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# Possible Adjuvant Role of Cineole in Controlling Vascular Smooth Muscle Dysfunction

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Chronic disorders such as diabetes, hypertension, cerebrovascular diseases, and others, are associated with vascular smooth muscle dysfunction. These diseases are among the main problems of public health worldwide. Vascular diseases combined with chronic morbidities result in social, economic, and public health problems. In addition, they are the diseases that cause the most deaths. The most recent update related to deaths by cardiovascular diseases dates back to 2021. According to the World Health Organization (*https://www.who.int/*), around 17 million people died from cardiovascular diseases, representing 32% of all global deaths. Individuals with these diseases are subject to blood perfusion problems and frequently require clinical attention due to difficulties in the adequate transport of essential metabolites for cellular tissues and also in regulating the tone of blood vessels [1]. Many of the clinical-therapeutic approaches targeting these diseases can induce unwanted side effects [2]. In view of this severity, become necessary new therapeutic interventions capable of minimizing the deleterious effects resulting from vascular dysfunctions. In this context, calcium channels are excellent molecular targets for drugs with antihypertensive and vasodilator action.

The calcium ion ($Ca^{2+}$) that enters into the cell via voltage-dependent calcium channels plays a crucial role in the contraction and relaxation of smooth muscle cells. In this process, its role is already well described in the literature [3]. The specific characteristics of voltage dependent $Ca^{2+}$ channels are essential for regulating the contractility of blood vessel smooth muscle, gastrointestinal tract, bladder, uterus and many others, playing a vital role in homeostasis and in response to physiological and pharmacological stimuli. These channels are transmembrane proteins found in the membranes of various excitable cells, including neurons, muscle cells and cells of the endocrine system. They play a key fundamental role in generating and transmitting of electrical signals in response to changes in the electrical potential of the cell membrane. When there is a change in the electrochemical potential of the cell membrane, $Ca^{2+}$ enters the smooth muscle cells through these voltage-dependent $Ca^{2+}$ channels, binding to calmodulin, a regulatory protein. This binding activates an enzyme called myosin kinase, which phosphorylates the myosin light chain, triggering the interaction between myosin and actin, consequently contracting smooth muscle, including vascular muscle, essential for regulating blood flow and blood pressure [4].

In this scenario, new phytochemicals, such as monoterpenes, which have a site-specific action on vascular smooth muscle, may provide more effective therapies, delaying disease progression and improving patients' quality of life. Among these monoterpenes we can highlight 1,8-cineole (CIN) also called eucalyptol. CIN is a cyclic terpene hydrocarbon with molecular formula $C_{10}H_{18}O$, widely distributed in nature. It is found in essential oils from many plants. Due to its therapeutic properties, CIN is traditionally used in pharmaceuticals and cosmetics products. Among its biological activities, the influence on smooth muscle and anti-inflammatory action stands out [5]. Interestingly, the literature describes that 1,8-Cineol blocks electromechanical coupling in tracheal smooth muscle through an action on the pore of the L-type voltage-dependent calcium channel, thus causing a bronchodilator effect [6]. In addition, there is evidence of its action on gastric volume, probably by acting directly on the smooth muscle of the stomach [7] and ileum of mammals, with relaxing properties through the blocking of calcium channels

[8]. In vascular smooth muscle (Figure 1), a significant blockade of contraction by norepinephrine [9]. and hypotensive activity with a significant drop in Blood Pressure (BP) and Heart Rate (HR) were found in rats treated with CIN Neves et al [7]. However, the probable mechanism of action of this hypotensive activity was not pointed out, since the measurement methods, were made by digital record of BP and HR, in data acquisition system Considering that individuals with chronic diseases associated with dysfunctions in vascular smooth muscle should be treated with more specific therapeutic approaches and with fewer side effects and the CIN activity is to block the calcium channels of various smooth muscles, we hypothesized that this monoterpene may play an antihypertensive and vasodilator role by blocking calcium channels of vascular smooth muscle calcium channels.

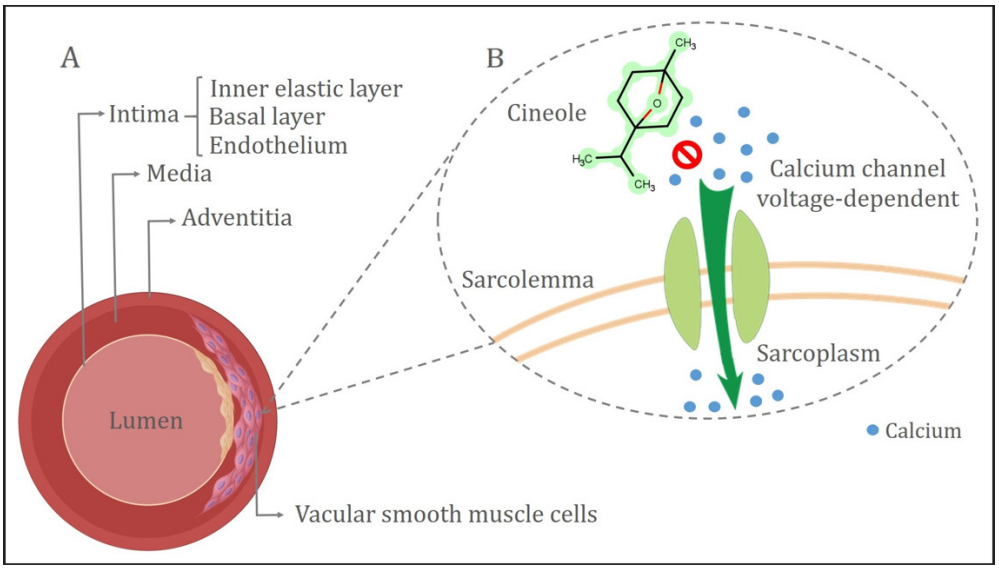


**Figure 1:** 1,8-Cineol-mediated calcium channel blockade in vascular smooth muscle.
(A) General scheme of the structural organization and layers of vascular smooth muscle.
(B) The scheme of the Type-L voltage-gated dependent calcium channel in vascular smooth muscle and its blockade, mediated by binding with 1,8-cineole. The calcium channel is schematized in Martian green, illustrating its transmembrane (Sarcolemma) topology. The inner and outer membranes are delineated by Victorian yellow lines. The grass green arrow shows the native path of calcium molecules, identified in French blue.

## Authors' Contribution

All authors contributed equally.

## Conflict of Interest Disclosures

The authors declare no conflicts of interest.

## Ethical Statement

Not applicable.

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