

## Could Concurrent Use of Herbal Medicinal Products and Prescription Drugs Raise Older Adults Risk of Vascular Dementia?

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### ABSTRACT

While the role of chemical insults or the buildup of chemical insults in cardiovascular pathogenesis continuously draws attention, the potential interference of a variety of currently used or investigational drugs on the ability of endothelial cells (ECs) which are responsible for providing a unique surface to allow the cellular elements of blood to flow without adhering to the vessel lining has been much less appreciated in drug discovery research. Activated ECs are more sensitive to long-term, continuous drug exposure than normal cells. Prolonged activation of ECs predisposes the blood vessel wall to vasoconstriction, leukocyte adherence, platelet activation, thrombosis, impaired coagulation, vascular inflammation, pro-oxidation, and atherosclerosis. The studies of hypercholesterolemia, homocystinemia, hyperglycemia, hypertension, smoking, inflammation, aging, diabetes mellitus, and heart rhythm abnormalities further lend credence for the contribution of perturbed EC structure and function in the development of heart attacks. These risk factors are often established in elders living with one or more chronic diseases and to some extent hold true across all adult age groups. Evidence indicates that vascular reactivity is an independent risk factor for dementia. Most people who have exhibited vascular dementia following a stroke had a high blood pressure or diabetes prior to the occurrence. Often adults with chronic diseases are treated with long-term, continuous, prescription drug(s) and self-administration of traditional medicines. Thus, an assessment of a combination of traditional medicines with widely used prescription drugs on activated ECs should be tested in experimental animal models of these diseases to demonstrate whether the long-term exposure of this combination therapy exacerbates vascular reactivity and worsens ischemic perfusion defect.

**Keywords:** Vascular dementia; Activated Endothelial Cells; Cardiovascular pathogenesis

### INTRODUCTION

No tissue of the biological species has a more universal influence on living systems than vasculature, the first organ system that arises and reaches a functional state during the fetal developmental stages [1]. The function of blood vessel networks is to interact with their macro-environment in order to maintain a two-way flow of information, energy, and essential nutrients to where they need to be in the body. The property of blood vessel networks helps to provide a “fit” place during development and growth of organisms. The anti-thrombotic, anti-adhesion,

permeability capacity, integration of fluid flow (blood flow, interstitial flow, and urine flow), the fluid/electrolyte balance, barrier tissue forming cell, new capillaries interconnecting pre-existing blood vessel regeneration, and paracrine/endocrine communicative abilities of blood vessel networks all render this organ system especially well-suited for its roles in the various biological species.

Whereas the inherent structure and functions of blood vessels suit this system so admirably for the genesis, growth, and survival of a biological species, problems associated with controlling the

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buildup of fatty material, narrowing of the blood vessels, and increased vascular reactivity are some of the most severe ever encountered by blood vessels. The response to injury theory suggests that the earliest event in atherogenesis is likely to result from endothelial cell injury triggered by a number of different insults and mechanisms, either alone or in combination.

## STROKE

Stroke, the largest single cause of adult disability, is the fifth leading cause of death [2]. There are two main types of stroke: hemorrhagic and ischemic. The most common kind of stroke is ischemic stroke caused by the narrowing of an artery interrupting blood flow to the brain. As such, the US food and drug administration (FDA) approved medications are those that interfere with this trigger to restore blood flow for the treatment of ischemic stroke [3]. Hypertension [4] and diabetes [5]-induced impaired blood flow are the most important contributing risk factors for stroke in both developed and developing countries [6]. Hemorrhagic stroke is commonly caused by the rupture of an aneurysm. After the hemorrhage, narrowing of blood vessels may occur. Hypertension is seldom implicated in this type of stroke. Ischemic stroke may result when a blood clot forms in areas damaged by atherosclerosis.

## VASCULAR DEMENTIA

Vascular dementia, a severe form of vascular cognitive impairment, is caused by stroke [5] in the elder population. The two major divisions of vascular dementia in the elderly brain are the multi infarct encephalopathy and Binswanger's Disease (BD, subcortical vascular encephalopathy). Multiple-infarct dementia [7] occurs after several small strokes and is caused by reduced blood flow to the brain tissue. BD, a form of small vessel vascular dementia, is triggered by the damage to the small blood vessels deep within the brain that deliver blood to the subcortical region of the brain, causing widespread damage to the white brain matter leading to the disruption of executive cognitive function. BD-induced decline in memory and thinking skills appears to be sudden or gradual and eventually progress over time. Thirty percent of adults who have vascular dementia after stroke previously had an untreated high blood pressure or diabetes. Hypertension [8] and diabetes-induced vascular dysfunction [9], the two concurrent chronic diseases in older adults [10], are associated with stroke, and thus are considered risk factors for dementia. The prevalence of dementia among ischemic stroke patients have risen over the last decade [11,12]. Treatment of vascular dementia involves reducing risk factors and managing the health conditions in order to reduce the risk of further vascular damage and slow the progression of cognitive decline.

## DISCUSSION

The concomitant use of prescription drugs and herbal medicines has been recognized as a major barrier in patient's care. According to estimates, while world population ages rapidly, data reveal the presence of a global heterogeneity in the survival experience of older adults and the elderly population [13]. A large segment of the older adults in both developing and developed countries rely on traditional medicines to meet their

health care needs [9,14,15]. It appears that some people employ herbal medicine in conjunction with prescription drugs. Traditional medicine use accounts for 22% of all complementary and alternative medicine (CAM) in the United States [10]. There is also a high prevalence of herbal medicine's use in educated people with chronic disease in the United State [15]. The aging populations are potentially not receiving a safe and effective treatment [16], perhaps due to patterns of supplement use as well. Although some of herbal medicinal products have promising potential [17] many drug-herbal medicinal product interactions remain untested, and since surprisingly considered harmless, older adults are concurrent users of both traditional medicine and prescription medication [10]. Traditional medicine effects have important implications for medication adherence, clinical outcomes, and the design of pharmaceutical trials. Untested and unregulated herbal medicines, non-native herbal medicines, or phytonutrients continue to grow globally [16]. While the assessment of major organ toxicity by some herbal medicines appears to be performed, their effects in combination with the prescription medicines on the normal and activated cells of vasculature are less appreciated. The concurrent use of both prescription drugs and traditional medicinal products can increase risk of potential adverse drug interactions and may result in suboptimal clinical outcomes. These combinations may react harmfully with the activated endothelial cells and exacerbate vascular reactivity in hypertensive and diabetic adults leading to an elevation of the risk of both macrovascular and microvascular complications, including stroke, atrial fibrillation, and abnormal heart rhythm. It is critical to investigate the long-term effects of all herbal medicinal products on activated ECs to show that they do not contribute to vascular dementia, unless designed for such a goal.

There is a positive linear correlation between the number and severity of adverse drug interactions and the number of drugs taken. Physicians, pharmacists, and health care policy makers should be aware of the risk factors for the concurrent usage of traditional medicine and prescription drug effects which can be addressed as features relating to the patient, physician, disease, drug, and interactions among them. Treatment interruption by traditional medicines can be one of the main risk factors of poor treatment outcome in hypertensive or diabetic patients. Thus, preventing the use of untested herbal medicine that may affect the integrity of older adults' heart and blood vessels can slow the rate at which vascular dementia gets worse.

According to multiple studies performed, a major cause of adverse drug reactions is the lack of reporting of traditional medications and supplements to health care providers, because it is generally assumed they are safe and have only good effects since they are all natural [18]. Many patients hear about the benefits of a plant-based product through media or from friends or family and are not aware that they are taking risks when it comes to their prescription medications. Popular drugs for chronic conditions such as vascular problems, diabetes, and nervous system disorders can have a delicate balance between intended effects and toxic side effects when it comes to the level of dosing. This balance can be disturbed by herbal supplements that alter proteins associated with metabolism of these drugs causing them to be removed from the body too quickly or not

quick enough creating a potential toxicity [19]. For this reason, the FDA recommends that patients inform their health care providers and pharmacists about all additional natural and dietary supplements taken, even if they seem harmless, so proper precautions can be taken to prevent unintended interactions with prescription medications [20]. A potential problem with this recommendation is that the acquisition of the information might be too late to restore the concurrent drug-herbal medicine-induced impaired endothelial cell function and potentially cognitive function in uncontrolled hypertensive adults.

Endothelial dysfunction is an independent risk factor for cardiovascular events in many age groups and in patients with chronic kidney disease. The presence of the endothelial dysfunction due to aging or after cardiovascular risk factors such as post-menopause state, smoking, hypercholesterolemia, and hypertension have been implicated in the pathogenesis of stroke. It has become overwhelmingly clear that a variety of inappropriate use of medicinal plants [9] in combination with the medicinal drugs are powerful risk factors which can contribute to the development or progressive worsening of endothelial function in older adults. Cardiometabolic diseases that include both cardiovascular diseases and metabolic diseases alter the endothelium structure with a subsequent deterioration in function [21], thus losing its protective role and ensuing the induction of prothrombotic and proinflammatory mechanisms.

## CONCLUSION

In conclusion, there is a paucity of clinical data to support majority of traditional medicines in the elderly population with compromised endothelial function. Neither assertions nor speculation can be substituted for evidence. The FDA cannot intervene unless a product is found to be unsafe and harmful. Thus, concurrent herbal medicines and prescription drugs should be subjected to rigorous scientific testing. Animal toxicity, acute and chronic toxicities, and clinical research need to be conducted. Then, additional research is needed to initiate a large, double blind clinical trial that will include various medicinal plant protocol in combination with standard therapy to ascertain their efficacy and safety in order to enable the practitioners to deliver a more targeted approach to cardiometabolic diseases. Future studies assessing the potential effects for concurrent use of herbal medicine and standard therapy in the cardiovascular health are needed to further support the safety and effectiveness of various herbal medicines in man.

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