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].

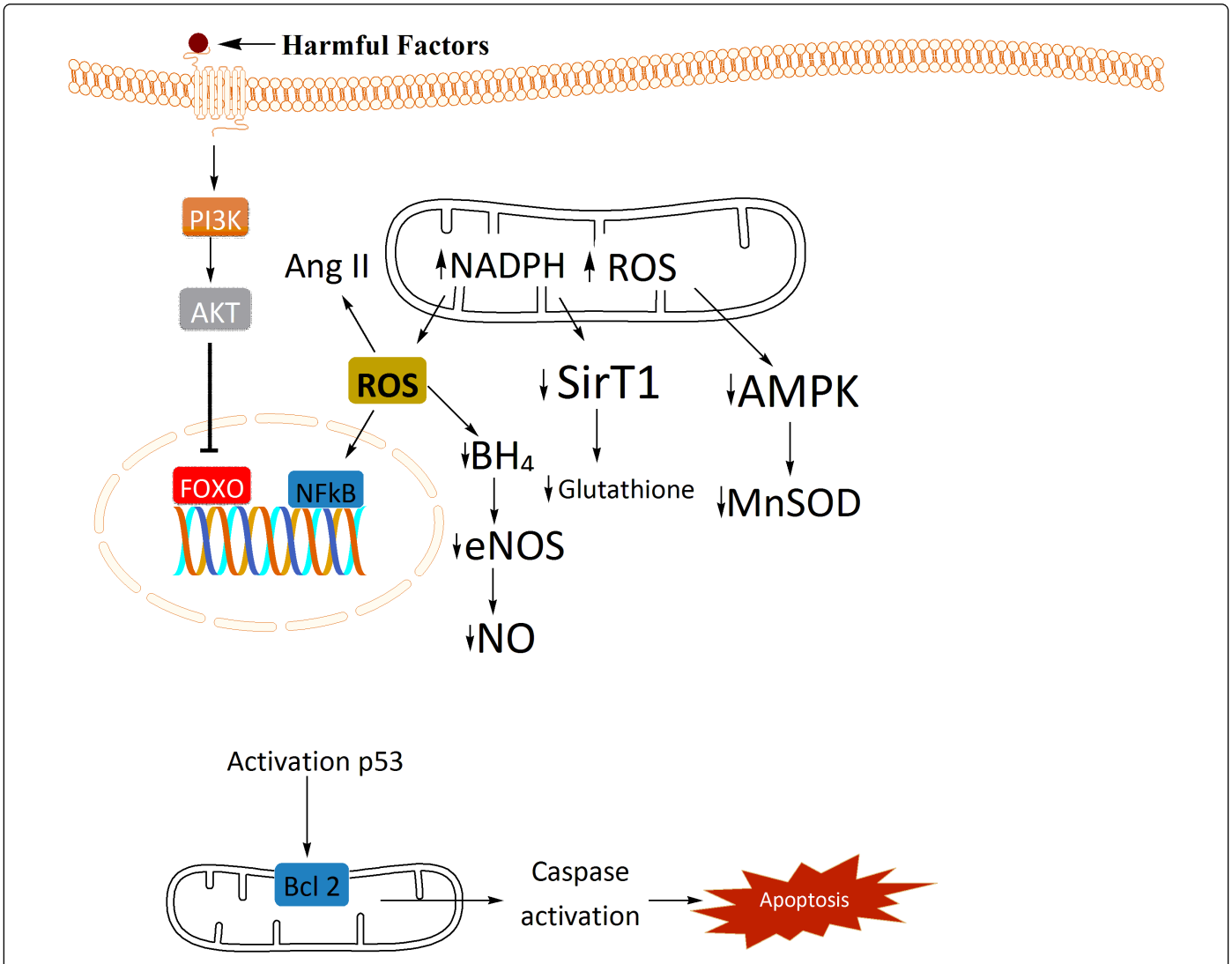

Figure 1: Multiple factors cause skin ageing. One of the major reasons that cause the wrinkle in the skin is the production of excessive reactive oxygen species. Stimuli i.e. insulin like growth factor, epidermal growth factors prevents FOXO *via* PI3K-AKT pathway. Excessive free radicals generation 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.

References:

1. Mukherjee PK, Maity N, Nema NK, Sarkar BK (2011) Bioactive compounds from natural resources against skin aging. Phytomedicine 19: 64-73.
2. Chowdhury W, Tisha A, Akter S, Zahur S, Hasan N (2017) The Role of Arsenic on Skin Diseases, Hair Fall and Inflammation: An Immunological Review and Case Studies. J Clin Exp Dermatol Res 8: 2.
3. Lipomi DJ, Vosgueritchian M, Tee BC, Hellstrom SL, Lee JA, et al. (2011) Skin-like pressure and strain sensors based on transparent elastic films of carbon nanotubes. Nat Nano PY 6: 788-792.
4. Masaki H (2010) Role of antioxidants in the skin: anti-aging effects. J Dermatol Sci 58: 85-90.
5. Dickel H, Kuss O, Blesius C, Schmidt A, Diepgen T, et al. (2001) Occupational skin diseases in Northern Bavaria between 1990 and 1999: a populationbased study. Br J Dermatol 145: 453-462.
6. Hay RJ, Johns NE, Williams HC, Bolliger IW, Dellavalle RP, et al. (2014) The global burden of skin disease in 2010: an analysis of the prevalence and impact of skin conditions. J Invest Dermatol 134: 1527-1534.
7. Dalgard FJ, Gieler U, Tomas Aragones L, Lien L, Poot F, et al. (2015) The psychological burden of skin diseases: a cross-sectional multicenter study among dermatological out-patients in 13 European countries. J Invest Dermatol 135: 984-991.
8. Molassiotis A, Fernadez Ortega P, Pud D, Ozden G, Scott JA, et al. (2005) Use of complementary and alternative medicine in cancer patients: a European survey. Ann Oncol 16: 655-663.
9. Chowdhury MRH, Sagor MAT, Tabassum N, Potol MA, Hossain H, et al. (2015) Supplementation of Citrus maxima Peel Powder Prevented Oxidative Stress, Fibrosis, and Hepatic Damage in Carbon Tetrachloride (CCl4) Treated Rats. Evidence-Based Complementary and Alternative Medicine 598179.
10. Sagor AT, Chowdhury MR, Tabassum N, Hossain H, Rahman M, et al. (2015) Supplementation of fresh ucche (Momordica charantia L. var. muricata Willd) prevented oxidative stress, fibrosis and hepatic damage in CCl treated rats. BMC Complement Altern Med 15: 115.
11. Cragg GM, Newman DJ (2013) Natural products: a continuing source of novel drug leads. Biochim Biophys Acta 1830: 3670-3695.
12. Kassim M, Achoui M, Mustafa MR, Mohd MA, Yusoff KM, et al. (2010) Ellagic acid, phenolic acids, and flavonoids in Malaysian honey extracts demonstrate in vitro anti-inflammatory activity. Nu Nutr Res 30: 650-659.
13. Mahmood T, Anwar F, Abbas M, Saari N (2012) Effect of maturity on phenolics (phenolic acids and flavonoids) profile of strawberry cultivars and mulberry species from Pakistan. Int J Mol Sci 13: 4591-4607.
14. Abu Taher S, Hasan Mahmud R, Nabila T, Biswajit S, Anayt U, et al. (2016) Supplementation of rosemary leaves (Rosmarinus officinalis) powder attenuates oxidative stress, inflammation and fibrosis in carbon tetrachloride (CCl4) treated rats. Curr Nutr Food Sci 12: 1-8.
15. Klimas J, Kmecova J, Jankyova S, Yaghi D, Priesolova E, et al. (2010) Pycnogenol® improves left ventricular function in streptozotocininduced diabetic cardiomyopathy in rats. Phytother Res 24: 969-974.
16. Cesarone MR, Belcaro G, Stuard S, Schönlau F, Di Renzo A, et al. (2010) Kidney flow and function in hypertension: protective effects of Pycnogenol in hypertensive participants—a controlled study. J Cardiovasc Pharmacol Ther 15: 41-46.
17. Mei L, Mochizuki M, Hasegawa N (2012) Hepatoprotective Effects of Pycnogenol in a Rat Model of Nonalcoholic Steatohepatitis. Phytother Res 26: 1572-1574.
18. Khan MM, Kempuraj D, Thangavel R, Zaheer A (2013) Protection of MPTP-induced neuroinflammation and neurodegeneration by Pycnogenol. Neurochem Int 62: 379-388.
19. Parveen K, Ishrat T, Malik S, Kausar MA, Siddiqui WA, et al. (2013) Modulatory effects of Pycnogenol® in a rat model of insulin-dependent diabetes mellitus: biochemical, histological, and immunohistochemical evidences. Protoplasma 250: 347-360.
20. Errichi S, Bottari A, Belcaro G, Cesarone M, Hosoi M, et al. Supplementation with Pycnogenol® improves signs and symptoms of menopausal transition. Panminerva Medica 53: 65-70.
21. Marini A, Grether Beck S, Jaenicke T, Weber M, Burki C, et al. (2012) Pycnogenol® effects on skin elasticity and hydration coincide with increased gene expressions of collagen type I and hyaluronic acid synthase in women. Skin Pharmacol Physiol 25: 86-92.
22. Khurana H, Pandey R, Saksena A, Kumar A (2013) An evaluation of vitamin E and pycnogenol in children suffering from oral mucositis during cancer chemotherapy. Oral Dis 19: 456-464.
23. Frontela C, Ros G, Martínez C, SánchezSiles LM, Canali R, et al. (2011) Stability of Pycnogenol® as an ingredient in fruit juices subjected to in vitro gastrointestinal digestion. J Sci Food Agri 91: 286-292.
24. Wilson D, Evans M, Guthrie N, Sharma P, Baisley J, et al. (2010) A randomized, doubleblind, placebocontrolled exploratory study to evaluate the potential of pycnogenol® for improving allergic rhinitis symptoms. Phytother Res 24: 1115-1119.
25. Lee HH, Kim KJ, Lee OH, Lee BY (2010) Effect of pycnogenol® on glucose transport in mature 3T3L1 Adipocytes. Phytother Res 24: 1242-1249.
26. Gao B, Chang C, Zhou J, Zhao T, Wang C, et al. (2015) Pycnogenol protects against rotenone-induced neurotoxicity in PC12 Cells through regulating NF-κB-iNOS signaling pathway. DNA Cell Biol 34: 643-649.

27. Peng YJ, Lee CH, Wang CC, Salter DM, Lee HS et al. (2012) Pycnogenol attenuates the inflammatory and nitrosative stress on joint inflammation induced by urate crystals. Free Radic Biol Med 52: 765-774.
28. Lee OH, Seo MJ, Choi HS, Lee BY (2012) Pycnogenol® Inhibits Lipid Accumulation in 3T3L1 Adipocytes with the Modulation of Reactive Oxygen Species (ROS) Production Associated with Antioxidant Enzyme Responses. Phytother Res 26: 403-411.
29. Grimm T, Schäfer A, Högger P (2004) Antioxidant activity and inhibition of matrix metalloproteinases by metabolites of maritime pine bark extract (pycnogenol). Free Radic Biol Med 36: 811-822.
30. Chowdhury N, Farooq T, Abdullah S, Mahadi A, Hasan M, et al. (2016) Molecular Enzymology and Drug Targets Matrix Metalloproteinases (MMP), a Major Responsible Downstream Signaling Molecule for Cellular Damage-A Review. Mol Enz Drug Tar 2: 3.
31. Taner G, Aydin S, Bacanli M, Sarigöl Z, Şahin T, et al. (2014) Modulating effects of pycnogenol® on oxidative stress and DNA damage induced by sepsis in rats. Phytother Res 28: 1692-1700.
32. Koláček M, Muchová J, Dvořáková M, Paduchová Z, Žitňanová I, et al. (2013) Effect of natural polyphenols (Pycnogenol) on oxidative stress markers in children suffering from Crohn's disease–a pilot study. Free Radic Res 47: 624-634.
33. Cho HS, Lee MH, Lee JW, No KO, Park SK, et al. (2007) Antiwrinkling effects of the mixture of vitamin C, vitamin E, pycnogenol and evening primrose oil, and molecular mechanisms on hairless mouse skin caused by chronic ultraviolet B irradiation. Photodermatol Photoimmunol Photomed 23: 155-162.
34. Sime S, Reeve VE (2004) Protection from Inflammation, Immunosuppression and Carcinogenesis Induced by UV Radiation in Mice by Topical Pycnogenol®. Photochem Photobiol 79: 193-198.
35. Cesarone M, Belcaro G, Rohdewald P, Pellegrini L, Ledda A, et al. (2006) Comparison of Pycnogenol® and Daflon® in treating chronic venous insufficiency: a prospective, controlled study. Clin Appl Thromb Hemost 12: 205-212.
36. Gillette B (2012) Pine bark extract improves skin aging signs.
37. Takano T, Kozai Y, Kawamata R, Wakao H, Sakurai T, et al. (2011) Inhibitory effect of maritime pine bark extract (Pycnogenol®) on deterioration of bone structure in the distal femoral epiphysis of ovariectomized mice. Oral Radiol 27: 8-16.
38. Coacci A, Palmieri B (2013) Efficacia e tollerabilità di un nutraceutico in formulazione perle nel trattamento del photo-aging cutaneo. Studio-pilota. Prog Nutr 15: 90-98.
39. Harman D (1956) Aging: a theory based on free radical and radiation chemistry. J Gerontol 11: 298-300.
40. Rowe JW, Kahn RL (1997) Successful aging. Gerontologist 37: 433-440.
41. Finch CE (2010) Evolution of the human lifespan and diseases of aging: roles of infection, inflammation, and nutrition. Proc Natl Acad Sci U S A 107: 1718-1724.
42. Raykov T, Tomer A, Nesselroade JR (1991) Reporting structural equation modeling results in Psychology and Aging: some proposed guidelines. Psychol Aging 6: 499.
43. Talbot LA, Morrell CH, Fleg JL, Metter EJ (2007) Changes in leisure time physical activity and risk of all-cause mortality in men and women: the Baltimore Longitudinal Study of Aging. Prev Med 45: 169-176.
44. Deeks SG (2011) HIV infection, inflammation, immunosenescence, and aging. Annu Rev Med 62: 141-155.
45. Finch CE, Crimmins EM (2004) Inflammatory exposure and historical changes in human life-spans. Science 305: 1736-1739.
46. Steenman M, Lande G (2017) Cardiac aging and heart disease in humans. Biophys Rev 9: 131-137.
47. Blume-Peytavi U, Kottner J, Sterry W, Hodin MW, Griffiths TW, et al. (2016) Age-associated skin conditions and diseases: current perspectives and future options. Gerontologist 56: S230-S242.
48. Gimble JM, Floyd ZE, Kassem M, Nuttall ME: Aging and Bone. In: Osteoporosis in Older Persons. Springer, Newyork.
49. Kern H, Hofer C, Loefler S, Zampieri S, Gargiulo P, et al. (2017) Atrophy, ultra-structural disorders, severe atrophy and degeneration of denervated human muscle in SCI and Aging. Implications for their recovery by Functional Electrical Stimulation. Neurol Res 2017: 1-7.
50. Rose MR, Cabral LG, Kezos JN, Barter TT, Phillips MA, et al. (2016) Four steps toward the control of aging: following the example of infectious disease. Biogerontology 17: 21-31.
51. Abdollahi M, Moridani MY, Aruoma OI, Mostafalou S (2014) Oxidative Stress in Aging. Oxidative Medicine and Cellular Longevity 876834.
52. Gorlé N, Van Cauwenberghe C, Libert C, Vandenbroucke (2016) RE: The effect of aging on brain barriers and the consequences for Alzheimer's disease development. Mamm Genome 27: 407-420.
53. Ryan JD, D'angelo MC, Kamino D, Ostreicher M, Moses SN, et al. (2016) Relational learning and transitive expression in aging and amnesia. Hippocampus 26: 170-184.
54. Newsome A, Dasinger JH, Intapad S, Davis G, Alexander B, et al. (2016) Effect of Aging on Kidney Function in Male Intrauterine Growth Restricted Rats. FASEB J 30: 1214.1216.
55. Alam MA, Chowdhury MRH, Jain P, Sagor MAT, Reza HM, et al. (2015) DPP-4 inhibitor sitagliptin prevents inflammation and oxidative stress of heart and kidney in two kidney and one clip (2K1C) rats. Diabetol Metab Syndr 7: 1-10.
56. Mohib MM, Rabby SMF, Paran TZ, Hasan MM, Ahmed I, et al. (2016) Protective role of green tea on diabetic nephropathy -A review. Cogent Biol 1248166.
57. Sagor MAT, Tabassum N, Potol MA, Alam MA (2015) Xanthine Oxidase Inhibitor, Allopurinol, Prevented Oxidative Stress, Fibrosis, and Myocardial Damage in Isoproterenol Induced Aged Rats. Oxidative Medicine and Cellular Longevity 2015:9.
58. Reza HM, Sagor MAT, Alam MA (2015) Iron deposition causes oxidative stress, inflammation and fibrosis in carbon tetrachloride-induced liver dysfunction in rats. Bangladesh J Pharmacol 10: 152-159.
59. Roos V, Elmståhl S, Ingelsson E, Sundström J, Ärnlöv J, et al. (2017) Metabolic Syndrome Development During Aging with Special Reference to Obesity Without the Metabolic Syndrome. Metab Syndr Relat Disord 15: 36-43.
60. Bokov A, Chaudhuri A, Richardson A (2004) The role of oxidative damage and stress in aging. Mech Ageing Dev125: 811-826.
61. Dröge W (2003) Oxidative stress and aging. In: Hypoxia. Adv Expl Med Biol 543: 191-200.
62. Kujoth G, Hiona A, Pugh T, Someya S, Panzer K, (2005) Mitochondrial DNA mutations, oxidative stress, and apoptosis in mammalian aging. Science 309: 481-484.
63. Bollati V, Schwartz J, Wright R, Litonjua A, Tarantini L, et al. (2009) Decline in genomic DNA methylation through aging in a cohort of elderly subjects. Mech Ageing Dev 130: 234-239.
64. Ames BN (1989) Endogenous oxidative DNA damage, aging, and cancer. Free Radic Res Commun 7: 121-128.
65. Lee HC, Wei YH (2007) Oxidative stress, mitochondrial DNA mutation, and apoptosis in aging. Exp Biol Med (Maywood) 232: 592-606.
66. Abdollahi M, Moridani MY, Aruoma OI, Mostafalou S (2014) Oxidative stress in aging. Oxid Med Cell Longev 876834.
67. Cutler R, Packer L, Bertram J, Mori A (2012) Oxidative stress and aging, aging (1st ed). Birkhäuser Basel, Switzerland.
68. Sagor M, Mohib M, Tabassum N, Ahmed I, Reza H, et al. (2016) Fresh Seed Supplementation of Syzygium Cumini Attenuated Oxidative Stress, Inflammation, Fibrosis, Iron Overload, Hepatic Dysfunction and Renal Injury in Acetaminophen Induced Rats. J Drug Metab Toxicol 7: 2.
69. Cadenas E, Davies KJ (2000) Mitochondrial free radical generation, oxidative stress, and aging. Free Radic Biol Med 29: 222-230.
70. Abu Taher Sagor M (2016) Angiotensin-II, a potent peptide, participates in the development of hepatic dysfunctions. Immunol Endocrine Metabolic Agents Med Chem 16:1-17.
71. Reza HM, Tabassum N, Sagor MAT, Chowdhury MRH, Rahman M, et al. (2016) Angiotensin-converting enzyme inhibitor prevents oxidative

stress, inflammation, and fibrosis in carbon tetrachloride-treated rat liver. Toxicol Mech Methods 26: 46-53.

72. Mohib MM, Hasan I, Chowdhury WK, Chowdhury NU, Mohiuddin S, et al. (2016) Role of Angiotensin II in Hepatic Inflammation through MAPK Pathway: A Review. J Hep 2: 2.
73. Nasri H, Shirzad H (2013) Toxicity and safety of medicinal plants. J HerbMed Plarmacol 2: 21-22.
74. Firenzuoli F, Gori L (2007) Herbal medicine today: clinical and research issues. Evidence-Based Complementary and Alternative Medicine 4: 37-40.
75. Chinembiri TN, Du Plessis LH, Gerber M, Hamman JH, Du Plessis J, et al. (2014) Review of natural compounds for potential skin cancer treatment. Molecules 19: 11679-11721.
76. Segger D, Schönlau F (2004) Supplementation with Evelle® improves skin smoothness and elasticity in a doubleblind, placebocontrolled study with 62 women. J Dermatolog Treat 15: 222-226.
77. Ding Xiang, Qiang Yi-zhong, Wang Li li, Cheng Yue jin, Jiang Jia gui, et al. (2011) Scavenging Effect of Pycnogenol on Free Radicals in Radiation Exposed Mice Organs. Industrial Health and Occupational Diseases 5: 5.
78. Kim YJ, Kang KS, Yokozawa T (2008) The anti-melanogenic effect of pycnogenol by its anti-oxidative actions. Food Chem Toxicol 46: 2466-2471.
79. Alam MB, Bajpai VK, Lee J, Zhao P, Byeon JH, (2017) Inhibition of melanogenesis by jineol from Scolopendra subspinipes mutilans via MAP-Kinase mediated MITF downregulation and the proteasomal degradation of tyrosinase. Sci Rep 7: 45858.
80. Pan CH, Jeng HA, Lai CH (2017) Biomarkers of oxidative stress in electroplating workers exposed to hexavalent chromium. J Expo Sci Environ Epidemiol 85.
81. Hruza LL, Pentland AP (1993) Mechanisms of UV-induced inflammation. J Invest Dermatol 100: S35-S41.
82. Scharffetter Kochanek K, Wlaschek M, Brenneisen P, Schauen M, Blaudschun R, et al. (1997) UV-induced reactive oxygen species in photocarcinogenesis and photoaging. Biol Chem 378: 1247-1258.
83. Saliou C, Rimbach G, Moini H, McLaughlin L, Hosseini S, et al. (2001) Solar ultraviolet-induced erythema in human skin and nuclear factor-kappa-B–dependent gene expression in keratinocytes are modulated by a French maritime pine bark extract. Free Radic Biol Med 30: 154-160.
84. Bito T, Roy S, Sen CK, Packer L (2000) Pine bark extract pycnogenol downregulates IFN-γ-induced adhesion of T cells to human keratinocytes by inhibiting inducible ICAM-1 expression. Free Radic Biol Med 28: 219-227.
85. Cui R, Widlund HR, Feige E, Lin JY, Wilensky DL, et al. (2007) Central role of p53 in the suntan response and pathologic hyperpigmentation. Cell 128: 853-864.
86. Leis Ayres E, Costa A, Eberlin S, Piatto Clerici S (2015) Estudo ex vivo para avaliação da atividade clareadora do Pycnogenol® após exposição à radiação ultravioleta, infravermelha e luz visível. Surg Cosmet Dermatol 7: 4.
87. Dvořáková M, Paduchova Z, Muchova J, Duračková Z, Collins A, et al. (2010) How does pycnogenol® influence oxidative damage to DNA and its repair ability in elderly people? Prague Med Rep 111: 263-271.
88. Sarikaki V, Rallis M, Tanojo H, Panteri I, Dotsikas Y, et al. (2005) In vitro percutaneous absorption of pine bark extract (Pycnogenol) in human skin. Journal of Toxicology: Cutaneous and Ocular Toxicology 23: 149-158.
89. Ni Z, Mu Y, Gulati O (2002) Treatment of melasma with Pycnogenol®. Phytother Res 16: 567-571.
90. Cesarone M, Belcaro G, Rohdewald P, Pellegrini L, Ledda A, et al. (2006) Rapid relief of signs/symptoms in chronic venous microangiopathy with Pycnogenol®: A prospective, controlled study. Angiology 57: 569-576.
91. Vinciguerra G, Belcaro G, Bonanni E, Cesarone M, Rotondi V, et al. (2013) Evaluation of the effects of supplementation with Pycnogenol® on fitness in normal subjects with the Army Physical Fitness Test and in performances of athletes in the 100-minute triathlon. J Sports Med Phys Fitness 53: 644-654.