

REVIEW ARTICLE



AN APPRAISAL ON THE MECHANISTIC APPROACH  
TOWARDS PHARMACOLOGICAL POTENTIAL OF PYCNOGENOL

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**ABSTRACT:**

Natural products are used in the treatment of numerous human ailments since the inception of life on earth. Pycnogenol (PYC), a standard extract is obtained from *Pinus pinaster* (*P. maritime*). The United States Pharmacopoeia describes the characteristic properties of the PYC. Chemically, PYC contains distinct units of epicatechin and catechin. Additionally it comprises of polyphenolic units, cinnamic or phenolic acids along with their glycosidal compounds. Due to the remarkable bioavailability of PYC, it finds application as dietary supplementation and in the management of various disorders of respiratory tract, cardiovascular system, reproductive system and so forth. Moreover, it finds application in mitigation of migraine, obesity, diabetes, osteoarthritis, urinary tract infection and COVID-19. PYC seems to provide the therapeutic effect due to its antioxidant potential owing to the presence of flavonoids, polyphenolic compounds and phenolic acids. The individual components of PYC serve to act in a synergistic manner to provide beneficial effects in human ailments and prevent from the side effects that the individual sub-units might have caused. The current review appraises the pharmacological potential of Pycnogenol paying specific emphasis on its clinical studies and its mechanistic approach.

**KEYWORDS:** Pycnogenol, Pine tree bark, Flavonoids, Pharmacological profile

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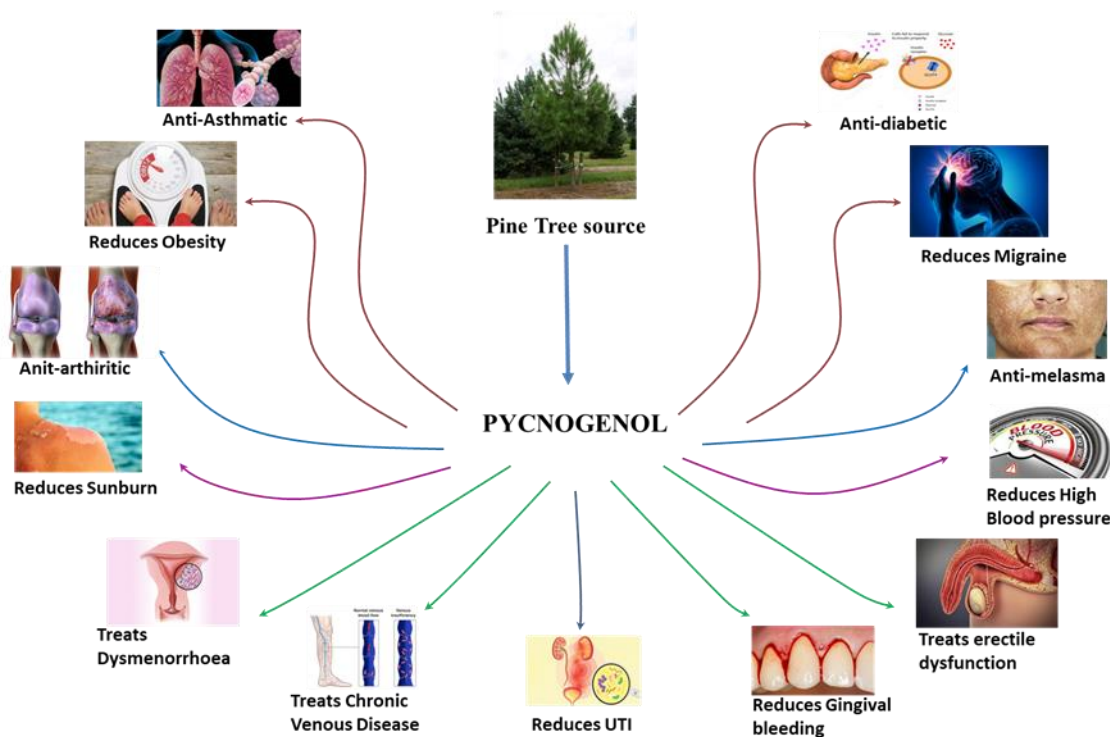
**INTRODUCTION:**

Pycnogenols are a category of flavonoids made up of flavan-3-ol derivatives. The term pycnogenol is obtained from the ancient Greek word *puknos*, which implies 'condensed', plus *genos*, which implies 'class or family'. Initially, Pycnogenol was the binomial name for this group of polyphenolic compounds [1-2], however nowadays it primarily describes a particular combination of procyanidin compounds derived from the coniferous tree bark (*Pinus pinaster*, previously recognized as *Pinus maritima*, Aiton, sub - species *Atlantica* des Villar), that is licenced underneath the brand names Pycnogenol (PYC) by Switzerland Horphag Research. The mechanistic approaches of PYC action are diverse. However, they seem to be primarily determined by PYC's capacity to effectively scrounge reactive O<sub>2</sub> and N<sub>2</sub> species [3-6]. The capacity of PYC to particularly entangle to proteins [7] is likely responsible for another greatest essential pharmacological implications, impacting respectively the composition and function of the protein characteristics.

Eventually, PYC is reported to partake in the antioxidant system at the cellular level and to influence the appearance of genes governed by cell redox system [8-10]. PYC's consequences, in specific, have indeed been studied in numerous *in vitro* models, as well as in animal and clinical investigations [11-12]. Significant antioxidant potential

was observed not only in laboratory experiments however as well in cultured cells analysis. Furthermore, towards its radical-scavenging potential, pycnogenol isolate has been demonstrated to impede  $\text{NF-}\kappa\text{B}$ -dependent expression of genes and reduce the activity of different enzymes [12]. Animal experimentation showed distinguishable biological effects. Such consequences encompass anti-thrombotic, antiinflammatory and cardiovascular potencies [13]. Platelet agglomeration was lowered and microcirculation was managed to improve in cardiovascular patients who were given maritime pine bark isolate [14]. In animal studies of inflammatory bowel disease, maritime pine bark extract was discovered to have anti-inflammatory properties [15]. PYC administration lowered urinal [16] or serum [17] leukotriene concentration levels. PYC was found to have analgesic properties in women suffering from menstrual cramps [18]. Furthermore, recent human trials specify that PYC is effectual in the topical management of certain induced oxidative dermatitis [19-20].

Prelox (an amalgamation of Pycnogenol and L-arginine aspartate) is also an enticing treatment option for clement to modest erectile afflictions [21]. PYC therapy of ADHD (Attention deficit Hyperactivity Disorder) in kids appears to normalize monoamine neurotransmitter levels, resulting in much reduced hyperkinetics and, as a result, less oxidative strain [22-23]. In terms of rheumatoid arthritis therapies, research shows that PYC helps to improve symptoms in individuals with mild to moderate rheumatoid arthritis [24], providing an alternative for lowering healthcare expenditures and adverse effects by avoiding anti-inflammatory drugs [25]. PYC fortification contributed to better diabetes prevention, reduced cardiovascular complications, and relatively low antihypertensive medication use compared to controls in individuals with type 2 diabetes who were at high risk for negative outcomes from CVD [26]. Despite the lack of powerful or reasonable scholarly proofs opposing the use of PYC for the above-mentioned therapies, there is no scientifically sound proof in favour of such uses. While curiosity in PYC is rising between research scientists, very less clinical studies support the applications of this magical phytomolecule. Thus, more clinical studies are required to establish the medicinal potency of this drug.



**Figure 1. Pharmacological Actions of Pycnogenol**

## PHARMACOLOGICAL PROFILE OF PYCNOGENOL

Figure 1 displays the major pharmacological actions of Pycnogenol which are further described in detail as follows:

### **Asthma:**

A study targeted to simplify the treatment of Asthma in various phases of clinical studies. It was observed that Pycnogenol (PYC) could inhibit the expression of 5-lipoxygenase and therefore reduce the leukotriene thresholds in asthma sufferers. It was discovered that anti-inflammatory potential of PYC could help on taking along with the inhalation corticosteroids, which finally helped in decreasing the dosage and frequency of administering the corticosteroids [27]. PYC was tested for its consequences on airway inflammation where it lowered production of nitric oxide as well as interleukins-1 & 6. PYC furthermore inhibited the appearance of inducible Nitric Oxide Synthase and Matrix Metalloproteinase-9 while increasing the utterance of Hemeoxygenase. PYC reduced the number of immune cytokines and the thresholds of interleukins-4, -5 and -13, and immunoglobulin-E in Bronchoalveolar lavage fluid or serum in the in vivo testing. Such conclusions are line with the observations of the histopathological evaluation that also displayed that PYC reduced the inflammation of the airways and mucus hypersecretion caused by OVA challenging task [28]. Further, PYC has a higher bioavailability and precludes the occurrence of OVA-induced respiratory inflammatory responses in rodents by hindering the IL-13/JAK/STAT6 passageway and obstructing acetylcholine discharge to decrease goblet cell metaplasia [29].

### **Chronic venous disease**

Chronic venous disease is a vasculature disease that impacts 1-5% of the inhabitants, with the older adults being among the most affected. Issues of CVI involve edoema and venous stasis ulcers, which could also boost mortality rates and wellness costs. Unfortunately, handful treatments available have showed substantial symptomatic improvement or illness resolution [30]. A research revealed that destretching and recovering after dilatation measurements revealed improved tonality and retrieval of the previous dimension in varicose segments from Pycnogenol patient populations. Varicose vein sections had greater enduring distention and dilation than standard vein sections. Pycnogenol appears to reduce passive distention and elongation while increasing tonic retrieval and suppleness in vein walls, allowing the blood vessels to recoup their primordial form following vibrant strains [31]. According to existing literature, PYC is used to treat chronic venous insufficiency (CVI) and connected venous disturbances counting Deep Venous Thrombosis (DVT), foot swelling during air travel, acute haemorrhoids and so forth. Its high anti-oxidant, anti-inflammatory, vasodilator and anti-thrombotic actions tend to make Clinical studies also show that pertinent implementation and/or oral dosing can decrease fluid retention of the foots in Chronic Venous Disease [32]. A comparison of Pycnogenol and Antistax-grape leaf extract in regulating the manifestations chronic venous disease was conducted in an eight weeks registration system study (CVI). Compaction is "standard management" for CVI; a cohort of similar participants was supervised to analyze the impact of stockings. Signs were directly measured using an analogue magnitude. Anguish and edoema were reduced with Pycnogenol. Safety profile and adherence were excellent. Elastic compaction was used accurately by 80 percent of the patient populations, implying that it will be more challenging to use, especially on hot days [33]. Furthermore, research suggests that pycnogenol, like diosmin/hesperidin, has had a combination therapy consequence on the rehabilitation of venous ulcers [34]. Furthermore, a research study shows Pycnogenol's clinical and microcirculatory effectiveness in CVI and venous microangiopathy. The investigation exhibited Pycnogenol's note worthy medical role (as a single treatment and in combination with compression) in the therapeutical management of this common health issue [35].

### **Attention deficient hyperactivity disorder (ADHD)**

Attention deficient hyperactivity disorder (ADHD), in terms of origin of disease, is a neuropsychiatric disorder. These are two types ADHD, genetic form and acquired form, comprising of numbers of different genes. 20% of cases are of acquired form. Some patients have both forms i.e, genetic and acquired form. This can be treated by medication and most favorable treatment of ADHD us the medicine and behavior towards the treatment [36]. A research study targeted to gain knowledge on the impact of Pycnogenol on the tiers of 8-oxo-7, 8-dihydroguanine in children with ADHD. DNA damage increases in ADHD children. The effect of 8-oxoG subsides within 1 month from the administration of PYC, as compared to beginners, the effect of 8-oxoG is getting lesser. If the direction of PYC is reduced or closed after 1 month, then immediately the TAS (Total Antioxidant Staus) started increasing [37]. It also reduced the level of GSSG (Glutathione Disulfide) and symbolic augment in  $\gamma$ -l-glutamyl-l-cysteinyl-glycine) thresholds [38].

### **Cramps and muscular pain**

While doing exercise, pain is perceived which results from an integration of factors including acid, ions and harmones. Most common substance responsible for this pain is lactic acid [39]. Since Pycnogenol increases blood flow to body tissue, a placebo-controlled study was conducted. A controlled trial with 66 sportspersons was conducted to examine the advantages of decreasing muscle cramps and anguish during and following intense exercise [40]. Pycnogenol has the potential to enhance blood flowability, enabling the body to attain peak muscular

strength and integrity. Pycnogenol helps our bodies endure strength training and vigorous exercise in a number of different ways. It has powerful antioxidant qualities that aid in the struggle against the negative effects of free radicals. Pycnogenol has the capacity to meet muscular requirements all through workout and to increase endothelial Nitric Oxide production (NO) [41].

### **Diabetes**

In past 20 years, the number of diabetes patients has become more than doubled. The most pessimistic feature of this hasty augment is the appearance of type 2 diabetes in young generation. The most common aspect for this disease is the changing and non-careful lifestyle. Although there are many factors leading to diabetes but the current matter of concern for researchers is diabetes has many risk factors that has been given attention, recent researches has focused on the involvement epigenetic pathways and the impact of the intra-uterine surroundings [42]. A number of laboratory and human studies have demonstrated the defensive consequences of Pycnogenol (PYC) in the administration of diabetes [43]. Supplement with 0.1gm PYC for 3 months throughout a stage of normal anti-diabetic therapy caused significant lowering in plasma glucose level as compared endothelium-1. Echelon of Nitric oxide in plasma was found to be elevated throughout the therapy in both clusters. Consumption of Pycnogenol to normal diabetes treatment lowered glucose level and improved endothelial function [44]. Therefore, PYC action could get better the hyperglycemia - persuaded bio-chemical and physiologic alterations in diabetes [45].

### **Diabetic microangiopathy**

Diabetic Microangiopathy is typified by irregular enlargement and rupture of minute blood vessels, which leads to restricted swelling and functional destruction of the depending tissues [46]. The vasodilation significantly increased the capillary pressure and it might lead to the both renal and extra-renal diabetic microangiopathy [47-48]. An experimental and clinical study investigating the efficiency of oral Pycnogenol was conducted in 30 individuals with severe microangiopathy but devoid of diabetic ulceration background. The patients were administered PYC capsules (50mg) orally thrice daily for one month. Research showed advancement in the echelon of microangiopathy, a remarkable decline in capillary filtration, and remarkable progress in the venoarteriolar retort in all the patients. Skin-flux in the big toe was noted to be slightly reduced. This research suggested that PYC could also help to prevent diabetic ulcers by regulating the amount of Microangiopathy [49].

### **Dysmenorrhea**

Dysmenorrhea is defined as difficult menstrual flow or painful menstruation. It is one of the most common gynaecologic complaints in young women or women in reproductive age. Dysmenorrhea is thought to be caused by the release of prostaglandins in the menstrual fluid, which causes uterine pain, cramping and discomfort. Prostaglandin usually rises right before menstruation begin. Dysmenorrhea can be explained in two wide categories primary and secondary. Primary dysmenorrhea occurs in the absence of pelvic pathology whereas secondary dysmenorrhea resulting detectable disease. The anti-inflammatory potential of pycnogenol and positive influence on endothelial health contribute to the beneficial effects of the extract on women's disease [50]. Dysmenorrhea usually occurs during the hormone free interval in oral contraceptives users. Progestin withdrawal activates NF-KB transcription factor, which unregulates both vascular endothelial growth factor (VEGF) and COX-2 expression in the endothelium [51]. The subsequent increase in Prostaglandin (PG) production facilitate endometrium breakdown and positively influences the intensity of dysmenorrhea and bleeding. Prostaglandins start accumulating in endomyometrium and starts increasing the concentration of vasopressin and leukotrienes in women with severe menstrual pain compare to usual pain. Increase leukotrienes, vasopressin and decreased prostacyclin levels contribute to the pathophysiology of dysmenorrheal [52]. The reduction in use of analgesics is important for minimizing the unpleasant effects of therapy with analgesics or anti-rheumatic substances. Less pain and increased quality of life, is being observed under use of pycnogenol [53].

### **Edema**

The term edema is known when excess fluid from the vein is diffused into the body's tissue and due to this swelling is caused. Due to high blood pressure edema can be mainly of 3 types: Brain edema, pulmonary edema, lower body edema (Legs, ankle, stomach, etc). Studies show that PYC exhibits an imperative impact against oedema in hypertensive patients, it controls the hypertension including when patient is also taking antihypertensive drugs. The two groups taken with PYC is angiotensin converting enzyme inhibitors and nifedipine (calcium antagonist) which decreased the blood pressure and increased vasodilation thus removing the excess of fluid. Pycnogenol itself can do work of ACE inhibitors and nifedipine [54]. The studies have reported that dosage of pycnogenol reduced the requirement of nifedipine for hypertensive patient. The enhancement of capillary integrity showed an anti-edema

effect and prevented microbleedings. Additionally, a research showed that pycnogenol increased the level of vasodilatory factors nitrogen oxide & prostacyclin and reduced the level of vasoconstrictor factor endothelin-1. Based on reviews pycnogenol quantity given to subject is around 150-300 mg, can heal the subject [55].

### **Erectile dysfunction**

Erectile dysfunction is a multi-faceted disorder. Normal male sexual dysfunction includes a modification in any of the parts of the erectile reaction, including natural, social and mental [56]. Attributable to its solid relationship with metabolic disorder and cardiovascular illness, heart appraisal might be justified in men with side effects of erectile brokenness. Surgical treatments are held for the subset of patients who have contraindications to these nonsurgical intercessions, the people who experience unfavorable impacts from clinical treatment and the individuals who likewise have penile fibrosis or penile vascular inadequacy [57]. Researchers have performed many clinical trials in both diabetic and non-diabetic patients and results showed that pycnogenol cured the erectile dysfunction. It was concluded that nitric oxide could relax the cavernous smooth muscle, which in turn lead to penile erection. So erectile dysfunction can be cured if the rate of endogenous nitrogen oxide is increased. In addition, pycnogenol is known to increase the rate of nitrogen oxide [58].

Pycnogenol is given with L- arginine for its better results. Pycnogenol does not affect the glucose rate or any lipid metabolism. In studies, it shows that PYC is more effective in diabetic patients having erectile dysfunction. As an outcome of the findings, oral dosing of L-arginine with PYC improves sexual performance in men with erectile dysfunction without causing any adverse reactions. It was observed that by daily increasing the dose of pycnogenol upto 120mg it could restore the fertility in men at remarkable extent. Pycnogenol not only treated the erectile dysfunctioning but also improved the fertility in subfertile males [59]. In further studies, it was also seen that spermatogenesis and level of reproductive hormones tend to their standard value after treatment with pycnogenol. Additionally, the oxidative variation persuaded by heat stress in testes is convalesce with the help of pycnogenol means helps in cure the male infertility [60].

### **High blood pressure**

It is a pressure generated by circulation of blood and exerts the force on the arterial wall. In this two types of pressure occurred-systolic and diastolic [61]. High blood pressure also cause cardiovascular disease, heart failure, arterial fibrillation, heart valve disorder and stroke etc [62-63]. For maintaining high BP pycnogenols also gives effective results. A trial showed that it helps in reducing systolic blood pressure in high BP patient [64]. Some Meta analysis showed that pycnogenols helps in controlling high BP by lowering the Blood pressure [65].

### **Melasma (chloasma)**

Melasma a common chronic disorder of hyperpigmentation affects the people with dark skin. Mostly women's exposed parts like face and neck in sun are affected from this. The aetiology and pathogenesis of melasma have been linked to a number of factors, including pregnancy, oral contraceptive, sun exposure, genetics etc [66]. Melasma's pathophysiology is not entirely known and therapies are generally ineffective and frequently accompanied by side effects. However, pycnogenol a French maritime pine extract is significantly more potent than vitamin E and recycles vitamin C. UV ray protection is provided by pycnogenol. Therefore, its effectiveness in the therapy of chloasmafaciei was looked into. 30melasma afflicted female has successfully finished one-month clinical experiment during which they consumed pycnogenol. When 30 days completed the patient's melasma suffering area decreased and the intensity of the pigmented region decreased with "NO SIDE EFFECTS" [67]. A clinical trial was carried out to assess the effectiveness, safety, and tolerability of 75 mg pycnogenol ingested orally twice per day versus a placebo in conjunction with the triple conjunction and wide ranging sunscreen for the therapies of facial melasma. The results showed that Pycnogenol is well absorbed and improves the efficacy of wide sunscreen and the triple combination in the treatment of female facial melasma [68].

### **Menopausal symptoms**

Females spend additionally one-third of their life beyond the climacteric. To address the variations in fitness and quality of life (QOL) that ladies undergo during these phases of life, clinicians must have a thorough understanding of the menopause transition (MT) and the postmenopausal era. Women undergo numerous post-menopausal manifestations, such as vasomotor symptoms, genitor-urinary syndrome, weight gain, mood alterations, reduced bone density and so forth [69]. PYC was discovered to relieve menstruation pain and decrease the LDL/HDL proportion. It is worth mentioning that no adverse reactions were revealed [70].

### **Osteoarthritis**

Osteoarthritis (OA) is an ongoing, moderate infection that especially influences weight-bearing joints, for example, hips and knees. It is dominatingly an illness of the older. The seriousness of OA changes from one individual to

another, yet all the same the consonant clinical signs incorporate torment, decreased scope of movement, aggravation and distortion. The whole joint is impacted by a blend of degradative and reparative cycles, which modify the life structures and capability of articular ligament, subchondral bone and other joint tissues [71]. Pycnogenol as a mitigating, anti-inflammatory, chondroprotective add on gives dependable constructive outcomes, for example improved actual portability and relief from discomfort for patients with gentle OA. It consists of a concentrate of polyphenols, made out of a few phenolic acids, catechin, taxifolin and procyanidins with assorted organic and clinical impacts. In the unique situation of the treatment of OA, the collaboration of Pycnogenol with matrix metalloproteinase (MMP) is of use [72]. Pycnogenol could be useful in OA by hindering the pernicious activities of MMPs. Pycnogenol works by its normal blend of short-and long-acting calming substances. It constitutes of substances like catechin, ferulic corrosive, and caffeic corrosive. As these constituents of Pycnogenol and its metabolites show mitigating activities, the advancing appearance of the different dynamic substances gives a durable help with discomfort, so patients feel less agony, additionally during the night. Thus, Pycnogenol's enduring activity depends on the progressive appearance of its assorted calming constituents and metabolites in circulatory system. The utilization of NSAID'S can thus be fundamentally decreased in this manner lessening undesirable impacts of NSAID'S [73].

### **Sunburn**

Sunburn is a radiation effect to the skin achieved by an overabundance of receptiveness to the sun's bright (UV) beams or phony sources like tanning beds [74]. Pycnogenol assists with securing and reestablishing the skin. Pycnogenol containing gels or salves save the skin against UV radiation by inactivating free radicals and by decreasing the inflammation following UV openness. Harm to the skin by UV radiation doesn't just speed up skin maturing, extreme radiation may even produce skin malignant growth. A salve containing 0.2% Pycnogenol, applied after UV radiation, had the option to lessen the quantity of tumors and to delay the ideal opportunity for appearance of growths in naked mice altogether. This examination exhibited that Pycnogenol doesn't act just as a sunscreen, however as a strong calming specialist. The oral admission of Pycnogenol can lessen the results of sun related burn, safeguarding the skin from inside against the inflammation delivered by UV radiation. Notwithstanding the security against UV harms, Pycnogenol balances the debilitating of skin structure by lytic proteins, annihilating fundamental design components of the skin. Following admission of 200mg Pycnogenol, the harming lattice metalloproteases, as collagenase and elastase are restrained in plasma of subjects. Surprisingly, Pycnogenol doesn't just safeguard structure components of the skin against UV or lytic compounds, it is additionally ready to animate the reestablishment of skin components. Biopsies from skin of 20 healthy ladies uncovered an expanded quality articulation for collagen blend and hyaluronic corrosive synthase following admission of 75mg Pycnogenol for a month and a half. Relating to the 40% higher quality articulation of the collagen delivering protein, ladies' skin flexibility, estimated through a cutometer, was expanded by 25% following a month and a half day to day admission of 75mg Pycnogenol. All the while, brought about by the increment of hyaluronic corrosive union, skin hydration, assessed by a corneometer, was altogether worked on by 21%. This improvement of skin flexibility and hydration by Pycnogenol was joined by a lower articulation of qualities incorporating melanin. This diminished quality articulation gave the clarification to Pycnogenol's belongings in lessening over-pigmentation of the skin. At last, a sound microcirculation is significant for the nourishment of the skin. 150mg Pycnogenol sped up the take-up of oxygen and the disposal of carbon dioxide from skin surface [75].

### **Systemic lupus erythematosus (SLE)**

Individuals suffering with SLE undergo a deficiency of self-resistance because of unusual immunological capability and the development of auto-antibodies that direct to the arrangement of safe edifices that might unfavorably influence sound tissue. Albeit the exact etiologic pathway is obscure, hereditary, hormonal, and natural variables, as well as safe anomalies, have been distinguished [76-77]. According to a pilot study, PYC can be securely utilized in subjects with SLE with gentle side effects (disappearing) conceivably staying away from some medication medicines that might cause after effects. PYC treatment decided a critical decrease of ROS creation, apoptosis, p56lck explicit action and erythrocyte sedimentation rate. Furthermore, the decline of SLEDAI (SLE Disease Activity Index) was huge in the Pycnogenol treated bunch. The outcomes acquired recommend that Pycnogenol might be helpful for 2<sup>nd</sup> line treatment to diminish the fiery element of Systemic Lupus Erythematosus [78].

### **Venous leg ulcers**

Venous leg ulcers are normal complexities of persistent venous deficiency that outcome in extreme corporal and cerebral enduring to individuals. A research study aimed to evaluate the impact of PYC and diosmin+hesperidin on the recuperating of venous ulcers. The outcomes of the study revealed that both the pycnogenol and diosmin+hesperidin medicines comparably affected the recuperating of venous ulcers and prompted a huge decline



in the boundary of impacted appendages. The outcomes propose that pycnogenol adjuvantly affects the recuperating of venous ulcers, like diosmin/hesperidin [79]. As known earlier pycnogenol has the property of altering venous microcirculation and increases endothelial function by producing more nitrogen oxide to vasodilate the veins and also leukocytic activity that helps in healing. This all activity of pycnogenol helps in removing excess fluid from the area of ulcer and thus heals the venous leg ulcer. Well, the correct mechanism of healing by pycnogenol is still unknown [80].

### **Gingival bleeding/plaque**

Gum bleeding is a measurable, objective indicator of inflammation that is connected to a number of periodontal disorders. Many different bleeding indices have been developed; some merely classify bleeding as present or absent, while others grade it in an effort to determine its severity. A thorough oral examination should include a measurement of gingival bleeding tendency. In clinical practise, it is more probable to detect locations at risk of future harmful activity when a graded bleeding index is used [81]. An antioxidant phytochemical known as Pycnogenol has been demonstrated to have anti-inflammatory effects in both in vitro and in vivo settings. The effects of chewing gums containing and not containing Pycnogenol on gingival bleeding and plaque development in 40 human volunteers were compared in a study where the double-blinded trial participants were randomized to either receive control gums devoid of pycnogenol or experimental gums containing pycnogenol at a dose of 5 mg. Chewing gum was used by subjects for 14 days. Before and after the experiment, measurements of gingival bleeding and plaque scores were made. Chewing gums containing Pycnogenol considerably reduced gingival bleeding, although ordinary chewing gum-using control participants' bleeding indices remained unchanged. During the two-week timeframe, dental plaque formation significantly increased in those utilising ordinary control gums. Subjects using Pycnogenol chewing gums did not experience an increase in plaque buildup. The results of this study indicate that chewing gums containing Pycnogenol can reduce gingival bleeding and plaque buildup [82].

### **High cholesterol**

High cholesterol is a condition wherein you have an excessive number of lipids (fats) in your blood. It is also called hyperlipidemia or hypercholesterolemia. Cholesterol is a fat-like substance, found in the circulation system and furthermore in organs and nerve fibres. It is presently established that hypercholesterolemia is a significant reason for coronary illness. Individuals with elevated cholesterol frequently have hypertension too [83]. An immense number of pharmacological and clinical investigations demonstrate that Pycnogenol, bears different ideal medical advantages for the conditions of hypercholesterolemia. Pycnogenol is fundamentally made out of phenolic acids, subsidiaries of benzoic and cinnamic corrosive, and procyanidins. The last options are biopolymers of catechin and epicatechin subunits, which are perceived as significant constituents in human sustenance [84].

### **Migraine**

Portrayed by "assaults of extraordinary... pulsating cerebral pain", headache migraine influences 10-20% of the total population, with additional female impacted than men. While a few hypotheses have been proposed, the genuine reason for headache migraine pain remains exceptionally intricate and challenging to comprehend. Presently a new study has found that pycnogenol, may give an elective treatment to migraine in grown-ups. In an investigation, patients recieved 10 capsule containing 120 mg of pycnogenol, 60 mg of L-ascorbic acid and 30 IU of vitamin E every day for a very long time of around 90 days. Every patient went through a neurological assessment one time each month and finished a migraine disability assessment (MIDAS) questionnaire. The MIDAS poll comprised of five inquiries concerning the quantity of days of lost or restricted efficiency in the past 90 days including work, school, family work, what's more, family, social, and recreation exercises. Besides the fact that the scientists found "a critical improvement" in the MIDAS score, there were too "huge decreases" in both the quantity of cerebral pain days and migraine seriousness. In particular, the typical number of cerebral pain duration was decreased from 44.4 days toward the start of the review to 26 days toward the finish of the review. Migraine seriousness was diminished by almost 27%. For the specialists, "antioxidant treatment... might be valuable in the treatment of headache potentially reducing migraine recurrence and seriousness" [85].

### **Obesity**

The pervasiveness of obesity, which has expanded paying little mind to district and country in late many years, is related with adipose fat tissue dispersion. Clinical examinations have additionally shown that PYC altogether diminished circumference waist and fatty oil and cholesterol levels. In vitro, PYC supplementation diminished the fatty oil level by animating lipolysis in adipocytes. Additionally, the investigators examined, interestingly, the impacts of PYC on expression of genes, which might give a clever methodology to forestalling and treating obesity

[86]. A Study to look at the viability of Pycnogenol use as an enhancement and its adequacy for further developed exercise execution, recuperation, and oxidative pressure. Initial, 100 mg/day of Pycnogenol was enhanced in healthy people during an 8-week readiness and preparing project to assess its consequences for actual wellness. They analyzed the impacts of 150 mg/day of Pycnogenol supplementation in marathon runners. The Pycnogenol bunch likewise played out a more noteworthy number of push-ups and sit-ups (as a feature of the APFT), and its oxidative pressure fundamentally was lower than that of the benchmark group. Regarding the marathon runners, in 32 men who enhanced with Pycnogenol, a quicker marathon time was noticed contrasted and that in the 22 control long distance runners (89 minutes 44 seconds versus 96 minutes 5 seconds, separately) [87].

### **Platelet aggregation**

Platelet aggregation is the interaction by which platelets stick to one another at locales of vascular injury. It has been perceived as basic for hemostatic plug formation [88]. Until recently, platelet aggregation was viewed as a clear cycle including the noncovalent connecting of integrin  $\alpha\text{IIb}\beta\text{3}$  receptors on the platelet surface by the dimeric cement protein fibrinogen. The impacts of long time utilization of the bioflavonoid combination pycnogenol were surveyed on collection of platelets from cigarette smokers and nonsmokers. The observations recommend that Pycnogenol supplementation lessens factor for cardiovascular sicknesses, that is to say, platelet aggregation in smokers. According to this, bioflavonoids in pycnogenol diminish the platelet aggregation [89-90].

### **Cardiometabolic health**

Antioxidant treatment has been shown to be effective in the prevention of cardiometabolic illnesses. A plethora of studies have shown that antioxidants can help with obesity-related comorbidities. A meta-analysis of randomised controlled trials (RCTs) to analyze the possible influence of pycnogenol supplementation on the cardio-metabolic characteristics Pycnogenol lowered fasting glucose, glycosylated hemoglobin, LDL, HDL, BMI, Diastolic and Systolic blood pressure substantially. According to the research results of the meta-analysis, pycnogenol may play a function in the prevention of cardiometabolic disease [91].

### **Retinopathy**

Retinopathy is one of the most dreaded intricacies of diabetes yet additionally one of the most preventable. Twenty years after the beginning of diabetes, practically all patients with type 1 diabetes and more than 60% of patients with type 2 diabetes will have some level of retinopathy. Indeed, even at the hour of determination of type 2 diabetes, about a fourth of patients have laid out foundation retinopathy. Treatment can now forestall visual impairment in most of cases, so it is fundamental to distinguish patients with retinopathy before their vision is impacted [92]. Primer and two-fold blind investigations have shown that everyday supplementation with Pycnogenol might slow the movement of retinopathy and further develop vision. Examinations have shown that Pycnogenol eases back the movement of retinopathy and further develops vision when given in normal measures of 120 to 150 mg each day [93].

### **COVID-19**

Corona virus disease 2019 (COVID-19) is caused by the Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV2) and has quickly spread throughout the world. Unlike other SARS viruses, SARS-CoV2 does not simply impact the respiratory system, but also causes endothelial cell inflammation, microvascular injuries, and coagulopathies, affecting multiple organs. Recent studies of SARS-CoV2 patients demonstrated that health issues remain even months after the first infection. Including over 90 human research trials, the French maritime pine bark extract Pycnogenol illustrated anti-inflammatory, vascular, and endothelium-protective effects. It is postulated that Pycnogenol may aid in recovering by relieving symptoms and long-term implications of SARS-CoV2 infection in COVID-19 sick people [94].

### **Urinary Tract Infection**

An open pilot registry study was designed to assess and make a comparison of the prophylaxis of Pycnogenol or cranberry extract in participants with prior, recurring UTIs or interstitial cystitis (IC). The research included 64 participants with reoccurring UTI/IC. At the outset, the three subject groups were compared. At the time of inclusion, all participants had severe symptoms (slight anguish, stranguria, frequent urination, and reduced, occipital abdominal discomfort). The individuals experienced no tolerability issues or side effects during the investigation. The occurrence of UTI symptoms reduced significantly when to the time prior to incorporation in the standard management (SM) group; there was a greater prominent reduction in the number of recurrent infections in the Pycnogenol group. The progress in individuals receiving Pycnogenol was considerably greater than the



consequences of cranberry. All participants in the Pycnogenol group seemed to be infection-free at the end of the research (vs. cranberry). Upon 60 days of treatment with Pycnogenol, markedly more participants (20/22) were entirely symptom-free than with cranberry (16/20). This pilot registration process recommended that Pycnogenol fortification for 2 months could reduce the frequency of UTIs and IC with no adverse effects and effectiveness preferable to cranberry [95].

## CONCLUSIONS

The current appraisal on Pycnogenol describes its complete pharmacological profile (summarized in Table 1). This study describes the utilization of PYC in asthma, chronic venous disease, ADHD, cramps & muscular pain, diabetes & related complications, oedema, erectile dysfunction, high blood pressure, melasma, osteoarthritis, sunburn, gingival bleeding, high cholesterol, migraine, obesity, retinopathy, urinary tract infection, COVID-19 and so forth. Moreover, the clinical studies and the mechanistic approach towards the treatment of various human disorders are described. However, the evidences regarding its mechanism at the molecular levels are insufficient. Although, PYC is a safer product than many of the synthetic options available in the market yet its safety needs to be assessed properly especially in the cases of serious disorders where the medication should not be taken without the intervention of a medical practitioner.

**Table 1: Summarizing the Pharmacological Profile of Pycnogenol**

S. No.	Pharmacological Action	Major Findings	References
1.	Anti-Asthmatic	could inhibit the expression of 5-lipoxygenase and therefore reduce the leukotriene thresholds in asthma sufferers	[27]
		lowered production of nitric oxide as well as interleukins	[28]
		reduced the inflammation of the airways and mucus hypersecretion caused by OVA challenging task	
		higher bioavailability and precluded the occurrence of OVA-induced respiratory inflammatory responses in rodents by hindering the IL-13/JAK/STAT6 passageway and obstructing acetylcholine discharge to decrease goblet cell metaplasia	[29]
2.	Chronic venous disease	reduced passive distention and elongation while increasing tonic retrieval and suppleness in vein walls, allowing the blood vessels to recoup their primordial form following vibrant strains	[31]
		pertinent implementation and/or oral dosing can decrease fluid retention of the foets in Chronic Venous Disease	[32]
		anguish and edema were reduced. safety profile and adherence were excellent.	[33]
3.	Attention deficient hyperactivity disorder	reduced the level of GSSG (Glutathione Disulfide) and symbolic augment in $\gamma$ -l-glutamyl-l-cysteinyl-glycine) thresholds	[38]
4.	Cramps and muscular pain	decreased muscle cramps and anguish during and following intense exercise	[40]
		enhanced blood flowability, enabling the body to attain peak muscular strength and integrity. Pycnogenol helps our bodies endure strength training and vigorous exercise in a number of different ways. It has powerful antioxidant qualities that aid in the struggle against the negative effects of free radicals	[41]
5.	Diabetes	significant lowering in plasma glucose level as compared	[44]

		endothelium-1. Echelon of Nitric oxide in plasma was found to be elevated throughout the therapy in both clusters	
		could get better the hyperglycemia - persuaded bio-chemical and physiologic alterations in diabetes	[45]
6.	Diabetic microangiopathy	a remarkable decline in capillary filtration, and remarkable progress in the venoarteriolar retort in all the patients	[49]
7.	Dysmenorrhea	Reduced pain and increased quality of life	[53]
8.	Edema	reduced the requirement of nifedipine for hypertensive patient increased the level of vasodilatory factors nitrogen oxide & prostacyclin and reduced the level of vasoconstrictor factor enothelin-1	[55]
9.	Erectile dysfunction	nitric oxide could relax the cavernous smooth muscle, which in turn lead to penile erection. increased the rate of nitrogen oxide	[58]
		improved the fertility in subfertile males	[59]
10.	High blood pressure	helped in reducing systolic blood pressure in high BP patient	[64]
		helped in controlling high BP by lowering the Blood pressure	[65]
11.	Melasma (chloasma)	patient's melasma suffering area decreased and the intensity of the pigmented region decreased with "NO SIDE EFFECT"	[67]
		well absorbed and improved the efficacy of wide sunscreen and the triple combination in the treatment of female facial melasma	[68]
12.	Menopausal symptoms	relieved menstruation pain and decreased the LDL/HDL proportion	[70]
13.	Osteoarthritis	hindered the pernicious activities of matrix metalloproteinase	[73]
14.	Sunburn	saved the skin against UV radiation by inactivating free radicals and by decreasing the inflammation following UV openness. sped up the take-up of oxygen and the disposal of carbon dioxide from skin surface	[75]
15.	Systemic lupus erythematosus	critical decrease of ROS creation, apoptosis, p56lck explicit action and erythrocyte sedimentation rate decline of SLEDAI (SLE Disease Activity Index)	[78]
16.	Venous leg ulcers	pycnogenol and diosmin+hesperidin medicines comparably affected the recuperating of venous ulcers and prompted a huge decline in the boundary of impacted appendages	[79]
		altered venous microcirculation and increases endothelial function by producing more nitrogen oxide to vasodilate the veins and also leukocytic activity that helps in healing	[80]

17.	Gingival bleeding/plaque	reduced gingival bleeding and plaque buildup	[82]
18.	High cholesterol	phenolic acids, subsidiaries of benzoic and cinnamic corrosive, and procyanidins advantages for the conditions of hypercholesterolemia	[84]
19.	Migraine	cerebral pain duration was decreased from 44.4 days toward the start of the review to 26 days toward the finish of the review	[85]
20.	Obesity	In vitro, PYC supplementation diminished the fatty oil level by animating lipolysis in adipocytes. The Pycnogenol bunch likewise played out a more noteworthy number of push-ups and sit-up	[87]
21.	Platelet aggregation	bioflavonoids in pycnogenol diminished the platelet aggregation	[89-90]
22.	Cardiometabolic health	lowered fasting glucose, glycosylated hemoglobin, LDL, HDL, BMI, Diastolic and Systolic blood pressure substantially	[91]
23.	Retinopathy	slowed the movement of retinopathy and further develop ed vision	[93]
24.	COVID-19	illustrated anti-inflammatory, vascular, and endothelium-protective effects may aid in recovering by relieving symptoms and long-term implications of SARS-CoV2 infection in COVID-19 sick people	[94]
25.	Urinary Tract Infection	Pycnogenol fortification for 2 months could reduce the frequency of UTIs and IC with no adverse effects and effectiveness preferable to cranberry	[95]

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