impaired diastolic function of the vessel and arises mainly from accelerated oxidation of nitric oxide (NO) due to interactions between NO and superoxid anions. Pharmacological methods have been shown to have antihypertensive impact on restoring endothelial function or complementing NO. Zhao and coworkers had demonstrated that Xyloketal-B can lower the blood pressure in 2K2C renovascular hypertensive rats [49]. Their results showed that Xyloketal-B induces relaxation in rat aortic rings *via* an endothelium-dependent pathway mediated by the NO-sGC-/cGMP pathway and an endothelium-independent pathway involving VDCC blockade mediated by Ca^{2+} entry into VSMCs. One drawback of the analysis is that in VSMCs neither the NO-sGC-/cGMP pathway, nor the Ca^{2+} signaling pathways underlying the antihypertensive effects of Xyloketal-B were confirmed. Hence, the mechanisms of antihypertensive activity of Xyloketal-B should be viewed with caution, and further *in vivo* experiments are needed to establish the exact mechanism.

CONCLUSION

The marine organisms have identified a significant number of novel molecules with powerful pharmacological properties. Although there are still only a few marine derivatives on the market, there are many marine natural products in clinical trials. In recent years, the production of medicines from marine natural products has experienced a revival. In the future, oceans can play a major role in delivering life-saving drugs over the world. While significant progress has been made in discovering new drugs from marine sources, there is still a need for large efforts to investigate these molecules for clinical applications. Xyloketals show different biological activities such as inhibition of acetylcholine esterase, inhibition of L-calcium channel. These molecules can relax blood vessels, improve angiogenesis, promote NO production of endothelial cells, and reduce oxidative stress induced by oxLDL, *etc*. The progress in the synthesis of xyloketals and their derivatives having specific biological activities and their mechanisms of action are thus the active area of research for both organic chemists as well as biochemists. Considering the large area of bioactivity of xyloketal natural products, we infer that these natural products will be promising drug candidates for a range of medical treatments.

LIST OF ABBREVIATIONS

Ach	=	Acetylcholine
AChE	=	Acetylcholinesterase
AChEI	=	Acetylcholinesterase Inhibitor
AngII	=	Angiotensin II
HUVEC	=	Human Umbilical Vein Endothelial Cell
NADPH	=	Nicotinamide Adenine Dinucleotide Phosphate
HO-1	=	Heme Oxygenase-1
Nrf-2	=	Nuclear factor erythroid 2-related factor 2
DPPH	=	2,2-Diphenyl-1-picrylhydrazyl
ROS	=	Reactive Oxygen Species
ABTS	=	2,2'-Azino-bis(3-ethylbenzothiazoline-6-sulfonic acid)
MPP+	=	1-Methyl-4-phenylpyridinium
GFP	=	Green Fluorescent Protein
DA	=	Dopaminergic
PC12 cell	=	Phaeochromocytoma cell
MTT	=	(3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide)
GSH	=	Glutathione
OGD	=	Oxygen-Glucose Deprivation
TUNEL	=	Terminal Deoxynucleotidyl Transferase-Mediated dUTP Nick End Labeling
NO	=	Nitric oxide
eNOS	=	Endothelial Nitric Oxide Synthase
sGP	=	Soluble Guanylyl Cyclase
cGMP	=	Cyclic Guanosine Monophosphate
VDCC	=	Voltage-Dependent Calcium Channel
VSMC	=	Vascular Smooth Muscle Cell
2K2C	=	2-kidney, 2 clip
C. elegans	=	*Caenorhabditis elegans*
oxLDL	=	Oxidized Low-Density Lipoprotein

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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