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EFFECTS OF PYCNOGENOL® ON CHRONIC ATHEROSCLEROSIS

EFEITOS DO PICNOGENOL® NA DOENÇA ATEROSCLERÓTICA CRÔNICA

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ABSTRACT

Chronic atherosclerosis is a highly prevalent condition and one of the main cardiovascular diseases linked to the aging process. Among the adjuvant therapeutic options, Pycnogenol® (Pinus pinaster bark extract) has been studied because of its antioxidant, anti-inflammatory and antiplatelet functions. This article is a narrative review aimed at evaluating the use of Pycnogenol® as a therapeutic option in the treatment of chronic atherosclerosis. The studies included were obtained from the following databases: PubMed, Scielo, The Cochrane Library, Scopus and LILACS. Case reports and case series with n≤5 were excluded due to their restrictions for therapeutic evaluation. As a result, the studies have indicated advantages in the use of Pycnogenol® in the treatment of chronic atherosclerosis as well as other cardiovascular diseases. However, the number of studies is still small (particularly clinical trials), and there are important sample size limitations, which restricts its current recommendation in clinical practice.

Keywords: Pinus; Atherosclerosis; Phytotherapy; Heart Defects, Conginital; Antioxidants.

RESUMO

A doença aterosclerótica crônica (DAC) é uma condição bastante prevalente em nosso meio e uma das principais doenças cardiovasculares ligadas ao envelhecimento. Dentre as opções terapêuticas adjuvantes, o Picnogenol®, extrato da casca do Pinus pinaster, tem sido alvo de estudo em decorrência de função antioxidante, anti-inflamatória e antiplaquetária. Este artigo é uma revisão narrativa, cujo objetivo é avaliar o uso do Picnogenol® como opção terapêutica da DAC. Os estudos incluídos foram pesquisados nas bases de dados: PubMed, Scielo, The Cochrane Library, Scopus e LILACS, sendo excluídos, considerando suas restrições para avaliação terapêutica, os relatos de caso e séries de caso com n ≤ 5. Como resultado, os estudos têm apontado vantagens do uso Picnogenol® no tratamento da DAC, assim como de outras doenças cardiovasculares, porém, o número de pesquisas ainda é pequeno (principalmente ensaios clínicos) e há importantes limitações de tamanho amostral, o que dificulta sua atual recomendação na prática clínica.

Descritores: *Pinus; Aterosclerose; Fitoterapia; Cardiopatias; Antioxidantes.*

INTRODUCTION

Cardiovascular diseases (CVD) are among the most important causes of death worldwide.[1] This is due to changes in the profile of the disease process worldwide, with a reduction in deaths associated with infectious and contagious diseases and an increase in the incidence of chronic noncommunicable diseases as well as life expectancy and social habits.[2]

Considering the high incidence of chronic atherosclerotic disease (CAD) in adult subjects, particularly those over 45 years of age, it is the main cardiovascular pathology associated with the aging process.[3] Although clinical symptoms of CVD are more common from middle age, the atherosclerotic process tends to begin in childhood.[1]

A broad approach including both traditional pharmacological treatment and the adoption of a healthy lifestyle is necessary to treat CVD, which has multiple factors.[2] Much effort has been made to improve and prevent the profile of patients affected by CVD, which has been a topic of great importance considering the number of people affected and health system costs arising from the difficulty controlling preventable diseases.[1]

Among the adjuvant therapeutic substances, Pycnogenol®, *Pinus pinaster* bark extract, has shown possible antioxidant, anti-inflammatory, and antiplatelet effects.[4,5] More than two-thirds of the Pycnogenol® extract consists of procyanidins, which are composed of subunits of catechins and epicatechins.[6] Its use has been studied in several medical applications and different pathologies, such as vascular retinopathy, venous insufficiency, ischemia, CAD, inflammatory diseases, and melasma as well as to delay

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the aging process[7,8] in addition to potentially decreasing C-reactive protein levels and the cellular toxicity caused by the administration of antitumor drugs.[9,10]

A systematic review and meta-analysis conducted by Zhang et al.[11] evaluating the effects of Pycnogenol® in patients with hypertension found a significant reduction in blood pressure (BP) levels in clinical trials. This finding was more pronounced in studies lasting for more than 12 weeks that included subjects with higher BP levels.

Some studies evaluated the efficacy of Pycnogenol® as an adjuvant therapeutic option in patients with CAD. The overall results were favorable despite the low number of studies conducted and their limitations.

METHODOLOGY

Here we reviewed studies to assess the effects of Pycnogenol® on CAD and focused on the pathophysiology of the disease and the pharmacology and therapeutics of the drug.

We searched the *PubMed, SciELO, Cochrane Library, Scopus,* and *LILACS* databases using combinations of the terms "pinus," "pycnogenol®," and "aterosclerose." Studies in English, Spanish, and Portuguese published in the last 15 years were evaluated. Case reports and case series with cohorts of N ≤ 5 were excluded since they pose restrictions on therapeutic evaluations.

PATHOPHYSIOLOGY OF CAD

Atherosclerosis is a slow and progressive multifactorial disease resulting from distinct forms of cellular and molecular responses. Factors such as the accumulation of lipids, fibrous elements, and inflammatory cells that are deposited over time on the arterial walls are responsible for the formation of stretch marks or fatty plaques, followed by their obstruction.[3] Cholesterol, triglycerides, phospholipids, and fatty acids are the most relevant lipids.[12]

Studies have indicated that fatty streaks are already formed in the intimal layer of the aorta from 3 years of age and in the coronary arteries throughout adolescence, with marked progression in adulthood after the third or fourth decades of life.[13]

The main risk identifier for the diagnosis of CAD is previous manifestation of the disease, followed by high-risk conditions such as diabetes mellitus 1 and 2, chronic kidney disease, and familial hypercholesterolemia.[12] Risk factors for the development of CAD are listed in Table 1.

In the process of atherogenesis, the functions of T lymphocytes, some macrophages derived from monocytes, endothelial cells, and smooth muscle cells are mediated. After the activation of these cells, cytokines, growth factors, adhesion molecules, lipid aggregation, and proliferation of smooth muscle cells interact with each other. Moreover, oxidative stress can induce inflammatory response.[3]

CHEMICAL PROPERTIES OF PYCNOGENOL®

Pycnogenol® is an aqueous extract primarily composed of secondary metabolites – flavonoids, catechin, phenolic acids, taxifolin, and cinnamic acids – and their glycosides.[14,15]

With regard to the antioxidant properties of Pycnogenol®, the components described through the action of the hydroxyl groups of the aromatic rings can eliminate free radicals including small hydroxyl radicals, avoiding lipid peroxidation through the formation of phenolic radicals, which are less susceptible to oxidation than the cyclopentadienyl radical.[16]

Table 1. Risk factors for the development of chronic atherosclerotic disease. Adapted from Xavier et al.[12] and Romaldini et al.[13]

Risk factors
Subclinical atherosclerosis
Diabetes *mellitus* 1 and 2
Dyslipidemia
Chronic kidney disease
Past atherosclerotic events
Family hypercholesterolemia
Hypertension
Obesity
Smoking

A study evaluating plasma Pycnogenol® metabolites after the consumption of one or more doses of 200 mg of Pycnogenol® 200 or 300 mg identified the following metabolites associated with its ingestion: catechin, caffeic acid, ferulic acid, taxifolin, and δ-(3,4-dihydroxy-phenyl)-γ-valerolactone (Figure 1).[6]

USE OF PYCNOGENOL® IN THE TREATMENT OF CAD

Some studies have indicated Pycnogenol® as an adjuvant therapy in cases of CAD. Its action has been associated with the inhibition of some adhesion factors, particularly Toll-like receptor 4 and nuclear factor kappa B (NF-κB), reducing the production of the pro-inflammatory cytokines tumor necrosis factor-α and interleukin-1β, which would protect the endothelium against inflammatory stimuli and the consequent atherosclerotic development.[9,17]

The possible benefits of Pycnogenol® against smoking, a risk factor for several CVDs including CAD[12,13,18] have been reported. The drug appears to interfere with the platelet activation process, and its use 30 minutes before smoking inhibited platelet activation and thromboxane formation.[17,19] A single dose of Pycnogenol® 100 or 150 mg showed normalization of platelet reactivity indexes after 10 days, although the author reported that only the 200 mg dose resulted in normalization for long periods but did not specify the duration.[19]

A study conducted by Belcaro et al.[20] evaluated the echogenicity of plaques in the carotid and femoral arteries of 79 asymptomatic subjects using a combination of Pycnogenol® 150 mg/day and *Centella asiatica* 450 mg/day for 6 months. They were divided into a group with prescription of lifestyle changes (LC) and another with prescription of LC + Pycnogenol® and *C. asiatica*. After 6 months, there was no significant intergroup difference in cholesterol reduction (16.8% in the therapy group vs 18.7% in the control group), but there was improvement in plaque stability (from 11.22;2.3 to 22.4;1.1, $p < 0.05$), improvement in plaque echogenicity (percentage of "whiter" components on the images) from 16.7;1.7% to 34.2;2% ($p < 0.05$), and a decrease in the number of plaques found in the carotid arteries and femoral bifurcations.

In a crossover study of 23 subjects with CAD[21] comparing the effect of Pycnogenol® 200 mg/day with placebo for

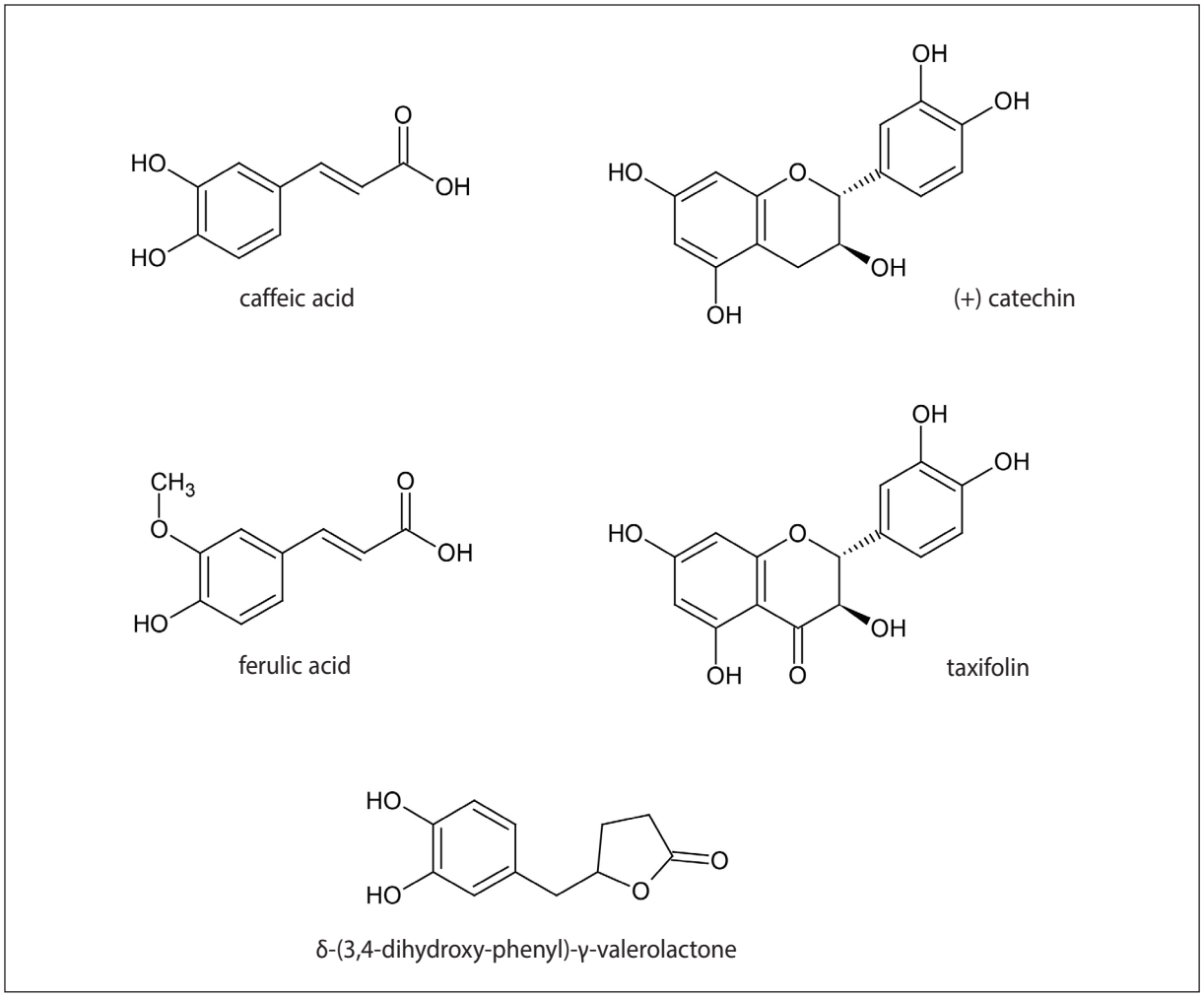

Figure 1. Plasma metabolites found after the ingestion of Pycnogenol®: caffeic acid, catechin, ferulic acid, taxifolin, and δ-(3,4-dihydroxy-phenyl)-γ-valerolactone.

8 weeks, flow-mediated dilatation improved in the therapy group (5.3 + 2.6 to 7.0 + 3.1), but the difference compared to the control group was not statistically significant. Nevertheless, the inflammatory markers, platelets, and blood pressure levels did not change in either group.

An observational study of 824 patients with atherosclerotic plaque stenosis (>50–60%)[22] found a beneficial effect of Pycnogenol® 100 mg/day. There was an even greater benefit when it was associated with a total triterpenic fraction of *C. asiatica* 100 mg/day. These results proved superior to those found in the groups that received daily doses of aspirin 100 mg/day, Pycnogenol® 50 or 100 mg, or aspirin 100 mg/day with Pycnogenol® 100 mg/day.

Pütter et al.[19] stated that an advantage of Pycnogenol® over aspirin as a platelet inhibitor is the fact that it does not cause bleeding due to cyclooxygenase inhibition. Despite its protective anti-atherosclerotic effect, this substance seems to cause a low decrease in the accumulation of macrophages in established plaques.[4]

FINAL CONSIDERATIONS

To date, several studies have reported favorable results from the use of Pycnogenol® and its clinical benefits in CVD such as better control of CAD, making it a good adjuvant therapeutic option. Despite these benefits, studies on the use of Pycnogenol® remain scarce, and the few existing studies are limited by their small sample size, design other than randomized clinical trial, or bias that could lead to clinical improvement as an incentive to practice physical exercise and food re-education. Therefore, better-defined studies without the limitations mentioned above are necessary to support the prescription of Pycnogenol® in clinical practice.

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

AUTHORS' CONTRIBUTIONS: Each author contributed individually and significantly to the development of this study. Original study design and conception: LSB. Literature review: LSB, MAOSV, NSBJ. Final drafting of the manuscript: LSB. Critical content review: MAOSV, NSBJ, AVCM.

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