Review Paper:

Review on compounds and pharmacological activities of *Pinus pinaster* Ait

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Abstract

Pinus pinaster Ait., commonly known as the maritime pine, is a resilient, fast-growing tree native to the Mediterranean region, capable of reaching heights of up to 40 meters. This species is distinguished by its straight trunk, thick, deeply fissured, fire-resistant bark and vibrant green needles that grow in pairs, extending up to 25 centimeters in length. Its large ovoid cones mature to a glossy brown, measuring up to 20 centimeters long. The maritime pine thrives in sandy, well-drained soils and is widely used in reforestation projects due to its adaptability and resilience. It plays a critical role in stabilizing soil and preventing erosion, particularly in coastal and degraded areas. Additionally, Pinus pinaster forests support biodiversity by providing habitat and food for various wildlife species. Economically, Pinus pinaster is highly valued for its timber and resin. The durable wood is extensively utilized in construction, paper production and furniture-making.

The resin, known as rosin or colophony, has applications in numerous industries including adhesives, varnishes and traditional medicine. Furthermore, the essential oils and resins of Pinus pinaster exhibit antiseptic and anti-inflammatory properties, making them beneficial for aromatherapy and topical treatments. The plant extract, known as Pycnogenol®, is a rich source of antioxidants and has been extensively studied for its therapeutic potential in cardiovascular health, skin care and immune system support. This review highlights the diverse bioactive compounds and pharmacological properties of Pinus pinaster, emphasizing its potential applications in medicine and healthcare.

Keywords: Aromatherapy, Anti-inflammatory, Antioxidant, Antimicrobial, Biodiversity, Cardiovascular health, Essential oils, Maritime pine, *Pinus pinaster,* Soil erosion.

Introduction

The maritime pine**,** scientifically known as "*Pinus pinaster"* belongs to the *Pinaceae* family and genus *Pinus.* Native to the western Mediterranean region of Europe, it thrives in countries such as France, Italy, Spain, Morocco and Portugal[13]. This adaptable species has also established itself in regions like Australia, New Zealand, South Africa, Chile, Argentina and Uruguay[20]. The maritime pine exhibits remarkable climate resilience, tolerating average temperatures of 13 to 15°C and winter lows of 8 to 10°C[13]. These trees are characterized by their deep taproot, which provides strong anchorage and drought resistance by accessing crucial water reserves during dry periods[3]. Furthermore, they can grow in nutrient-deficient soils, as observed in regions like Marmara, the Black Sea and the Aegean[31].

Additionally, a well-developed secondary root system aids in efficient nutrient uptake. The bark of the maritime pine is a distinctive feature, characterized by its thick, reddish-brown color with deep furrows that add texture to the trunk[2]. The crown, where branches and leaves reside, has a rounded shape, resembling a majestic crown. The needles grow in pairs and are quite long, typically ranging from 10 to 25 cm[22]. Beyond its impressive physical characteristics, the maritime pine holds significant promise for human health. The bark is a treasure trove of polyphenols, natural compounds with potent antioxidant properties that help to fight cell damage and offer a promising avenue for the prevention of neurodegenerative diseases such as Parkinson's, Alzheimer's and Huntington's disease[2]. Researchers suggest that pine bark extracts may even extend the shelf life and nutritional value of food[12].

The potential benefits of these extracts extend beyond food preservation. Pine bark extracts are beneficial for skincare and various health treatments and their promising properties may lead to their inclusion as dietary supplements in the future United States Pharmacopoeia (USP)[21]. Another fascinating aspect of *Pinus pinaster* is its resin, which yields turpentine, a substance with a long history of medicinal use[8]. Turpentine may help in treating different ailments such as bladder and kidney issues, chronic venous insufficiency, asthma and rheumatic pain[23].

Additionally, pycnogenol, derived from pine bark, is known for its benefits in cardiovascular health, liver function, diabetes management, cancer treatment, digestive health, retinal problems and reproductive health including infertility[17].

Bioactive compounds: Biologically active compounds are natural substances produced by plant extracts that exhibit various biological properties[29]. Pine extracts from bark, needles and seeds have numerous industrial applications including use as food additives for preservation,

pharmaceuticals, nutraceuticals and cosmetics[12]. Polycyclic aromatic hydrocarbons (PAHs) such as fluoranthene, phenanthrene, fluorene and pyrene have been detected in maritime pine needles[25]. Essential oils are plant extracts known for their high biological activity and extracts of *Pinus pinaster* contain the most procyanidin B2, a flavonoid polyphenol[12]. These extracts include anthocyanins, naringenin, flavonols, flavonones, isoflavonones, tannins and non-flavonoids like phenolic acids, hydroxycinnamics, hydroxybenzoic acids, stilbenes and lignans[12].

The polyphenols in these extracts consist of o-coumaric acid, rosmarinic acid, ellagic acid, naringin, apigenin and resveratrol[2]. Additionally, the knots in the wood contain lignins, stilbenes such as resveratrol, pinosylvin, pinostilbenes and pterostilbenes as well as flavonoids like taxifolin, pinocembrin and aromadendrin[15].

These flavonoids are linked by simpler molecules like catechin and epicatechin and their size influences their properties[21]. Interestingly, these extracts contain smaller procyanidins built from taxifolin, catechin and epicatechin, with taxifolin being particularly abundant[17]. Taxifolin is a key component in water extracts of pine bark[4]. Notably, other polyphenols like procyanidin, hydrazoic acid and caffeic acid were only found in extracts using ethanol[12]. Phenolic acids have excellent properties due to their versatility, which serves as a building block for bioactive compounds used to treat various diseases[10]. Phenolic acids include caffeic acid, ferulic acid, procatechuic acid and gallic acid[24].

Pycnogenol, the bark extract of *Pinus pinaster*, is rich in larger molecules, containing 65-75% procyanidins, particularly polyphenols[10]. These biopolymer chains, built from catechin and epicatechin contain 2-12 building blocks and include B-type (B1, B3 and B7) procyanidins. Additionally, it contains beneficial acids such as protocatechuic acid, vanillic acid and ferulic acids which can attach to glucosides, aglycons and esters[2,4]. Pycnogenol, used as an antioxidant either alone or in combination with other antioxidant molecules, enhances glutathione peroxidase activity and reduces glutathione reductase activity[17]. The components, their phytochemical classes and pharmacological activities are summarized in table 1.

Pharmacological activities

Antioxidant activity: Pycnogenol, an antioxidant powerhouse derived from the bark of the French maritime pine (*Pinus pinaster*), has garnered significant attention for its potent ability to neutralize harmful free radicals[17]. Research has demonstrated that pycnogenol administration at doses of 10 or 20 mg/kg significantly ameliorates CCl_4 induced liver injury. This protective effect was evidenced by a dose-dependent reduction in serum alanine aminotransferase and aminotransferase activities, a decrease in malondialdehyde levels and an elevation in glutathione levels. Additionally, pycnogenol markedly increased the activities of catalase, superoxide dismutase and glutathione-S-transferase in liver tissues, underscoring its efficacy in safeguarding against CCl_4 induced oxidative damage in rats[1].

Table 1
Bioactive compounds and pharmacological activities of *Pinus pinaster*

Name of the bioactive compound	Molecular formula	Phytochemical class	Pharmacological activities
Protocatechuic acid	$C_7H_6O_4$	Phenolic acids	Anti-oxidant activity[21]
Vanillic acid	$C_8H_8O_4$	Flavonoids	Anti-oxidant activity[5]
Ferulic acid	$C_{10}H_{10}O_4$	Phenolic acid	Antioxidant activity[21]
Procyanidin	$C_{30}H_{26}O_{13}$	Flavonoids	Anti-radical activity[2]
Proanthocyanidin	$C_{31}H_{28}O_{12}$	Polyphenols	Anti-diabetic effect[28]
Catechin	$C_{15}H_{14}O_6$	Polyphenols	Antioxidant activity[32]
Taxifolin	$C_{15}H_{12}O_7$	Flavonoids	Antioxidant and antibacterial activity[24]
Stilbenes	$C_{14}H_{12}$	Polyphenols	Anti-bacterial activity[14]
Quercetin	$C_{15}H_{10}O_7$	Flavonoids	Antioxidant activity[32]
Resveratrol	$C_{14}H_{12}O_3$	Polyphenols	Anti-oxidant, anti-inflammatory activity[11]
Nortrachelogenin	$C_{20}H_{22}O_7$	Lignans	Anti-malarial and neuroprotective activity[5]
Pinoresinol	$C_{20}H_{22}O_6$	Lignans	Anti-breast cancer activity[5]
Gallic acid	$C_7H_6O_5$	Phenolic acids	Antioxidant activity[32]
Caffeic acid	$C_9H_8O_4$	Phenolic acids	Anticancer activity, antioxidant activity[11]
p-Coumaric acid	$C_9H_8O_3$	Phenolic acids	Anticancer activity[11]
Naringenin	$C_{15}H_{12}O_5$	Flavonoids	Anti-cancer activity[30]

In a separate study, rats were fed a diet enriched with pine extract (PE) for 8 weeks to evaluate its postprandial effects. Following this regimen, the PE-treated group demonstrated a significant increase in total plasma antioxidant capacity compared to both the control and postprandial groups. Additionally, in the postprandial assessment, two hours after ingestion, the group supplemented with procyanidin-rich pine extract (500 mg/kg body weight) exhibited a markedly higher ferric reducing antioxidant power than the control group. These findings underscore the potent antioxidant properties of *Pinus pinaster* and suggest its potential protective role against conditions associated with oxidative stress[19].

Anti-inflammatory activity: A study by Schafer et al[27,28] (2006) explored the anti-inflammatory effects of *Pinus pinaster* bark extract (PBE) by assessing its impact on cyclooxygenase (COX-1 and COX-2) activity in human serum. Blood samples were collected from five healthy volunteers before and after a 5-day oral administration of 200 mg PBE, which led to a moderate suppression of both COX-1 and COX-2 activities. In a subsequent phase, ten participants received a single 300 mg dose of PBE, with blood samples taken 30 minutes' post-ingestion. This resulted in a statistically significant increase in the inhibition of COX-1 ($P < 0.02$) and COX-2 ($P < 0.002$), highlighting the anti-inflammatory potential of PBE in humans.

Neuroprotective effects: Reports on the neuroprotective effects of pycnogenol supplementation and its mechanisms against ischemic injury following transient forebrain ischemia (TFI) in gerbils are limited. Pycnogenol, an extract from French maritime pine bark is known for its strong antioxidative properties. In a study, gerbils were pre-treated with 30, 40, or 50 mg/kg of pycnogenol daily for 7 days before TFI surgery. Notably, the 50mg/kg dose significantly protected hippocampal CA1 pyramidal cells from ischemic injury and improved learning and memory. This dose also enhanced the activity of antioxidant enzymes and reduced oxidative stress markers. Interestingly, the neuroprotective effect was nullified by sodium azide indicating that pycnogenol's efficacy is linked to its antioxidative properties[18].

In an experimental study on Alzheimer's disease pathology, female APP-transgenic mice were treated with pycnogenol, a standardized extract from the bark of the *Pinus pinaster*. The study involved two treatment paradims: pre-onset starting at 40 days of age before any detectable amyloid- beta (Aβ) plaques and post-onset, starting at 50 days of age after the initial appearance of plaques. Mice received a daily dose of 30 mg/kg pycnogenol dissolved in water via oral administration until they were sacrificed at 105 days (15 weeks). The effects of pycnogenol were analysed through various methods including immunohistochemistry to examine Aβ plaques, neuron counts, glial coverage, myelination patterns and cortical axon coverage. The results revealed that pycnogenol significantly reduced the number of Aβ plaques in both the pre-onset and post-onset treatment groups.

However, the treatment did not impact the levels of soluble Aβ or did not modify the gene expression of APP processing enzymes such as BACE1, IDE and ADAM10. Morphological analyses showed no significant changes in the number of microglia, astrocytes, neurons, myelination patterns, or axonal morphology. The behavioral tests indicated that pycnogenol improved spatial memory in the pre-onset treatment group, but no such effect was observed in the post onset group. These findings suggest that while pycnogenol may reduce plaque formation and improve memory when administered early, its effects on established AD pathology and related molecular processes are limited.

Anti-diabetic activity: In a study involving 77 patients with type II diabetes, daily supplementation with 100 mg of pycnogenol over twelve weeks led to a significant reduction in plasma glucose levels, with a decrease of 1.96 mmol/L ($p < 0.01$), compared to a 1.11 mmol/L reduction in the placebo group. This anti-diabetic effect was especially pronounced in patients whose baseline fasting glucose levels exceeded 10 mmol/L. Additionally, after one month, glycosylated haemoglobin levels showed a significant decrease in the pycnogenol group. The supplement also reduced plasma endothelin-1 levels by over 20% and increased 6-keto prostaglandin F1α, a marker of PGI2 production, by more than 10% compared to the placebo group ($p < 0.01$). The researchers concluded that pycnogenol significantly improved endothelial function and demonstrated potent anti-diabetic properties[33].

Anti-microbial activity: Ferreira-Santos et al[11] examined the antimicrobial properties of *Pinus pinaster* extracts against various bacteria and fungi, finding that extracts at a concentration of 50 mg/mL were particularly effective against Gram-positive bacteria including *Bacillus cereus, Listeria monocytogenes, Staphylococcus aureus and* notably *Clostridium perfringens*[2]. Increased bacterial presence at wound sites can impede healing, but research on *Pinus pinaster* suggests that its antimicrobial properties may aid in wound healing.

Curkovic-Perica et al[7] assessed the antibacterial activity of an aqueous bark extract of *P. pinaster* against multidrug-resistant *Acinetobacter baumannii* demonstrating significant antibacterial effects at concentrations below 200 mg/mL. These effects were attributed to the presence of catechin, gallic acid, epicatechin, vanillin and caffeic acid identified via high-performance liquid chromatography. Furthermore, a related study assessed the antibacterial potential of various polarity extracts of *P. pinaster* against *Escherichia coli, Staphylococcus aureus, Pseudomonas aeruginosa* and *Proteus vulgaris.* Phytochemical analysis revealed the presence of flavonoids, tannins, terpenes, sterols, coumarins and saponins, all of which are known to contribute to the extract's antimicrobial properties[31].

Anti- cancer activity: Pycnogenol, a standardized extract from the bark of *Pinus pinaster*, has been studied for its potential anticancer effects. In a study by Harati et al[16], the impact of pycnogenol and its metabolites was examined on human fibrosarcoma cells (HT1080) and in healthy volunteers who ingested a single 300 mg dose. Through flow cytometry and RNA microarray analysis, the researchers found that pycnogenol effectively induces apoptosis in HT1080 cells. These findings underscore the need for further *in vivo* research to fully assess pycnogenol's anticancer potential.

David et al[9] explored the potential of a procyanidin rich extract from from *Pinus pinaster* (Pyc), known for its antioxidant and anti-inflammatory properties, as a protective agent against tumour growth. Mice were administered saline, 25 mg/kg resveratrol, or 100 mg/kg Pyc over 20-days with Pyc providing the maximum safe dose based on prior toxicity studies. After inducing Ehrlich ascites tumours, the study measured abdominal expansion, weight gain, ascitic fluid characteristics and various inflammatory and tumour markers. Both Pyc and resveratrol significantly reduced weight gain (by over 30%), decreased abdominal girth and lowered ascitic fluid volume.

Pyc specifically resulted in a 26% reduction in tumour cell volume, a 35% decrease in tumour cell count, a 20% increase in apoptosis within ascitic fluid and more than doubled survival times compared to the control group. These findings suggest that Pyc effectively reduces oxidative stress, inflammation and tumour progression, making it a promising dietary strategy for cancer prevention.

Climacteric syndrome: In a double-blind**,** placebo-controlled study, approximately 200 peri-menopausal women were enrolled to assess the effects of pycnogenol 200mg daily on climacteric symptoms. The womens health questionnaire was used to evaluate these symptoms and participants underwent checks for antioxidative status and routine clinical chemistry. Of the initial participants, 155 women completed the study. The findings suggest that pycnogenol, an extract from French maritime pine bark may effectively alleviate climacteric symptoms, offering a potential alternative treatment with minimal side effects[34].

Chronic Obstructive Pulmonary Disease: Pycnogenol (Pyc), a standardized extract from *Pinus pinaster* bark has shown promise as a treatment for chronic obstructive pulmonary disease (COPD). In a 2016 study by Shin et al[26], Pyc was tested on human airway epithelial cells (NCI-H292) exposed to cigarette smoke extract (CSE) and in a mouse model of COPD induced by cigarette smoke and lipopolysaccharide (LPS). Administered at doses of 15 mg/kg and 30 mg/kg, Pyc significantly reduced Erk phosphorylation, sp1 expression, MUC5AC and pro-inflammatory cytokines in a dose-dependent manner. In the COPD mouse model, Pyc also lowered the number of inflammatory cells and decreased pro-inflammatory cytokine levels in bronchoalveolar lavage fluid. These findings suggest that Pyc may effectively reduce inflammation and serve as a potential treatment for COPD[26].

Conclusion

Beyond its economic and structural attributes, *Pinus pinaster* offers considerable health benefits. The bark is abundant in polyphenols, which have potent antioxidant properties that could aid in preventing neurodegenerative conditions such as Parkinson's, Alzheimer's and Huntington's disease. Pine bark extracts also show great promise in skincare, food preservation and may potentially be included in future dietary supplements. Additionally, the resin derived from *Pinus pinaster* produces turpentine, a substance historically used for medicinal purposes including treating bladder and kidney disorders, asthma and rheumatic pain.

Pycnogenol, an extract from pine bark, is recognized for its benefits in supporting cardiovascular health, liver function, diabetes management, cancer therapy and reproductive wellness. This review provides comprehensive information on the plant's bioactive compounds and offers insight into their potential therapeutic activities for treating various diseases and disorders. However, many aspects of the *Pinus pinaster* plant remain to be explored, further emphasizing its potential significance.

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