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Rejuvenation of Metabolic Cascades for Controlling Aging through Bioactive Compounds: A Review

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Abstract

Consumption of vegetables and fruits has always played a crucial role in curing several disorders. But, the underlying mechanism behind such effect was unknown previously. With the advancement in research, the presence of several bioactive compounds and their unique role in modulating several metabolic cascades is coming into the picture. Chronic metabolic disorders are increasing at an alarming rate worldwide. The complications associated with these diseases are many but aging is one of them. Research evidences have already unravelled the several pathways of aging. And aging is related to a number of metabolic disturbances. Bioactive compounds are one the emerging pharmacogenic agents, gaining importance due to its capability in re-setting the metabolic clock of aging. In this paper, the authors have attempted to deliver the importance of specific bioactives acting on metabolic pathways for controlling the phenomenon of aging.

Keywords: Anti-aging; Bioactive compounds; Signaling cascade; Metabolic pathway

Introduction

Aging is an inevitable process of human life involving metabolic, genetic and biochemical factors which result in physiological and psychological changes. Aging individuals experience changes in skin, hair, slowing down of function of different organs leading to even loss of organ functions. Scientific research is being carried out to elucidate the different factors responsible for aging, which are primarily of two types, programmed and damage-related. Regulation by programmed factors depends on changes in gene expression affecting systems responsible for maintenance, repair and defence responses. Damage-related factors include an array of internal and external factors affecting living organisms over time. Such factors induce collective damage at various levels, which gives rise to the proposed nine "hallmarks" of aging, which has been discussed in the subsequent section of this article [1].

There exists a relationship amongst life expectancy and the capacity to repair DNA, detoxify receptive oxygen atoms, counteract stress, and supplant worn-out cell [2]. Research studies in pursuit of search for anti-aging techniques include gene therapy, hormonal supplementation, calorie restriction, nutritional modulation and intervention by the application of bioactive compounds, antioxidants and other molecules.

Bioactive compounds are extranutritional constituents found in vegetables, fruits, nuts, oils and whole grains that encourage physiological and cellular activities, which in turn reduce disease risk preventing aging, cancer, cardiovascular and other diseases. Different types of bioactive compounds include carotenoids, polyphenols and phytosterols, lycopene, resveratrol, lignan, tannins and indoles. Flavonoids are found in grains, vegetables, nuts, olive oil, vegetables, organic products, tea and red wine. Phenolic compounds have antioxidant property, cell reinforcement properties, revealing their action as cancer prevention agents, enzyme inhibitors and inducers, inhibitors of receptor activities and inducers and inhibitors of gene expression [3].

Curcumin initiates cellular stress reactions in typical human skin fibroblasts through phosphatidylinositol 3-kinase/Akt pathway and redox signaling [4]. Berry phenolics act as both antioxidant and antimicrobial agent, prevent oxidation of cellular lipids, induce endogenous antioxidant enzymes and also modulate signal transduction mechanism [5]. Even, fermented food and beverages having phototherapeutic plant parts shows medicinal effects, which is mainly attributed to the modulatory effects on metabolic pathways [6,7].

A specific blend of resveratrol and procyanidin may be a promising strategy to support

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treatments for the reduction of skin wrinkling, as well as reducing systemic and skin oxidative stress. Ample varieties of phytomolecules such as aloin, ginsenoside, curcumin, etc. scavenge free radicals from skin cells, prevent trans-epidermal water loss, include a sun protection factor (SPF) of 15 or higher contribute to protect skin from wrinkles, leading to glowing and healthy younger skin [8].

The causes of aging as described by the 9 hallmarks of aging along with the effects of specific bioactive compounds like flavonoids, peptides, alkaloids and phenolics on antiaging process are discussed below.

Metabolic Pathways of Aging

Aging is an integrated time dependant metabolic process mostly controlled by genetic and biochemical pathways, conserved in the evolution. The phenomenon is mostly characterized by cellular damage and its accumulation, resulting in decreasing physiological integrity. Several studies measuring telomere length, transcriptional signatures, gene methylation concluded the existence of a "metabolic clock" responsible for aging. Multiple inborn defects, hyper-caloric nutrition, physical inactivity and other activities featuring "Western-life style" disturb the metabolic clock resulting in detrimental pathological and physiological aging [9]. Telomere shortening, loss of proteostasis, genomic instability, epigenetic alteration, stem cell exhaustion, cellular senescence, deregulated nutrient sensing, mitochondrial dysfunction, altered intercellular communication are the 9 hallmarks of aging [1].

Telomere shortening, associated with cellular senescence, has evolved as a biomarker in aging. It is mostly attributed by the inactivation of telomerase RNA component or telomerase reverse transcriptase. Glucose intolerance, insulin resistance and β cell failure gets accelerated by telomerase inactivation [10]. Mitochondrial turnover is limited by telomere erosion and increases demands of glucose for maintaining energy homeostasis [11].

Aging and its associated metabolic disorders are also associated with protein homeostasis. The biological function of any protein is associated with its structural integrity. Chaperone mediated structural re-shaping and proteasome mediated ubiquinylated protein degradation, lysosome mediated autophagy are the decisive factors for maintaining the homeostasis of proteins with the human system [12]. Signaling pathways controlling the proteostasis are also linked to onset of age- related disorders. Scientific evidences suggest that hexoamine pathway is one the major factor to resist proteolytic stress. Loss of homeostasis, improper metabolic functioning and changes in subcellular compartments is mostly responsible for proteolytic stress. Therefore, proper functioning of hexoamine pathway can control aging [13]. Generally, nuclear DNA damage gets repaired by intracellular mechanisms. But patients with Werner Syndrome and Hutchinson-Gilford Progeria Syndrome are prone to develop type 2 diabetes, depicting the fact that DNA damage can unpair the metabolic signalling pathways [10]. Studies suggest that persistent DNA damage not only hampers the circuitries related to bioenergetic metabolism but also affects the anabolic reactions driven by signals of growth hormone 1 (GH1), insulin like growth factor 1 (IGF1) and insulin (INS) requisite for cell proliferation [14].

Epigenetic alterations as well as non-coding RNA expression explain the processes how parental metabolic alterations during lactation or gestation period favour the transfer of several aspects of metabolic changes onto their next generation. Pre-mature upregulation of "transcriptomic age" is associated with metabolic disorder characterized by high blood pressure and high cholesterol and glucose levels [15]. Parabiosis studies and Heterochronic transplantation experiments delineated the metabolic alterations responsible for the progressive impairment of stem cell function and its accompanying complications of aging [16]. Assessment of metabolism revealed that stem cell experiences changes in maintaining homeostasis between oxidative stress, oxidative phosphorylation and glycolysis. HSCs (haematopoetic stem cells) are highly sensitive to RO and its levels increase within the cellular compartments with increase in age. Treatment of these cells with antioxidant may induce the proliferative action of the cells [17,18].

De-regulation of cascades sensing the fluctuation in nutrient availability occurs during aging. One of the prominent pathways having aging modulating effects is "insulin and IGF1 signaling" (IIS) pathway. Consistent evidences suggest that age- stimulating effects of obesity as well as normal aging are a result of downregulation or inactivation of IIS pathway [19].

Progressive mitochondrial dysfunction is also linked to human aging. The deterioration is linked to decrease in NAD^+ and consequent impairment of deacetylase SIRT1. Low activity of SIRT1 inactivates PGC1α, HIF1A and MYC. As a result, PGC1α dependant mitochondrial protein expression; as well as HIF1A and MYC dependant TFAM (a mitochondrial transcription factor) expression is limited. Thus, intracellular alteration of a single metabolite impairs mitonuclear communication contributing to mitochondrial aging [20].

Alteration of multiple metabolic pathways is intertwined with the orchestration of multicellular functioning. Immunological pathways, neuro-endocrine signalling are few of the complex pathways involving muticellular compartments. Therefore, alteration in one single factor could be detrimental for the entire functioning of the system as the pathways are interlinked. Such alteration is more prone to adult individuals compared to younger ones [21].

Role of Bioactive Compounds in Anti-Aging

Flavonoids

Flavonoids are products of plant secondary metabolism and comprise of a large group of polyphenolic compounds [22,23]. Abundantly flavonoids are found in several dietary components like fruits, corns, vegetables, tea, cocoa and wine, possess health beneficiary effects with wide applications in medicine, nutraceutical and cosmetics field [24].

Cyanidin was found as an anti-aging component when used in WI-38 human diploid fibroblasts (derived from lung tissue) under stress-induced premature senescence (SIPS). Under stress condition, lipid peroxidation increment, reduced cell lifespan, increment of mRNA and protein expressions of nuclear factor-κB (NF-κB) occur in lung tissue derived diploid fibroblasts. In this condition, cyanidin facilitate in the increment of cell viability and inhibition of lipid peroxidation. Thus, cyanidin delayed the progression of aging by diminishing oxidative stress [25].

Malvidin also acts in anti-aging by regulating the expression of proteins associated with oxidative stress, including COX-2, NF-κB and inducible nitric oxide synthase [26]. In human, skin epidermis and dermis protects skin from harsh environmental condition. Ultraviolet rays (UV-A and UV-B) affect the skin leading to immune suppression, hyperpigmentation, photo-aging, sunburn etc. In this

scenario delphinidins inhibit NF-κB, activator protein-1 as well as COX-2 expression in UV exposed epidermis and counteract skin-aging [27].

Oxidative damage and redox metal homeostasis loss are the two main factors in case of brain aging. Oxidative species along with intracellular free iron results in the production of highly reactive hydroxyl radicals. The flavonoid, Baicalein can prohibit this detrimental effect by scavenging Reactive Oxygen Species (ROS) activity and iron chelation [28].

Mitochondrial respiration is associated with cellular energy production and support physical performance and physiological well-being. Malfunction of the mitochondria resulted in longevity reduction through SIRT1 deactivation. The flavonol, myricetin plays a crucial role in decrease of PGC-1α acetylation through SIRT1 activation in mitochondria which shows anti-aging efficacies [29]. Myricetin also facilitates in curing UV-induced photo aging of skin. Damage to collagen fibers, extreme deposition of abnormal elastic fibers and increment of glycosaminoglycans resulted in wrinkled, coarse, unevenly pigmented and brown spots on the skin. It reduced UVB-induced epidermal thickening of skin, supress metalloproteinase-9 (MMP-9) protein expression, reduce Raf kinase activity by binding with ATP in an noncompetitive manner [30].

Another flavonol, Rutin helps in increment of the mRNA expression of collagen, type I, alpha 1 (COL1A1) and in another way decreased the mRNA expression of matrix metallopeptidase 1 (MMP1) in human dermal fibroblasts (HDFs) and also proven as ROS scavenging activity. Moreover it increases the elasticity and decreases the length, sagging, area and number of wrinkles of the skin [31].

Reactive species (RS) triggered the formation of advanced glycation endproducts (AGE) through the reaction of carbohydrates and a free amino group of proteins. On the other side AGE increase the generation of RS and help in the binding of AGE to a specific AGE receptor (RAGE). RAGE induces the activation of redox-sensitive, pro-inflammatory transcription factor, nuclear NF-κB. AGE and RAGE are well known for aging and age-dependent disease. Kaempferol, a flavonol prohibits the increment of AGE and RAGE formation and help in delayed age by suppressing NF-κB expression, decreasing phosphorylation of the IκBα [32]. Kaempferol significantly acts on anti-wrinkles activity by reducing the expression of matrix metalloproteinase-1 (MMP-1) protein and promoting cell proliferation/pro-collagen production [33].

In human dermal fibroblasts the isoflavonoid, daidzein fights against solar UV induced matrix metalloproteinases (MMPs). Several signalling pathways like mitogen-activated protein/extracellular signal-regulated kinase (MEK)/extracellular signal-regulated kinase (ERK), mitogen-activated protein kinase (MKK)3/6/p38 and MKK4/c-Jun N-terminal kinases (JNK) modify the function of MMP-1. Daidzein inhibits the enzyme activity of protein kinase C (PKC)α which inhibits the degradation of collagen in skin thus helping in delayed aging [34].

For women, changes in estrogen levels are concomitant with epidermal thinning, fine wrinkling, diminishing dermal collagen content, skin dryness and reduced laxity. Through two estrogen receptors ERα and ERβ, estrogen acts on skin. The isoflavonoid, genistein acts as an estrogen receptor modulator (SERM) binding to ER β and prohibits the changes in skin aging [35].

Alkaloids

The following alkaloids and phenols possess properties which may be beneficial for treating problems of skin aging.

Capsaicin, a vanilloid from chilli pepper fruit (genus *Capsicum*), is absorbed from the stomach and whole intestine. Glutathione is present in the form of tripeptide in capsaicin and plays an important role in antiaging. [36].

In the presence of glutathione, GSH (γ-L-glutamylcysteinylglycine) plays a main role in defense mechanism against an imbalance amid the systemic expression of ROS and biological systems, reduction of lipid peroxides and hydrogen peroxides [37].

The herb, Nettle (*Urtica dioica* L., family *Urticaceae*), has anti oxidant and anti aging properties and can be used in cosmetic applications [38]. It possesses ROS scavengers which ultimately reduce free radicals and improvise the skin. It avoids wrinkles by reducing the loss of skin elasticity due to the inhibition of elastase and collagenase degrading enzymes. Ursolic acid, present in nettle roots are elastase inhibitors, while quercetin, accumulated in the leaves, are one of the most prominent antioxidants [39].

Guarana (*Paullinia cupana*, family *Sapindaceae*), contains phenolics, tannins (catechin, epicatechin and proanthocyanidins), caffeine and contributes as Central Nervous System (CNS) stimulant. The roasted seeds of guarana have enhanced resistance against oxidative stress and muscle function decline, which is an aging marker [40].

Sparteine is an alkaloid, extractable from scotch broom, which arouses the mechanism of cardiovascular system and stabilizes the cardiac irregularities. Some alkaloids in scotch broom extract are responsible for tightening the blood vessel and connective tissue with the appropriate combination of saponins and their aglycons. Compounds in scotch broom are effective for dark circle area in eye, skin tightening, and against oedema [36].

Resveratrol, a phytoalexin is a type of natural phenol and an antioxidant found in the skin of red grapes, peanuts, red wine, and raspberries [41]. Unique properties of resveratrol like signal transduction for modulation of genetic expression, phyto-hormonal effects and inhibitor of inflammatory mediators make it a potent anti aging agent. It also binds the receptor of estrogen, and estrogen having the capability to hold high dermal water, maintains elasticity of skin, increases the amount of glycosaminoglycan and reduces skin wrinkles [42,43].

Olive oil, a rich source of the monounsaturated fatty acid, oleic acid, also contains phenols, pigments and tocopherols in minor amounts. Few phenolics like, oleuropein, hydroxytyrosol, and oleocanthal are responsible for improving inflammation, reducing the risk of cardiovascular and improving age related problems [44,45].

Bioactive peptides

Peptides are chain of amino acids joined by peptide bond. Peptides are mostly involved in protein regulation, angiogenesis, cell proliferation, melanogenesis, cell migration and inflammation [46]. Since past few decades bioactive peptides from plants (soybean, rice), enzymes (elastrase), marine (carnosine, anserine) etc. are widely used in cosmetic industry [47]. Peptides need to have low molecular weight (<500 Da), high stability, solubility to ease peptide diffusibility across the epidermal layers [48]. Over the years, science has developed

small, stable, and synthetic peptide fragments which activate collagen production and reduces facial wrinkles and pigmentation. Peptides can be classified into four major groups viz. signal peptides, enzyme-inhibitor peptides, carrier peptides and neurotransmitter-inhibitor peptides.

Signaling peptides are released from the extracellular membrane and are also known as collagen stimulators [49]. These peptides help in increasing glycosaminoglycan, collagen proliferation, elastin, fibronectin and proteoglycan which ultimately reduce fine lines, wrinkles, pigmentation from UV-damaged skin and promote regeneration of the epidermal cells. Palmitoyl Tripeptide-1 is a messenger signal peptide which stimulates collagen renewal [50]. This peptide acts on transforming growth factor beta (TGFβ) to activate fibrillogenesis, which helps in reducing wrinkles. Trifluoroacetyl-tripeptide-2 has positive effects on reducing wrinkles and increasing firmness of the tissue [51]. Another plant based peptide derived from apple stem cell containing urea, creatine and palmitoyl tripeptide-38 showed significant increase in tissue elasticity, softness as well as anti-wrinkle effects. Tripeptide-10, Citrulline, Palmitoyl Tripeptide-1, Palmitoyl Pentapeptide-4 and Hexapeptide-14 are few more signalling peptides which help to remove signs of ageing [52].

Some of the peptides are enzyme inhibitors, like peptides derived from soybean, silk and rice bran act on skin cells inhibiting enzymes like proteinases. Soy peptides being potential source of antioxidant compounds are abundantly used as anti-ageing, skin moisturizer, anti-solar, cleansing detergent and hair-promoting agent. Topically applied soy peptides considerably increased Bcl-2 protein expression and decreased cyclobutane pyrimidine dimers-positive cells, apoptotic cells, p53 protein expression and Bax protein expressions in the epidermis of UVB-irradiated skin [53]. Silk fibronin peptides boost the anti-inflammatory activity of tTAT-superoxide dismutase, which exert anti-oxidative activity on cells and tissues [54]. Formulations with non-ionic surfactant like niosomes with rice peptide improve anti-aging properties. Keratin-based peptides are structural proteins helping in maintaining equilibrium condition within internal and external environmental changes. They provide protection from radioactive rays, promote cell repair and improves the texture, elasticity and water holding capacity of the skin [55].

Carrier peptides act as transporters which carry trace ions like calcium and manganese that are essential for anti-ageing and wound healing of dermal tissues. They are also known as penetrating peptides or membrane transduction peptides having basic transduction domains in their structures. GHK-Cu (Copper tripeptide) promotes collagen, proteoglycan and glycosaminoglycan synthesis which improves skin appearance, coarse wrinkles, fine lines and hyperpigmentation [56]. Tripeptides in combination with Gly-Gly-His (GGH) help in reducing tumor necrosis factor alpha (TNF-α) induced cytokines IL-6 [57] which promote skin renewal and removes wrinkles from the skin. Manganese Tripeptide-1 is another example of carrier peptide used in anti-ageing dermal creams. Several clinical trials have been carried out to test efficacy of GHK-Cu in combination with vitamin K cream, where fine lines and wrinkles have reduced visibly [58].

The most common visible sign of ageing is wrinkles which can be reduced by muscle contraction through release of neurotransmitter. Acetylcholine binds to its receptor located in muscle cells, and leads to muscle contraction. This peptide penetrates skin and relaxes muscles, causing the reduction of wrinkles. Acetylhexapeptide-3 improves elasticity of the skin by inhibiting neurotransmitter release and catecholamine secretion [59]. Tripeptide-3 acts at the postsynaptic membrane, and is a reversible antagonist of the acetylcholine receptor which also shows positive effect on anti-ageing symptoms.

Conclusion

From the above discussion, it can be concluded that with the increase in understanding of metabolic pathways and its related factors, it is possible to decipher the factors driving the phenomenon of aging in humans. On the other hand, the role of bioactive compounds derived from natural food source is guiding to understand the way to combat the inevitable but unwanted aging and its phenotypic expression. Though aging is a natural process, but aging due to internal and external factors can be prohibited. Consumption of foods with anti-aging property and application of antiaging natural bioactive compounds on skin can be a replacement of chemical cosmetics. As these natural anti-aging components directly act on the signalling/metabolic pathways involved in aging process, thus the process can be prevented, regenerated and delayed by implementing the concept of naturopathy.

References

1. López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. The hallmarks of aging. Cell. 2013; 153: 1194-1217.
2. Rattan SIS. Anti-ageing strategies: Prevention or therapy? EMBO reports. 2005; 6: S25-S29.
3. Kris-Etherton PM, Hecker KD, Bonanome A, Coval SM, Binkoski AE, Hilpert KF, et al. Bioactive compounds in foods: Their role in the prevention of cardiovascular disease and cancer. The American Journal of Medicine. 2002; 113: 71-88.
4. Lima CF, Pereira-Wilson C, Rattan SI. Curcumin induces heme oxygenase-1 in normal human skin fibroblasts through redox signaling: Relevance for anti-aging intervention. Molecular Nutrition & Food Research. 2011; 55: 430-442.
5. Paredes-López O, Cervantes-Ceja M L, Vigna-Pérez M, Hernández-Pérez T. Berries: Improving Human Health and Healthy Aging, and Promoting Quality Life-A Review. Plant Foods for Human Nutrition. 2010; 65: 299-308.
6. Dash A, Kundu D, Das M, Bose D, Adak S, Banerjee R. Food Biotechnology: A step towards inproving nutritional quality of food for Asian countries. Recent Patents on Biotechnology. 2016; 10: 43-57.
7. Das M, Kundu D, Singh J, Rastogi A, Banerjee R. Physiology and biochemistry of indigenous tribal liquor haria: A state of art. Advances in Biotechnology and Microbiology. 2017; 6: 1-5.
8. Mukherjee PK, Maity N, Nema NK, Sarkar BK. Bioactive compounds from natural resources against skin aging. 2011; 19: 64-73.
9. Lopez-Otin, L, Galluzzi L, Freije JMP, Madeo F, Kroemer G. Metabolic Control of Longevity. Cell. 2016; 166: 802- 821.
10. Shimizu I, Yoshida Y, Suda M, Minamino T. DNA damage response and metabolic disease. Cell Metabolism. 2014; 20:967–977.
11. Sahin E, Colla S, Liesa M, Moslehi J, Mu¨ ller FL, Guo M, et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature. 2011; 470: 359–365.
12. Vilchez D, Saez I, Dillin A. The role of protein clearance mechanisms in organismal ageing and age-related diseases. Nature Communication. 2014; 5: 56-59.
13. Denzel MS, Storm NJ, Gutschmidt A, Baddi R, Hinze Y, Jarosch E, et al. Hexosamine pathway metabolites enhance protein quality control and

prolong life. Cell. 2014; 156: 1167–1178.

14. Garinis GA, van der Horst GT, Vijg J, and Hoeijmakers JH. DNA damage and ageing: new-age ideas for an age-old problem. Nature Cell Biology. 2008; 10: 1241–1247.

15. Peters MJ, Joehanes R., Pilling LC, Schurmann C, Conneely KN, Powell, et al. The transcriptional landscape of age in human peripheral blood. Nature Communication. 2015; 6: 8570.

16. Goodell MA, Rando TA. Stem cells and healthy aging. Science. 2015; 350: 1199–1204.

17. Ito K Hirao A, Arai F, Takubo K, Matsuoka S, Miyamoto K, Ohmura M, et al. Reactive oxygen species act through p38 MAPK to limit the lifespan of hematopoietic stem cells. Nature Medicine. 2006; 12: 446–451.

18. Castilho RM, Squarize CH, Chodosh LA, Williams BO, Gutkind JS. mTOR mediates Wnt-induced epidermal stem cell exhaustion and aging. Cell Stem Cell. 2009; 5: 279-289.

19. Lapierre LR, Hansen M. Lessons from C. *elegans:* Signalling pathways for longevity. Trends in Endocrinology and Metabolism. 2012; 23: 637–644.

20. Gomes AP, Price NL, Ling AJ, Moslehi JJ, Montgomery MK, Rajman L, et al. Declining NAD(+) induces a pseudohypoxic state disrupting nuclear-mitochondrial communication during aging. Cell. 2013; 155: 1624–1638.

21. Claesson MJ, Jeffery IB, Conde S, Power SE, O'Connor EM, Cusack S, et al. Gut microbiota composition correlates with diet and health in the elderly. Nature. 2012; 488: 178–184.

22. Kumar S and Pandey AK. Chemistry and biological activities of flavonoids: An overview. The Scientific World Journal. 2013; 2013: 1-16.

23. Pérez-Cano FJ, Castell M. Flavonoids, inflammation and immune system. Nutrients. 2016; 8: 1-4.

24. Panche AN, Diwan AD and Chandra SR. Flavonoids: An overview. Journal of Nutritional Science. 2016; 5: 1-15.

25. Choi MJ, Kim BK, Park KY, Yokozawa T, Song YO, Cho EJ. Anti-aging effects of cyanidin under a stress-induced premature senescence cellular system. Biological and Pharmaceutical Bulletin. 2010; 33: 421-426.

26. Seo HR, Choi MJ, Choi JM, Ko JC, Ko JY, Cho EJ. Malvidin protects wi-38 human fibroblast cells against stress-induced premature senescence. Journal of Cancer Prevention. 2016; 21:1-40.

27. Watson RR, Schönlau F. Nutraceutical and antioxidant effects of a delphinidin-rich maqui berry extract Delphinol®: A review. Minerva Cardioangiol. 2015; 63: 1-12.

28. Moslehi M, Yazdanparast R. Protective Effects of Flavonoid Baicalein against Menadione-Induced Damage in SK-N-MC Cells. CellBio. 2013; 2: 35-44.

29. Jung HY, Lee D, Ryu HG, Choi BH, Go Y, Lee N, et al. Myricetin improves endurance capacity and mitochondrial density by activating SIRT1 and PGC-1α. Scientific Reports. 2017; 7: 1-10.

30. Jung SK, Lee KW, Kim HY, Oh MH, Byun S, Lim SH, et al. Myricetin suppresses UVB-induced wrinkle formation and MMP-9 expression by inhibiting Raf. Biochemical Pharmacology. 2010; 79: 1455-1461.

31. Choi S, Youn J, Kim K, Joo da H, Shin S, Lee J, et al. Apigenin inhibits UVA-induced cytotoxicity in vitro and prevents signs of skin aging in vivo. International Journal of Molecular Medicine. 2016; 38: 627-634.

32. Kim JM, Lee EK, Kim DH, Yu BP, Chung HY. Kaempferol modulates pro-inflammatory NF-κB activation by suppressing advanced glycationendproducts-induced NADPH oxidase. AGE. 2010; 32: 197-208.

33. Lee KH, Kong HJ, Cho YL, Joo CG, Kwon SS, Hwang JS, et al. Anti-microbial and anti-wrinkle effect of kaempferol and kaempferolrhamnosides isolated from Hibiscus cannabinus L. Korean Journal of Medicinal Crop Science. 2012; 20: 454-460.

34. Lim TG, Kim JE, Lee SY, Park JS, Yeom MH, Chen H, et al. The daidzein metabolite, 6,7,4'-Trihydroxyisoflavone, is a novel inhibitor of PKCα in suppressing solar UV-induced matrix metalloproteinase 1. International Journal of Molecular Sciences. 2014; 15: 21419-21432.

35. Irrera N, Pizzino G, D'Anna R, Vaccaro M, Arcoraci V, Squadrito F, et al. Dietary management of skin health: The role of genistein. Nutrients. 2017; 9: 1-10.

36. Lautenschläger H. Alkaloids in cosmetic applications. Kosmetik International. 2014; 12: 22-25.

37. Rebrin I, Sohal RS. Pro-oxidant shift in glutathione redox state during aging. Advanced drug delivery reviews. 2008; 60: 1545-1552.

38. Shailajan S, Hande H, Singh D, Tiwari B. Estimation of ursolic acid from Urticadioica L. using validated HPTLC method. Journal of Applied Pharmaceutical Science. 2014; 4: 92.

39. Bourgeois C, Leclerc ÉA, Corbin C, Doussot J, Serrano V, Vanier JR, et al. Nettle (Urticadioica L.) as a source of antioxidant and anti-aging phytochemicals for cosmetic applications. Comptes Rendus Chimie. 2016; 19: 1090-1100.

40. Peixoto H, Roxo M, Röhrig T, Richling E, Wang X, Wink M. Anti-Aging antioxidant potential of Paulliniacupana var. sorbilis: Finding in Caenorhabditis elegans indicate a new utilization for roasted seeds of Guarana. Medicines. 2017; 4: 61.

41. Roy H. Lundy S, Kalicki B. Resveratrol, Pennington Nutrition Series. 2005; 7: 1-4.

42. Gehm BD, McAndrews JM, Chien PY, Jameson JL. Resveratrol, a polyphenolic compound found in grapes and wine, is an agonist for the estrogen receptor. Proceedings of the National Academy of Sciences. 1997; 94: 14138-14143.

43. Verdier-Sévrain S. Effect of estrogens on skin aging and the potential role of selective estrogen receptor modulators. Climacteric. 2007; 10: 289-297.

44. Owen RW, Giacosa A, Hull WE, Haubner R, Spiegelhalder B, Bartsch H. The antioxidant/anticancer potential of phenolic compounds isolated from olive oil. European Journal of Cancer. 2000; 36: 1235-1247.

45. Dell'Agli M, Fagnani R, Galli GV, Maschi O, Gilardi F, Bellosta S, et al. Olive oil phenols modulate the expression of metalloproteinase 9 in THP-1 cells by acting on nuclear factor-κ B signaling. Journal of Agricultural and Food Chemistry. 2010; 58: 2246-2252.

46. Fields K, Falla TJ, Rodan K, Bush L. Bioactive peptides: Signaling the future. Journal of Cosmetic Dermatology. 2009; 8: 8-13.

47. Venkatesan J, Sukumaran A, Se-Kwon K, and Min Suk S. Marine fish proteins and peptides for cosmeceuticals: A review. Marine Drugs. 2017; 15: 143.

48. Mitragotri S. Modeling skin permeability to hydrophilic and hydrophobic solutes based on four permeation pathways. Journal of Control Release. 2003; 86: 69–92.

49. Gorouhi F and Maibach HI. Role of topical peptides in preventing or treating aged. International Journal of Cosmetic Science. 2009; 31: 327–345.

50. Lintner K and Peschard O. Biologically active peptides: From a laboratory bench curiosity to a functional skin care product. International Journal of Cosmetic Science. 2000; 22: 207–218.

51. Loing E, Suere T and Lamarque E. Trifluoroacetyl-tripeptide-2 to target senescence for anti-aging benefits. Cosmetics & Toiletries. 2012. 127: 274-280.

52. Sanz MT, Campos C, Milani M, Foyaca M, Lamy A, Kurdian K, et al. Biorevitalizing effect of a novel facial serum containing apple stem cell extract, pro-collagen lipopeptide, creatine, and urea on skin aging signs. Journal of Cosmetics and Dermatology. 2016; 15: 24–30.

53. Zhou BR, Ma LW, Liu J, Zhang JA, Xu Y, Wu D, et al. Protective effects of soy oligopeptides in ultraviolet B-induced acute photo damage of human skin. Oxidative Medicine and Cellular Longevity. 2016; 2016: 5846865.

54. Kim DW, Hwang HS, Kim DS, Sheen SH, Heo DH, Hwang G, et al. Effect of silk fibroin peptide derived from silkworm Bombyxmori on the anti-inflammatory effect of Tat-SOD in a mice edema model. BMB Reports. 2011; 44: 787–792.

55. Barba C, Méndez S, Roddick-Lanzilotta A, Kelly R, Parra JL, Coderch L. Wool peptide derivatives for hand care. Journal of Cosmetic Sciences. 2007; 58: 99–107.

56. Pickart L, Schagen S. New data of the Cosmeceutical and tripeptide GHK. SOFW Journal. 2015; 9: 141.

57. Campbell JD, McDonough JE, Zeskind JE, Hackett TL, Pechkovsky DV, Brandsma CA, et al. A gene expression signature of emphysema-related lung destruction and its reversal by the tripeptide GHK. Genome Medicine. 2012; 4: 67.

58. Hussain M, Goldberg DJ. Topical manganese peptide in the treatment of photodamaged skin. Journal of Cosmeticsand Laser Theraphy. 2007; 9: 232–236.

59. Krishnan G, Roberts MS, Grice J, Anissimov YG, Moghimi HR, Benson HA. Iontophoretic skin permeation of peptides: An investigation into the influence of molecular properties, iontophoretic conditions and formulation parameters. Drug Delivery and Transcriptional Research. 2014; 4: 222–232.