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Pycnogenol: A Miracle Component in Reducing Ageing and Skin Disorders

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Abstract

The world is becoming uninhabitable owing to wide globalization. A large number of industries are contributing in water, soil, air, and environment pollution. Increased use of chemicals and accidental chemical spills are also hampering their surroundings. CFC containing tools and technologies are increasing due to higher demand in the market resulting ozone layers are highly affected which make the UV free towards the earth. Several environmental toxins and UV-radiation are the primary reasons for skin dysfunctions as a result skin loses its tone, strength, flux, density, and glamour that further lead to wrinkles and ageing. Chronic UV exposure may also lead to skin cancers. Pycnogenol, on the other hand, has been a major source for both flavonols and polyphenols, which is very potent against several diseases. Evidences suggest that pycnogenol prevents from multiple skin dysfunctions. Its components are equally potent against skin cancers as well. Moreover, several harmful downstream kinases and proteins are also inhibited by this component. In addition, it has been strongly proven beneficial in reducing ageing by preventing free radical generations, at the same time; it also helps in cell regeneration and replication. Thus, in this study we tried to identify the correlate possible molecular theories on ageing and related skin diseases. Finally, a possible benefit of pycnogenol using on skin disorders would be established.

Keywords: Ageing; Radiation; Oxidative stress; Anti-oxidants; Pycnogenol

Introduction

Skin, the most visible and attractive organ in the body and it is the only organ which is exposed to almost everything. Ageing has always been considered as a problem for people in different time; neither males nor females want to be aged. However, ageing is a very complex evitable system of a human life. There have been many mythical stories related to different parameters that reduce age which proves that how fascinated people have always been regarding this issue [1,2]. On the other hand, skin diseases are now mostly prevalent due to UV-radiation, chemical and environmental exposures. Researchers are trying to find out the exact reasons for ageing in order to establish a therapeutic strategy that will reduce age [3,4].

It has been reported that 60% of people suffer from several skin diseases at some point during their lifespan. Occupational environment and exposure in underdeveloped countries lead to several skin diseases like wart, mycosis, dermatitis, skin ulcer, acne, hives, scabies, atopic dermatitis, skin infections, skin allergy and sometimes skin cancers [5,6]. Sometimes skin problems are manageable, others are severe enough to kill as a result it has now been a major concern and interest for the researchers and specialists [7]. In the recent era, herbal products are being more focused to prevent several dysfunctions. There has been a growing concern in the use of complementary and alternative medicines, due to the having several unwanted effects associated with synthetic molecules and as a result more natural treatment options are in verge [8,9]. Phyto-nutrient compounds from extraction of plant roots, flowers, bulbs, barks, fruits, leaves, peels, stems and others are being shown hopeful potential as potent drug or for serving as lead compounds in the creation of new drugs [10]. There are few disadvantages of natural products and traditional medicines have been noticed lately including difference in preparation methods and thus also chemical composition, dosage fixation and adjustment, and the appropriate route of administration [11]. Interestingly, flavonol and phenolic acid derivatives molecules are taking the most attention as these possess several biochemical responses [12-14].

Pycnogenol is a well-known component which is generally extracted from the pine bark of a tree known as Pinus pinaster. The other major important sources of pycnogenol are peanut skin, grape seed, and witch hazel bark. It has been showing highly protective properties against several diseases such as cardiovascular dysfunctions [15], kidney diseases [16], hepatic dysfunctions [17], neuro cognitive disorders [18], diabetes [19], reproductive dysfunctions and infertility [20], skin diseases [21], cancer [22], digestion [23], retinal diseases [24] and other dysfunctions. In fact, beneficial effects of pycnogenol have been showing all over the biological system on both animals and human studies. While establishing molecular mechanisms, Pycnogenol was noticed in blocking p38 MAPK signaling on mature 3T3L1 adipocytes [25]. It has been also reported nuclear transcriptional factor NF-κB on against rotenone-induced neurotoxicity in PC12 cells [26]. Inhibitory activity of pycnogenol was also showed well against SAPK/JNK, ERK1/2 and p38 MAP kinases, iNOS and COX-2 expression in synovial tissue and articular cartilage [27]. NOX-4, PPAR-ϒ, C/EBP-α, and adipocyte protein 2 expressions were down regulated when pycnogenol was applied in 3T3-L1 adipocytes [28]. Blockage property

of MMP-1, MMP-3 and MMP-9 were also noticed by pycnogenol administration [29,30]. Studies also noticed that pycnogenol supplementation proved as a potent antioxidant which enhanced tFAM, Mn-SOD, reduced GSH, catalase and mitochondrial biogenesis [31,32]. On the contrary, pycnogenol administration also proved to be effective against MDA, NOX and 15 f2t isoprostane; along with inhibitory effects of TNF-α, TGF-β, AP-1 and MAPK were also established [31,33]. However, pycnogenol has been mostly found protective against several types of skin diseases including dermatitis, psoriasis, skin allergy and skin cancers [34]. Moreover, elasticity, hydration, flux, wrinkle and glamour of skin were also enhanced when pycnogenol was administrated on both human and animal model [35,36]. Furthermore, mitochondrial biogenesis and reducing ageing were significantly noticed by pycnogenol treatment on several skin tissues [37,38]. Hence, how skin and ageing are affected by free radical-mediated oxidative stress would be disclosed. Finally, an approach could be drawn where skin diseases and ageing will be prevented by using pycnogenol administration.

Ageing and its consequences

It is a common phenomenon by which a living creature loses its regenerative ability and moves toward old state. Ageing is a measurement between how much cells are producing and how many of them are dying. Though ageing is a continuous process that leads to the inability of the cell to reproduce, this cycle depends to be a more or less direct function of the metabolic rate and this sequentially varies species to species [39,40]. Physical activities, psychological disturbances, metabolic changes, emotional stress, trauma, emotion, surrounding environment and genetic off spring may contribute in early ageing [41-43]. Often diseases, infection, inflammation, chemical exposure, food habit and unhealthy lifestyle may accelerate in ageing [44,45].

Ageing hampers all over the body although more complexities are often seen after middle age. Ageing makes heart bigger and blood vessels stiffer as a result heart needs to pump more and develop several cardio-vascular diseases [46]. With ageing, skin may loses its tone, strength and glamour that further develop wrinkle and reduce natural glow [47]. Bone development is also affected by ageing and sequentially makes a person shorter. It weakens bone development and makes them more susceptible to fracture or loss of ability of walking [48]. Owing to ageing, muscles usually lose strength and tone resulting less coordinated or have trouble balancing movement which ultimately leads to muscle atrophy [49]. Body immunity is decreased with ageing as result infections have become more prominent that eventually cause death [50]. Environmental factors as well as chemical exposures during life may lead in progression towards the end of functional reproductive phase. Ageing also affects normal reproductive functions and leads toward infertility [51]. In addition, loss of brain functions and involuntary movements have been reported with ageing which turn to Alzheimer's, Parkinson's, epilepsy and amnesia [52,53]. Along with that, ageing would lower the number of nephrons which consequently diminish normal kidney functions by affecting glomerular filtration rate, excess uric acid production, accumulation of creatinine in blood and loss of total kidney function [54,55]. Besides, diabetes [56], hypertension [57] and liver dysfunctions [58] have often been correlated with ageing [59].

Oxidative stress and ageing

The free radical-mediated oxidative stress theory in Aging was first projected in 1956, which is currently one of the most reliable clarifications for how ageing is occurred at the cellular or molecular level [60]. Although the exact reason behind ageing is yet to be clear, several evidences suggest on damage-based theories. In the recent time, there is an increasing amount of investigation and explanation which suggest the positive connection between free radical-mediated oxidative stress and ageing. It has been acknowledged that the amount of oxygen taken up per specific time and body weight is inversely correlated with the maximum life span of species. Reactive Oxygen Species (ROS) and Reactive Nitrogenous Species (RNS) are most harmful chemicals that interfere with almost all the biochemical steps [61]. DNA damage has been primarily focused when an oxidant hits on DNA and shows its real damageable properties [62]. DNA methylation as well as DNA oxidation is being major plot to establish theories in favor of ageing (Figure 1) [63,64]. Sometimes oxidant-induced apoptosis may cause ageing in experimented subjects [65].However, it has been investigated through several *in vitro* studies that reactive oxygen species and free radicals induce lipid peroxidation, protein modifications, base alteration and DNA strand breakage which may lead to ageing [66]. Reports also notice that oxidative-mediated stress can cause necrosis or apoptosis and often lysis of the cell resulting ageing (Figure 1) [67]. Several drug molecules may also help in the generation of free radicals when it is given as overdose [68]. Sometimes mitochondrial ATP production may generate free radicals that eventually interact with several necessary cellular components and hamper in further biogenesis process. NOX-4, a highly reactive oxidant which hampers electron transport in the mitochondria and may lead to ageing [69]. Several other theories on anti-oxidants have been proposed in favor of ageing. Superoxide anion reduces superoxide dismutase, hydrogen peroxides destroy catalase production, malonaldehyde and 15 f2t isoprostane often interact with membrane protein and break cell membrane. Besides, less production and presence of glutathione, melatonin, thiols, Co enzyme Q-10, vitamin E and β-carotene may also turn to ageing [68,70,71]. Inhibition of antioxidant genes like Nrf-2, Sirt-1 and HO by oxidants or pro-oxidants can cause cellular aging [56,72].

Role of pycnogenol on ageing

Several treatment strategies are being suggested to reduce ageing. Nutritionists and dieticians are currently recommending fruits and vegetables to avert ageing. Many physicians think that taking herbal and nutrition from natural resources are much more effective and safer compared to synthetic molecules [73,74]. Inhibition of oxidants is another target as these hamper in cellular replications. On the other hand, mitochondrial biogenesis has been a prime target (Figure 1) to replicate the cells for preventing ageing. In addition to these, prevention of DNA damages and alteration of genetic codes may be another good target for preventing ageing [75]. With growing age, skin generally alters roughness and loses elasticity which is a visible signs of cutaneous ageing. A double-blind, placebo-controlled study with 62 women (age between 45-72) was undertaken for 12 weeks whom 10mg pycnogenol was given. After 12 weeks of treatment pycnogenol administrated group showed improved skin elasticity and roughness when compared to control group that further indicated prevention against cutaneous ageing [76]. Leibniz Research Institute for Environmental Medicine, in Dusseldorf took an effort for 12 weeks to understand the ageing preventive activity of pycnogenol (75 mg/day)

on 20 healthy women (age 55-68). After 12 weeks of pycnogenol treatment it was observed that 25% skin elasticity, 8% skin hydration and 6% skin smoothness were enhanced. At the same time, 3% skin wrinkles and skin fatigue were reduced considerably (Table 1) [36]. Investigations showed that the anti-inflammatory and anti-free radical properties of pycnogenol may be helpful against ageing. 31 patients were participated in a trial for 60 days whom pycnogenol was provided with a dosage of 2 pearls per day. Statistical results proved significant improvement of skin hydration and elasticity on pycnogenol given subjects. The study also showed good activity on preventing photo-ageing by pycnogenol treatment [38]. In mice, pycnogenol found to be beneficial by reducing MDA content, however, effect of SOD noticed insignificant [77]. Pycnogenol was also investigated for its ability to inhibit oxidants and pro-oxidants on B16 melanoma cells (B16 cells). Biochemical assay proved inhibition activity of peroxynitrite ($ONOO^-$), superoxide ($^{\cdot}O_2$), nitric oxide ($NO^{\cdot}$), and hydroxyl radical ($^{\cdot}OH$) in *in vitro*. The treatment also up-regulated the reduced glutathione/oxidized glutathione ratio [78].

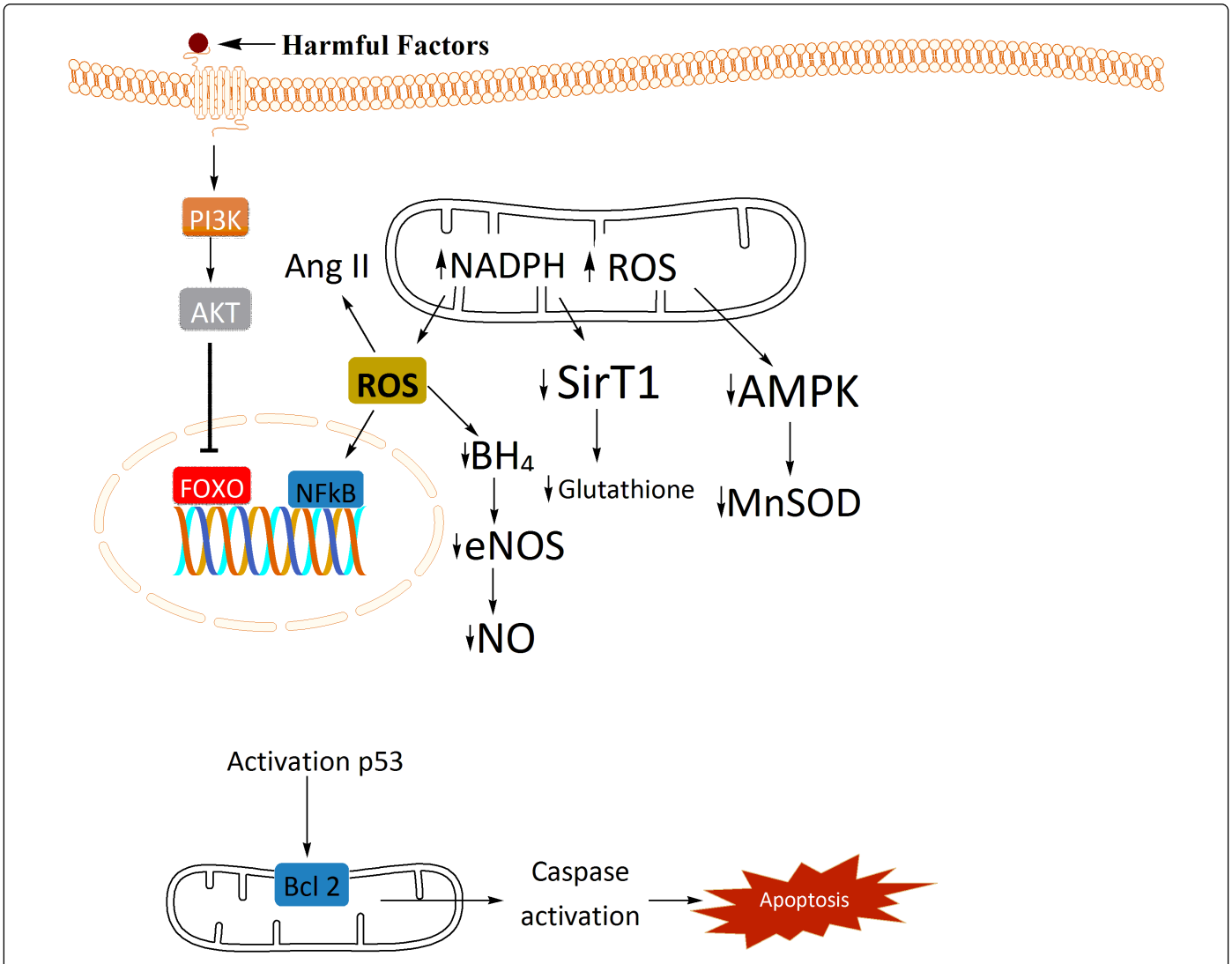

Figure 1: Multiple factors cause skin ageing. One of the major reasons that cause the wrinkle in the skin is the production of excessive reactive oxygen species. Stimuli i.e. insulin like growth factor, epidermal growth factors prevents FOXO *via* PI3K-AKT pathway. Excessive free radicals generation leads to NF-κB activation, which causes the expression of pro-inflammatory cytokines. ROS also inhibits nitric oxide and glutathione production. Excess mitochondrial free radical generation inhibits the production of AMPK and MnSOD. It demonstrates that the excessive ROS production destruct cellular antioxidant defense. On the contrary, other intracellular stimulus activates p53 which causes caspase activation which leads to cellular apoptosis.

Role of pycnogenol on other skin diseases:

There are various mechanisms and biochemical pathways responsible for preventing and curing actions of herbal compounds such as induction of caspase activity, inhibition of angiogenesis and inhibition of the effects of other promoting proteins such as PI3-K, PKC, IKK, Bcl-2, AP-1, STAT3 and MMPs [75]. Preventing inflammatory marker accumulation, anti-radiation activity, protecting genetic materials, saving endoplasmic reticulum, stabilizing skin cell membrane and blockage of harmful downstream proteins can be good target for pycnogenol on skin lesion. Several animals, cell culture and

human trials have shown good activities when pycnogenol was applied on these studies [79,80]. Solar stimulated radiation, especially in the UV range of 290 to 400 nm, is responsible for various biological events inside the skin. An acute exposure to ultraviolet radiation may lead to several inflammatory responses, skin erythema, rash, irritation and skin ulcers [81], on the other hand, chronic UV exposures can produce carcinoma and photo-aging [82]. Several protective mechanisms have been proposed so far from both animal and human subjects. 1.66 and 10 mg pycnogenol per kg body weight for the first 4 weeks to observe protecting effect on human skin against solar UV-simulated light-induced erythema subjects. After 4 weeks of oral pycnogenol treatment an inhibition of NF-κB–dependent gene expression found to be lowered which further blocked inflammatory signaling [83]. Intercellular adhesion molecule-1 and interferon-ϒ play one of the pivotal roles for signaling inflammation in leukocytes. An investigated on the interaction of T cells with keratinocytes after activation with IFN-ϒ was undertaken to observe the possible beneficial role of pycnogenol administration. A 50 mg/ml dose of pycnogenol and a 12 hr pre-treatment time provided maximal 70% inhibition of inducible ICAM-1 expression in HaCaT cells (Table 1) [84]. Hyper-pigmentation is a common dermatological symptom when overproduction of Melanin is observed, and generally linked with exposure to the UV and often found difficulty of its treatment [85]. An *ex vivo* experimental model after exposure to UV A and B, infrared-A radiations and visible light on human skin fragments which was obtained from elective plastic surgery, when pycnogenol was applied on the skin; it was reported that a reduction in the deposition of this pigment and melatonin concentration after irradiation [86]. Another randomized, double blind, placebo controlled study was to aim the possible effect of pycnogenol on skin DNA repair. Three month of consecutive treatment of pycnogenol on older subjects found a relationship between the level of 8-oxoG and repair ability of DNA [87].

Subjects	Outcomes of the study	References
Model: Mouse Diseases induced by: Chronic UV- B Treatment: Mixture of vitamin C, vitamin E, pycnogenol and evening primrose oil Dose: 1,130 mg/kg/day	Reduced UVB-induced wrinkle formation, Decreased significant of epidermal thickness, and UVB-induced hyperplasia, acanthosis, and hyperkeratosis, and Prevented the UVB-induced expressions of MMPs, MAP kinase, AP-1, TGF-β2 expression.	[33]
Model: Women Diseases induced by: Previously Induced Treatment: Pycnogenol Dose: 25 mg/day	Improved significantly hydration and elasticity of skin, and Significantly increase in the mRNA expression of hyaluronic acid synthase-1 and collagen de novo synthesis.	[21]
Model: Women Diseases induced by: Previously Induced Treatment: Evelle (Pycnogenol) Dose: 10 mg	Skin elasticity was found to be statistically significantly increased, Skin roughness was also reported to be significantly lowered, and Improve visible signs of cutaneous ageing	[76]
Model: Cell culture/calorimeter assay Diseases induced by: N/A Treatment: Pycnogenol Dose: 1mg/1mL	Inhibitory activities of MMP-1, MMP- and MMP-9 were observed	[29]
Model: Human skin Diseases induced by: Previously Induced Treatment: Pycnogenol Dose: 5% w/v solution	Showed good activity of absorption through human skin	[88]
Model: Mice Diseases induced by: Solar-simulated ultraviolet radiation Treatment: Pycnogenol Dose: 0.05 and 0.1% Pycnogenol	Protected from UV radiation, Treatment show anti-tumor property, and Also prevented inflammation and immune-suppressive activities.	[34]
Model: Women Diseases induced by: Previously Induced Treatment: Pycnogenol Dose: 75mg tablet/day	Decreased the average melasma area of the patients, Reduced average pigmentary intensity, and Other associated symptoms such as fatigue, constipation, pains in the body and anxiety were also improved.	[89]
Model: Human Diseases induced by: Previously Induced	Inhibited UVR-induced NF-kB–dependent gene expression in a concentration-dependent manner, and	[83]

Treatment: Pycnogenol Dose: 1.10 and 1.66 mg/kg body weight	Reduced erythema in the skin.	
Model: Human Diseases induced by: Previously Inducedvenous ulcerations subjects Treatment: Pycnogenol Dose: 150mg/day	Progressive decreased in skin flux, and Improvement in the symptomatic score and a Reduction in edema was reported	[90]
Model: Human keratinocyte Diseases induced by: IFN-Y Treatment: Pycnogenol Dose: 50 µg/ml	Significantly inhibited expression of ICAM-1 expression in HaCaT cells, and Inhibited IFN-Y-mediated activation of Stat1.	[84]
Model: Cell culture Diseases induced by: Cultured B16 melanoma cells Treatment: Pycnogenol Dose: 5–50 µg/ml	Inhibited tyrosinase activity and melanin biosynthesis, Suppressive effects against peroxynitrite, superoxide, nitric oxide, and hydroxyl radicalwere reported, and Up-regulated the reduced glutathione/oxidized glutathione ratio.	[78]
Model: Human Diseases induced by: Severe chronic venous insufficiency Treatment: Pycnogenol Dose: 150mg/day	A progressive decrease of skin flux at rest (RF), and An improvement in the symptomatic venous score (ASLS) and a reduction in edema was found.	[35]
Model: Human Diseases induced by: Previously Induced Treatment: Pycnogenol Dose: 75mg/day	Decreased skin fatigue considerably, Enhanced skin elasticity by 25% and skin hydration by 8 percent, and Reduced skin wrinkles by 3 percent and increased skin smoothness by 6 percent	[36]
Model: Human Diseases induced by: Previously Induced Treatment: Pycnogenol Dose: 150mg/day	Found a relationship between the level of 8-oxoG and repair ability of DNA in this group.	[87]
Model: Human Diseases induced by: N/A Treatment: Pycnogenol Dose: 100mg/day	Improved physical fitness, Significant improvement in both males and Females in the 2-mile running time, and Enhanced swimming, biking and running scores activities.	[91]
Model: Mouse Diseases induced by: UV Treatment: Pycnogenol Dose: N/A	Shows certain anti-radiation effect through Scavenging the superoxide anion and hydroxyl Radical without increasing SOD content.	[77]
Model: Mice Diseases induced by: Ovariectomy Treatment: Pycnogenol Dose: 120mg/L/day	Prevented BMD loss and trabecular architectural deterioration in osteoporosis, and Helped in bone development and aging.	[37]
Model: Human Diseases induced by: Previously Induced Treatment: Pycnogenol Dose: N/A	Improved hydration, TEWL and skin elasticity, and Prevented skin photo-aging	[38]
Model: Human skin Diseases induced by: UV- A and UV-B, infrared-A radiations, and visible light	Showed a reduction in the deposition of this pigment after irradiation.	[86]

Treatment: Pycnogenol Dose: 10% solution		

Table 1: Role of Picnogenol on various skin diseases and aging.

Conclusion and Future Directions:

Recent studies showed several side effects and adverse effects when a synthetic molecule is recommended. On the contrary, natural products often show good results with very few unwanted effects. However, treatment with Pycnogenol seems to be an appropriate approach for skin diseases among the local strategies like ascorbic acid, retinoic acid and α-tocopherol. Similarly, use of this product against skin cancers and chemo-prevention are being quite popular. As this product possesses both polyphenols and flavonols, it could be used in several new areas to identify new targets. As most of the studies showed herein about the beneficial effects of pycnogenol has been participated either *in vitro*, using cell cultures, or utilizing various animal models, additional data on its beneficial activity and exact molecular mechanisms in humans must be warranted. Furthermore, safety and toxicological data must be established on wide and larger human clinical trials.

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Conflict of Interest

The authors declare no conflict of interest.

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