



Proof-of-concept

## COLCHICINE AND THERAPY OF CARDIOVASCULAR DISEASE: NOT MERELY A THEORY

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*The cytoskeleton is a sophisticated cellular system consisted of actin filaments, intermediate filaments and microtubules (MT) accompanied by a large number of associated structural and motor proteins. Microtubules are dynamically assembling and disassembling structures. They are pivotal for many cell functions, e.g. intracellular traffic of membrane-bound organelles in endocytosis and protein secretion, also a variety of inflammatory and signal transduction pathways. Tubulin is the major building protein of MT. Depended on doses, agents that bind to tubulin inhibit its assembly, that is, MT formation, or disassemble the preformed MT. Such tubulin-binding agents are named MT-disassembling agents or antitubulins, colchicine being a classical member of these agents. Herein, we describe in brief the scientific saga of colchicine as related to the therapy of cardiovascular diseases such as acute coronary syndromes, myocardial infarction, atrial fibrillation, pericarditis, and hypertrophic cardiomyopathy. **Biomed Rev 2023; 34:181-184***

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## INTRODUCTION

The cytoskeleton is a sophisticated cellular machinery consisted of actin filaments, intermediate filaments and microtubules (MT) accompanied by a large number of associated structural and motor proteins such as actin, myosin, spectrin, titin, septin, dystrophin, desmin, vimentin, keratin, and MT-associated proteins (MAP1, 2, 4, 6, 7, tau proteins, kinesins, dyneins, *etc*). The motor protein kinesin is an MT-activated adenosine triphosphatase (ATP-ase), an anterograde, MT's plus end-directed motor. The dynein is also such an ATPase, but operates as a retrograde, MT's minus end-directed motor. Microtubules are unstable, dynamically assembling and disassembling structures. They are pivotal for many cell functions, e.g. intracellular traffic of membrane-bound organelles in endocytosis and protein secretion and a variety of inflammatory and signal transduction pathways. Tubulin, the major building protein of MT, is a heterodimer consisting of  $\alpha$  and  $\beta$  subunits. Depended on doses, agents that bind to tubulin block its assembly resulting in the inhibition of MT formation or disassemble the preformed MT – cytoplasmic and mitotic. Such tubulin-binding agents are usually termed MT-disassembling agents or *antitubulins*, colchicine being a classical member of this group of agents.

Herein, we describe in brief the conceptual saga of the antitubulin colchicine as related to the therapy and/or secondary prevention of cardiovascular diseases (CVD), which are *bona fide* inflammatory diseases (1, 2).

### ***An old wine in a new bottle***

Colchicine is one of the oldest remedies still in use. It is derived from the *Colchicum autumnale* plant. The name “colchicine” comes from the ancient and legendary kingdom of Colchis where *C. autumnale* plants were widespread. Colchicine is an effective anti-inflammatory drug that has been used for decades for the inhibition of acute inflammatory processes - firstly in gouty arthritis and later in familial Mediterranean fever, Behçet's disease, liver cirrhosis, scleroderma, psoriasis, aphthous stomatitis, Sweet's syndrome, amyloidosis, and epidermolysis bullosa.

### ***Antitubulins - a concept for therapy of cardiovascular diseases***

Based on the results published for the first time during the 1970's and early 1980's by one of us (GNC), we had proposed that antitubulins, particularly colchicine, could be effective in the therapy of CVD (3-13).

Recently, this concept was repeatedly appreciated by other colleagues in patients with CVD such as acute coronary syndromes, myocardial infarction, atrial fibrillation, pericarditis, and hypertrophic cardiomyopathy administered at 0.5 mg/day or twice daily, the so-called LoDoCo (low-dose colchicine) therapy (14-29).

Intriguingly, George Cooper's group has demonstrated that the excess presence of MT in cardiomyocytes is related to myocardial contractile dysfunction suggesting that this may be one mechanism contributing to the development of heart failure caused by cardiac hypertrophy (25). Accordingly, colchicine treatment leads to striking improvement in contractile function of cardiomyocytes. Likewise, chronic beta-adrenergic blockade instituted early might delay or prevent the appearance of the pathological microtubule phenotype (25).

Moreover, advancement in pharmaceutical design may lead to the production of highly specific pharmaceuticals targeting key molecules such as MAPs, kinesins and dyneins involved in the regulation of MT functions, thus raising a hope for further development of antitubulin therapy for CVD.

Atherosclerosis complications (erosion and rupture of the plaque fibrous cap) resulted in acute coronary syndromes, myocardial infarction or stroke. Of note, arterial smooth muscle cells (SMC) of the innermost media undergo phenotypic modulation towards a secretory state involved in (pro)collagen and other matrix proteins production. The risk of plaque rupture is inversely correlated with the presence of secretory phenotype SMC and collagen fibrils within the plaque fibrous cap (8-10).

## CONCLUSION

We argue that one of the present challenges in vascular biology is to consider antitubulins, particularly colchicine's anti-inflammatory action for therapy of CVD, concomitantly addressing how we could boost SMC secretion of matrix proteins for atherosclerotic plaque fibrous cap stabilization (8-10, 14, 22). This would immensely aid efforts in CVD therapy, including in thoracic aortic aneurysms related to Marfan syndrome (30). In acute coronary syndromes patients undergoing percutaneous coronary intervention (PCI), it is feasible to discontinue aspirin therapy and administer low-dose colchicine on the day after PCI in addition to P2Y12 inhibitors (ticagrelor or prasugrel), wrote Seung-Yul Lee and colleagues (23, see also 24). Recently, the US Food and Drug Administration approved colchicine 0.5 mg tablets as the first anti-inflammatory drug shown to reduce the risk for myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adult patients with either established atherosclerosis or multiple risk factors for CVD.

In effect, antitubulin concept for CVD therapy is no more a theory now. Thus, we may, just for an intellectual fun, suggest this new approach to be named Burnstock-Chaldakov therapy for CVD.

Isn't "Fact is the sweetest dream of labor knows.

*My long scythe whispered and left the hay to make".*

**Robert Frost**, from "Mowing"



Photography: Credit Nikolai G. Chaldakov

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