Polyphenols & OPCs

An Overview of their sources and bioactive properties

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1. WHAT ARE POLYPHENOLS ?

An inherent feature of plants, alongside photosynthesis, lies in their capacity to synthesize secondary metabolites, which, unlike primary metabolites, are not indispensable for plant growth and development but serve pivotal roles in their interactions with the environment. The array of secondary metabolites synthesized in plants is vast, with polyphenols emerging as one of the most prevalent categories. Polyphenols, also referred to as phenolic compounds (PCs), play a crucial role in safeguarding plants against various biotic and abiotic stressors such as light, UV radiation, temperature fluctuations, and heavy metal exposure [1, 2], thereby bolstering the organism's survival within its ecosystem. The qualitative and quantitative distribution of PCs within plants varies depending on factors such as species, organs, tissues, and developmental stages. They also contribute significantly to the organoleptic attributes of plant-derived foods, including color, flavor, astringency, and bitterness[1, 2].
Polyphenols (PCs) are characterized by the presence of one or more phenolic rings (refer to Figure 1) and are classified based on their chemical structure into distinct subclasses, including flavonoids (e.g., flavonols, flavones, flavanones, flavan-3-ols, and anthocyanins), phenolic acids (e.g., hydroxybenzoic acids, hydroxycinnamic acids), lignans and stilbenes (refer to Figure 2) [2, 3].

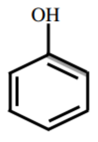


Figure 1 : Structure of the phenol ring

Amongst all the flavonoids, the subclass of flavanol also called flavan-3-ol give rise to proanthocyanidins whose structure can vary depending on the degree of polymerization, stereochemistry, and substitution patterns of the flavanols units [3].

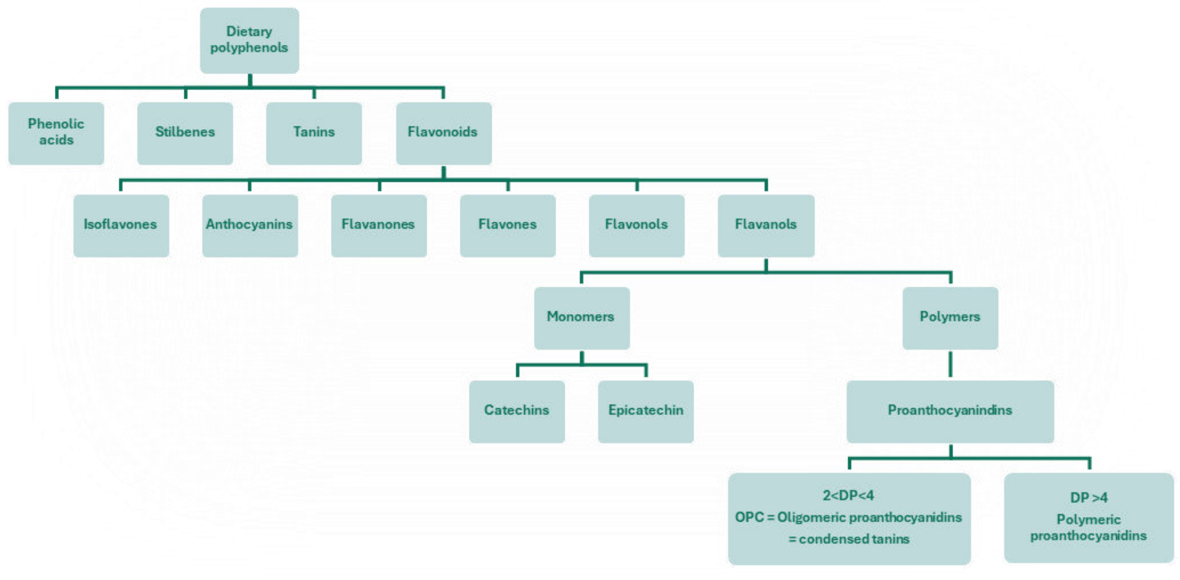


Figure 2 : Classification and representative compounds of dietary polyphenols (Li et al., 2023)

1. FROM FLAVANOLS TO OLIGOMERIC PROANTHOCYANIDINS (OPCS)?

Oligomeric proanthocyanidins (OPCs) represent polymers characterized by a conventional flavonoid scaffold, wherein the monomeric unit consists of a flavan-3-ol structure. This flavan-3-ol configuration comprises two aromatic rings denoted as rings A and B, alongside an oxygenated heterocycle designated as ring C (refer to Figure 3a).

Within the realm of botanical sources, two primary categories of oligomeric proanthocyanidins exist: A-type oligomeric proanthocyanidins and B-type oligomeric proanthocyanidins, with the distinction contingent upon their linking pattern. Furthermore, proanthocyanidins are stratified based on their degree of polymerization (DP), resulting in their classification into either oligomeric proanthocyanidins or condensed tannins (DP = 2–4), and highly polymeric proanthocyanidins (DP > 4) [4].

Proanthocyanidins are a very diverse family of polyphenols based on the number and position of hydroxyl groups on the A and B rings, their degree of polymerization and the number and position of bonds linking the flavanol units together. This complexity makes them some of the most abundant polyphenolic substances in the plant kingdom. Another particularity of these molecules is their high affinity for proteins. The formation of complexes with salivary proteins are responsible for the astringent character of grapes, wine, and cider [5].

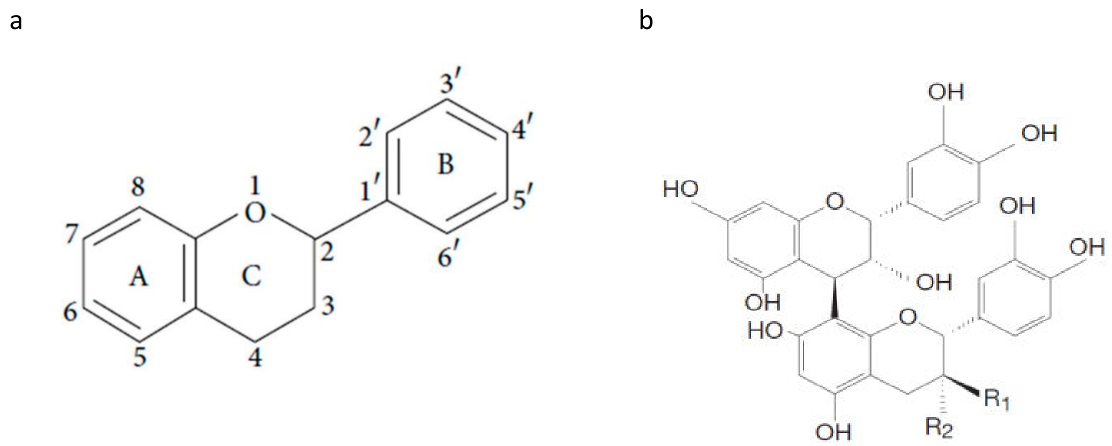


Figure 3 : The structural formula of flavonoids (a) and proanthocyanidins (b).

2. WHERE CAN WE FOUND POLYPHENOLS AND OPC ?

Polyphenols, encompassing OPCs, are ubiquitous constituents within a diverse array of plant-derived foods and beverages, spanning from seeds to the aerial part of plants. In Western dietary practices, prominent sources of flavonoids include tea, red wine, fruits, vegetables, cocoa, chocolate, and legumes.

Proanthocyanidins predominantly populate berries and fruits, with notable concentrations found in cranberries, black elderberries, black chokeberries, black currants, and blueberries. Additionally, proanthocyanidins are widespread among various fruits such as apricots, walnuts, silverberries, and pomegranates.

Grapes and grape-derived products represent particularly rich reservoirs of OPCs, with grape seeds exhibiting notably elevated concentrations compared to grape skin and pulp. Extracts derived from the bark of trees such as pine and oak serve as additional sources of OPCs, commonly integrated into dietary supplements and herbal remedies [6].

The levels of polyphenols and OPCs are subject to variation influenced by diverse factors including biotic and abiotic stressors, stage of ripeness, varietal differences, and processing methodologies.

3. OVER THE RAINBOW: THE POT OF GOLD IS IN YOUR PLATE!

Hunter-gatherers are described as heavy animal protein consumers. But recently, a study identified that dating back at least 15 000 years in Italy, and around 11 500 years in the central Balkans their diet was rich in plant-based food [7]. Wild cereals, seeds and forest fruits were also part of human evolution, emphasizing the point that the sugars and phytonutrients-content of those food might be important for us.

Unfortunately, the consumption of a diet plenty of plant-based food decreased drastically all over the world in the last decades. This phenomenon leads Governments to develop health recommendation for the population. Several action plans are proposed, notably in the United States with The Dietary Guidelines for Americans 2015-2020 Eighth Edition [8] and the National Health and Nutrition Program 2019-2023 – fourth [9] edition in France. Those guidelines encourage people to have a more colorful and diverse nutrient-dense food-plate by consuming more fruits and vegetables but less added sugars, saturated fats, and sodium. These recommendations are based on several epidemiological studies having demonstrated the beneficial effect of consuming a certain amount of plant-based food daily to decrease the risk of developing chronic diseases. One of these studies investigated the impact of fruit and vegetable color on health outcomes. A daily increase of 25 grams in consumption of orange fruits and vegetables was associated with a notable 26% reduction in the risk of coronary disease (CD). Similarly, each additional 25 grams per day of white fruits and vegetables correlated with a 9% decrease in stroke risk. Notably, apples and pears constituted the majority (55%) of the white fruit and vegetable intake among participants.

Additionally, a comprehensive meta-analysis conducted by Aune et al. revealed a range of associations between various types of fruits and vegetables and different health outcomes. For instance, apples, pears, citrus fruits, cruciferous vegetables, green leafy vegetables, tomatoes, and fruits rich in beta-carotene (such as carrots), as well as vitamin C-rich citrus fruits, showed inverse associations with coronary heart disease (CHD), stroke, or cardiovascular disease (CVD) [10]. Conversely, cruciferous and yellow-green vegetables were linked to a reduced risk of cancer, while apples, pears, berries, citrus fruits, cruciferous vegetables, potatoes, and leafy greens or salads were associated with lower all-cause mortality [10].

Unfortunately, a study ran in 2016 demonstrated that only 25% of the French population follow the PNNS recommendations – 5 fruits and vegetable per day – and 54% eat less than 3,5 serving per day [11]. Outside Europe, it is the same observation. Only 12% of Americans meet the target for combined fruit and vegetable intake recommendations (Figure 4). This implies that the quantity of polyphenols such as flavonoids and anthocyanins daily consumed (9 mg/d in the US vs 19 mg/d in France) are below the amount necessary to have a positive impact on health. A recent review of dietary intervention studies with berry polyphenols found that most intervention studies were conducted with anthocyanidin intakes in excess of 200 mg/d, which is much higher than the usual intake in Europe and in the US.

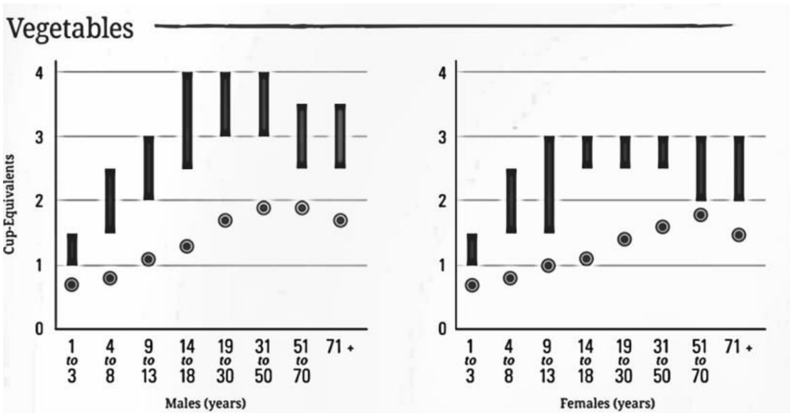


Figure 4: Average Daily Food Group Intakes by Age-Sex Groups, Compared to Ranges of Recommended Intake (Dietary guidelines for Americans 2015-2020, Eighth edition).

The modern human being is not ready to put a rainbow in its plate. Adding some functional foods, beverages of dietary supplements rich in polyphenols or OPCs could be helpful to improve the daily consumption of phytonutrients to improve the wellbeing of a population.

4. OPCs IN HEALTH

Grape seed and pine bark extract containing OPCs are known for their potent antioxidant activities, attributed to their ability to scavenge free radicals and protect against oxidative stress-induced damage. Grape seed and pine bark OPCs are well described in the scientific literature for their protective roles against inflammation. Both mechanisms - oxidative stress and inflammation - are possible processes associated with the alteration of several health disorders such as cardiometabolic, cardiovascular, digestive, skin and neuroprotective effects. The ability of OPCs to act at the root cause of the development of all those disorders make them attractive for nutraceutical and cosmeceutical applications.

6. OPCs FROM GRAPE SEED EXTRACT

6.1 Characteristics of the OPC from Grape seed extract (GSE)

One of the most important features of grape seeds is that they contain the highest concentration of bioactive molecules compared to the other parts of the grape, with approximately 30% of total proanthocyanidins stored therein, compared to 15% in the skin [5, 12].

The primary phenolic compounds found in grape seeds comprise anthocyanins, flavan-3-ols, flavonols, stilbenes, and phenolic acids, with flavan-3-ol units as the predominant constituents of grape seed OPCs, particularly catechin and epicatechin, interconnected via C4-C8 or C4-C6 bonds [4, 12]. In grape seed, OPCs frequently exist as dimeric, trimeric, and tetrameric proanthocyanidins [4, 12].

These active oligomeric proanthocyanidins (OPCs) are a special class of polyphenols scientifically shown to be highly bio-available and extremely biologically active with a substantial list of significant physiological health benefits.

6.2 OPCs in cardiometabolic disorders

Cardiometabolic diseases encompass a cluster of interrelated health conditions characterized by abnormalities in metabolic processes and cardiovascular function. These diseases primarily involve disorders such as obesity, insulin resistance, hypertension, dyslipidemia, and glucose intolerance, among others. These conditions substantially increase the risk of developing cardiovascular diseases, as well as metabolic disorders such as type 2 diabetes mellitus. Effective management and prevention strategies targeting cardiometabolic diseases typically involve comprehensive lifestyle modifications, pharmacotherapy, and interventions aimed at addressing underlying risk factors and promoting cardiovascular health and metabolic balance. Recent clinical studies pointed out the positive roles of OPC's from grape seed extract in order to help people suffering from cardiometabolic disease to help them in their journey to a healthier life.

Recently a double-blind randomized controlled trial vs. placebo evaluated the effect of 300 mg/day of grape seed extract during 12 weeks in overweight or obese people along with a restricted-calorie diet. At the end of the study the participants, exhibited a significant improvement of inflammation (decreased of tumor necrosis factor alpha, and high sensitivity C-reactive protein), lipid profile (increased of high-density lipoprotein cholesterol (HDL-C) and HDL-C/low-density lipoprotein cholesterol (LDL-C) and anthropometric parameters (reductions of body weight, body mass index, waist circumference, and waist to hip ratio), compared to the placebo group [13, 14].

In order to investigate the mechanism of action of GSE explaining these encouraging results on cardiometabolic improvement, the authors measured also neuropeptide Y that is an orexigenic peptide. The lowering effect of GSE on neuropeptide Y in this human study confirm what was previously shown in preclinical studies, i. e. GSE could modulate food intake by decreasing the level of neuropeptide Y [13].
In preclinical studies several mechanisms were described to explain the improvement of cardiometabolic disorders. Amongst them, anti-oxidative and anti-inflammatory effects were demonstrated as well as effects on glucose level and insulin-resistance, adipose tissue, and GLP-1 for example [15].

6.3 OPCs in cardiovascular disorders

Cardiovascular disease (CVD) refers to a group of disorders affecting the heart and blood vessels, including the arteries, veins, and capillaries. These conditions encompass a wide spectrum of pathologies, including coronary artery disease, myocardial infarction (heart attack), stroke, peripheral artery disease, heart failure, and arrhythmias. CVD arises from various factors, including but not limited to, atherosclerosis (accumulation of plaque in arterial walls), hypertension, dyslipidemia, diabetes mellitus, obesity, smoking, sedentary lifestyle, genetic predisposition, and environmental influences. The clinical manifestations of cardiovascular disease can range from asymptomatic to life-threatening events and may lead to significant morbidity, mortality, and impaired quality of life. Effective prevention and management strategies for cardiovascular disease involve lifestyle modifications, pharmacotherapy, interventions targeting risk factors, and timely medical interventions such as revascularization procedures and cardiac rehabilitation programs.

As for cardiometabolic disorders, GSE demonstrated positive results in the improvement cardiovascular health, two conditions that are closely related. In a recent double-blind randomized controlled trial vs. placebo, the effect of 300 mg/day of GSE on systolic blood pressure in mild hypertensive people were analyzed. After 16 weeks without any other medication, a reduction of systolic blood pressure of −4.6 mmHg (95% C.I.: −6.9 to −2.3) and diastolic blood pressure of −3.2 mmHg (95% C.I.: −5.1 to −1.4) was observed in men. The results for women were not significantly different vs. Placebo due to a very strong placebo effect in that sub-group [16]. Another important parameter for blood pressure was evaluated during all the time-course of the study: perceived stress. At the end of the study mood related to stress perception slightly decreased. These results need to be confirmed in further clinical trials as mental components can especially impact blood pressure and finally the health of the blood vessels [16].

6.4 OPCs in vascular health

Several other mechanisms of OPCs are also well documented for their veino-lymphatic and vasculo-protective effects. In clinical studies, grape seed extract has demonstrated positive effect on capillary or vascular fragility associated with different conditions: ageing, subjects presenting diabetic nephropathy, hypertension or ocular microangiopathies. The daily dose consumed for all the population studied and demonstrating a positive impact on capillary or vascular resistance was 150 mg/day.

In the case of legs functional problems like chronic venous insufficiency or venous tone, GSE OPCs demonstrated beneficial effects by improving notably heaviness, pain, nocturnal cramps, pruritus, and paresthesia. In a double-blind, placebo-controlled study, the effect of 150 mg/day of OPCs from grape seed extract was evaluated in a population of 50 subjects suffering from abnormal venous tone. In the group receiving the OPCS, a significant improvement in venous tone determined by the results from vascular rheography and vascular thermography was observed after a month of supplementation. Moreover, the improvement in biological indicators (degree of improvement between start and end of study) was Excellent or Good in 16 out of 25 subjects on GSE (64% of the cases) compared to 2 out of 25 subjects on placebo (8% of the cases) [17].

The physiology of women is particularly dependent of hormone fluctuations during life but also during a month. This implies that around menstrual period or by taking oral estroprogestative or progestative oral contraceptives, hormonal balance can be altered, with potential implication on the vascular tone. Studies with OPCs extract from grape seed aimed to explore if they can have beneficial effect on those women manifesting functional signs of veno-lymphatic dysfunction. During three months, 4729 women with venous insufficiency and under hormonal treatment took 300mg/day of OPCs from a GSE. Five biological indicators (nocturnal cramps, restlessness, tingling sensation, burning sensation and cyanosis) were assessed at day 0, 45 and 90 in both legs. The Global Score evaluating the biological indicators dropped from an average of 7.2 on day 0 to 3.5 on day 45 ($p<0.0001$), and to 1.7 on day 90 ($p<0.0001$) in the woman taking the OPCs. The author concluded that the beneficial effects of GSE in women manifesting venous abnormalities (venous insufficiency) were highly satisfactory [18].

The mechanisms of action behind the positive's actions of OPCs from GSE were largely studied in preclinical models. It includes a protection of the vascular wall from degradation by hydrolytic enzymes, scavenging of free radicals, improvement of collagen synthesis and strengthens of the vascular wall by increasing endothelial cell-basal membranes interaction. All of which greatly reinforce the vascular wall and support vascular- and lymphatic function. This could be linked to the fact that the OPCs were found in the wall of mainy arterial trunks, rich in glycosaminoglycans and collagen structures.

The overall results discussed here demonstrated that OPCs from GSE improve vascular tone and capillary fragility, promote capillary strength and healthy microvascular circulation provide robust evidence of the beneficial relationship between the OPCs and veino-lymphatic function.

6.5 OPCs in neuroprotection

A neurodegenerative disease is a class of disorders characterized by progressive dysfunction and degeneration of neurons in the central nervous system (CNS) or peripheral nervous system (PNS). These diseases typically involve the gradual loss of neuronal structure and function, leading to impairments in motor control, cognition, behavior, and/or sensory processing. Neurodegenerative diseases are often associated with the accumulation of abnormal protein aggregates, oxidative stress, (neuro)inflammation, and synaptic dysfunction. Neurodegenerative diseases include Alzheimer's disease and Parkinson's disease for example.

Preclinical studies identified grape seed extract as a candidate to improve disorders associated with neurodegenerative disorders, notably thanks to its anti-oxidative and anti-inflammatory effects on specific pathways involved in neurodegenerative disorders such as Alzheimer disease. Some of these pathways involved increase of anti-oxidative enzymes (glutathione and superoxide dismutase), suppress mitochondria-associated oxidative stress, prevent the release of proinflammatory mediators, including 5-lipoxygenase (5-LOX) and the induction of neuroinflammation by preventing a decrease in acetylcholine levels in the Alzheimer's brain. Moreover, gallic acid derived from grape seed extract (GSE) has demonstrated a reduction in amyloid fibril formation by 49% and a concomitant decrease in brain amyloid-beta (Aβ) levels [19], two hallmark neuropathology's of the disease.

In a nutshell, GSE components mitigate inflammation, oxidative stress, and mitochondrial dysfunction, thereby influencing the pathophysiological processes associated ischemic injury, and aging-related cognitive decline [19]. For the moment, the results of clinical data remain controversial.

6.6 OPCs in skin

Skincare from Mother Nature is one of the major trends in the last few years. The use of plant extracts as a source of active ingredients in cosmetics as gain more and more value recently. This modern trend of phytocosmetology, has meant that researchers became increasingly interested in the cosmetics and skin properties of grape OPCs.

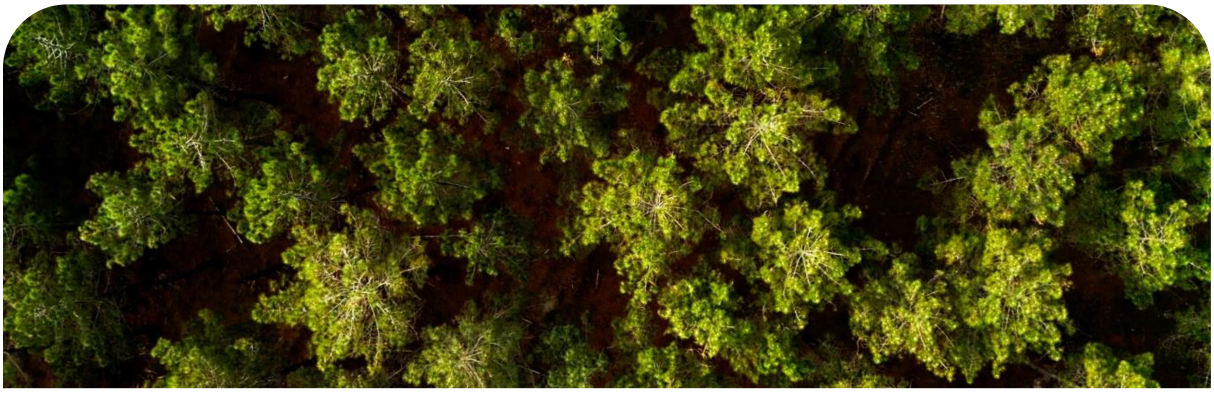
Different grape extracts can be used in cosmetics products as per the CosIng database, V. vinifera fruit (*Vitis viniferae* fructus) is listed as a viable skin-conditioning agent, while the seeds of *V. vinifera* (*Vitis viniferae* semen) are recognized for their utility as skin-protective and conditioning components. Additionally, grape seeds have exhibited many skin potential including anti-seborrheic, antimicrobial, mainly linked to its global anti-inflammatory and anti-oxydant activities [20].

Clinical studies evaluated the effects of grape seed extract on the skin, notably on photoaging. Photoaging refers to the premature aging of the skin caused by prolonged exposure to ultraviolet (UV) radiation from the sun. It is characterized by a range of visible and histological changes in the skin, including wrinkles, fine lines, uneven pigmentation (such as sunspots or age spots), loss of elasticity, and rough texture. Photoaging is distinct from chronological aging, as it is primarily driven by external factors rather than intrinsic aging processes. UV radiation penetrates the skin and induces various molecular and cellular alterations, including the breakdown of collagen and elastin fibers, DNA damage, increased production of reactive oxygen species (ROS), and activation of inflammatory pathways. These cumulative effects contribute to the accelerated aging of the skin, leading to a prematurely aged appearance. Effective prevention and management strategies for photoaging typically involve sun protection measures, such as the use of broad-spectrum sunscreen, protective clothing, and seeking shade, along with skincare interventions aimed at promoting skin repair and regeneration.

The effectiveness of a sunscreen and GSE formulation on improvement of age-related changes was conducted in Asia. The application of sunscreen containing 3% GSE twice daily yielded significant reductions in melanin and erythema levels, accompanied by improvements in overall skin tone. Furthermore, hydration levels notably increased within 3 hours post-application and remained elevated for up to 5 hours. Participants across all age categories (35-59 years) demonstrated enhancements in skin elasticity parameters, including Young's modulus, retraction time, and viscoelasticity. Additionally, participants perceived an improvement in overall skin appearance with the use of sunscreen formulated with GSE [21].

6.7 Others positives activities of OPCs

In the last decades, a new way to trigger different health disorders excluding the anti-oxidative and anti-inflammatory effects of OPCs was prebiotic effect. In 2016 a new current consensus definition was proposed by ISAPP (International Scientific Association for Probiotics and Prebiotics) to define a prebiotic: as « a substrate that is selectively utilized by host microorganisms conferring a health benefit". Before, a prebiotic referred to substrates that target health-promoting groups of bacteria in the gut: usually, bifidobacteria and lactobacilli. Based on the new definition of a prebiotic, polyphenols can have a prebiotic effect with beneficial effects on the composition of the gut microbiota associated with improvement of the host at the digestive but also at the extra-digestive level. This has been demonstrated mainly in gut barrier function, cardiometabolic disorders and preclinical models of ulcerative colitis. Those effects were linked both to the modulation of the microbiota and production of specific molecules such as short chain fatty acids but also thanks to the bioactive polyphenolic metabolites produced via the metabolization of the polyphenols by the microbiota.



7. OPCS FROM PINE BARK EXTRACT

7.1 Characteristics of the OPC from pine bark extract (PBE)

OPCs derived pine bark extract exhibits distinctive characteristics compared to OPCs from grape seed extract, owing to their unique compositions and sources.

The primary constituents of pine bark are recognized to be phenolic compounds, which can be broadly categorized into monomers (such as catechin and epicatechin) and condensed tanins (known as procyanidins). Procyanidins are primarily composed of flavan-3-ol units of (+)-catechin and are identified as the predominant phenolic components in pine bark. B-type procyanidins constitute the majority of procyanidins found in pine bark extracts, typically containing little to no prodelphinidins (less than 10%). The chemical structure of B-type oligomers is defined by the presence of (epi)catechin units. The presence of A-type procyanidins is subject to debate, as not all studies consistently identify them in analyses. Others minor molecules can identified as gambiriins A, and flavonols and their derivatives [22].

7.2 OPCs in cardiometabolic disorders

Several clinical studies and reviews have evaluated the beneficial effect of OPC from PBE on metabolic syndrome which is a part of cardiometabolic risks. Metabolic syndrome refers to the presence of a cluster of risk factors specific for cardiovascular disease. Metabolic syndrome greatly raises the risk of developing diabetes, heart disease, stroke, or all three. Metabolic factors include abdominal obesity, high blood pressure, impaired fasting blood glucose, high triglyceride levels, and low HDL cholesterol. Metabolic syndrome is diagnosed when a person has 3 or more of these factors.
For example, an open controlled study evaluated the effects of 6 months supplementation with pine bark extract on health risk factors in subjects with metabolic syndrome. PBE supplementation (150mg/day) decreased waist circumference, triglycerides levels, blood pressure and increased HDL cholesterol level at the end of the study. Other clinical studies confirmed the positives effects of PBE, notably in lowering plasma glucose [23].

Several mechanisms were identified in preclinical models to explain these beneficial effects. Inhibition of α-glucosidase [24], increased glucose uptake in adipocytes [25], potentiation the antioxidant defense system [26]. decreasing inflammatory markers [27] and the levels of glycosylated hemoglobin (HbA1c) [26].

These positives effects and mechanisms of actions are important in order to decrease the prevalence of cardiometabolic syndrome but also the rick associated with cardiovascular diseases.

7.3 OPCs in the cardiovascular disorders

High blood pressure has a strong negative impact on vascular health. Several clinical studies and meta-analysis demonstrated the beneficial effect of OPCs from PBE on high blood pressure (BP). A systematic meta-analysis identified nine trials involving 549 patients who received PBE (ranging from 150 mg to 200 mg per day). Compared to the control, the pooled estimated change in systolic and diastolic BP were −3.22 mmHg (95% CI: −6.20, −0.24) and −3.11 mmHg (95% CI: −4.60, −1.62), respectively. Subgroup analyses showed higher BP reduction among hypertensive participants or those who received intervention for more than 12 weeks [28].

The improvement of the health of the vascular tone was also demonstrated in people suffering from type 2 diabetes associated with microangiopathy. Patients without a history of diabetic ulcerations were treated with 50 mg of PBE times a day. After 4 weeks, microcirculatory and clinical evaluations showed a progressive decrease in skin flux at rest in the foot, a significant decrease in capillary filtration, and a significant improvement in the veno-arteriolar response in all treated subjects. This study confirms the clinical efficacy of PBE in patients with diabetic microangiopathy [29].

Further preclinical studies evaluated the beneficial effects of PBE in high glucose-treated renal tubular cells. PBE demonstrated an anti-apoptotic effect and an improvement of several key markers of oxidative stress and inflammation. PBE's demonstrated an anti-oxidative and anti-inflammatory efficacy in suppressing lipid peroxidation, total reactive species (RS), superoxide (*O2), nitric oxide (NO*), peroxynitrite (ONOO−), pro-inflammatory inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2) and nuclear factor-kappa B (NF-κB) nuclear translocation [30].

These investigations demonstrated the positive effects of PBE by improving hyperglycemia but also in acting on its consequences i.e glycation, nephropathy and microangiopathy.

7.4 OPCs in neuroprotection

Brain aging is a complex and multifactorial process broadly involving changes in the brain's structure, neuronal activity, and biochemical profile. These changes in brain function have also been linked to age-associated variations in cognitive function. Recent research has suggested a role of increased oxidative stress and reduced cognition in older people. Therefore, studies that examine the effects of antioxidants on cognitive performance are important, particularly in the context of an increase in elderly populations in most Western countries.

PBE was tested from health young subjects to elderly people with cognitive functions. In a clinical study with young adults receiving PBE at a dosage of 50mg twice daily over an eight-week period, improvements in attention, memory, executive functions, and mood ratings were observed compared to the control group. The beneficial effects of PBE in healthy adults were confirmed in a second clinical study. Sixty subjects experiencing elevated oxidative stress levels, received 150mg/day of PBE over a 12-week. At the end of the study, daily functional capabilities, mental acuity, alertness and a enhancement in memory performance were improved [31].

The beneficial effects of PBE were also confirmed in older subjects. Two groups of individuals, of 65 years of age, were assessed twelve months post-enrollment to examine potential alterations in cognitive function and oxidative stress levels. Forty-five participants were administered a daily dose of 150mg PBE, while 44 individuals served as a control group without supplementation. The control group exhibited a modest decline in memory, executive functions, and activities of daily living. Cognitive impairment, as assessed by the Short Blessed Test, was mitigated. Conversely, those receiving PBE demonstrated significant enhancements across all evaluated parameters, encompassing attention, cognitive performance, memory, and daily functional tasks such as interpersonal interactions, financial management, and decision-making. These findings underscore that PBE supplementation could be an efficient approach to improve cognitive function in young but also in older people.

Furthermore, preclinical data gave encouraging results on the effects of PBE on Alzheimer disease. Indeed, several studies identified mechanisms of action by which PBE could prevent the progress of the disease. One major effect is through anti-oxidative effects, but also protection of vascular endothelial cells from Beta-amyloid -induced injury [32] .

7.5 OPCs in woman health

PBE is also documents in several conditions associated with woman health such as: dysmenorrhea, endometriosis, climacteric syndrome and menopausal transition.
Perimenopause and menopause are two phases impacting women health in its fifties. While both share some symptoms, the intensity and duration of these symptoms may vary for everyone. Additionally, symptoms experienced during perimenopause may continue into menopause, albeit with potential modifications in severity and harbor different features, even if some are shares.

Some characteristics of perimenopause are:

- Irregular periods: Women may experience changes in menstrual cycle length, frequency, and flow.
- Hot flashes: Sudden feelings of warmth, flushing, and sweating, often accompanied by rapid heartbeat and chills.
- Mood swings: Fluctuations in mood, including irritability, anxiety, and depression.
- Sleep disturbances: Difficulty falling asleep, staying asleep, or experiencing poor-quality sleep.

- Vaginal dryness: Reduced lubrication in the vaginal area, leading to discomfort during intercourse.
- Changes in libido: Decreased interest in sex or changes in sexual desire.

While menopause can be depicted with:

- Cessation of periods: Menopause is defined as the permanent cessation of menstrual periods for at least 12 consecutive months.
- Hot flashes and night sweats: Although hot flashes may diminish over time, they can persist during menopause and are often accompanied by night sweats.
- Mood changes: Women may continue to experience mood swings, anxiety, or depression during menopause.
- Vaginal and urinary changes: Increased vaginal dryness, urinary frequency, and urinary incontinence may occur due to hormonal changes.
- Bone loss: Estrogen decline increases the risk of osteoporosis and bone fractures.
- Skin and hair changes: Thinning hair, dry skin, and changes in skin texture may occur due to hormonal changes.

In order to cope with modifications, several treatments are possible and also complementary remedies. One of them is PBE. A randomized, double-blind, placebo-controlled trial was conducted to investigate the effects of PBE on climacteric syndrome. On the 200 peri-menopausal women enrolled, and treated with 200mg of PBE daily, 155 women completed the study. Result indicates that all climacteric symptoms improved, antioxidative status increased and LDL/HDL ratio was positively altered. No side effects were reported. This study suggests that PBE may offer an alternative method to reducing climacteric symptoms [33].

In another double blind, placebo-controlled study on perimenopausal women, 30 mg of PBE significantly decreased total Kupperman's index for perimenopausal symptoms severity score by 56% as compared with placebo (-39%) after 12 weeks of treatment. It was found especially effective for improving vasomotor and insomnia/sleep problem symptoms, which were significantly better after 4 and 12 weeks, than the placebo [34].

Transition symptoms were also evaluated in a clinical study. Women supplementation with 100 mg of PBE for 8 weeks contributes to reduce signs and symptoms associated with menopausal transition. A subset of six most common symptoms comprising hot flushes, night sweats, mood swings, irregular periods, loss of libido and vaginal dryness showed a decrease from average 2.67/4 to 1.45/4 after 8 weeks supplementation with PBE, while the control group of women showed no change from initial average 2.72/4 to 2.73/4 after eight weeks. Also, the sensation of "electric shocks" and digestive problems improved significantly with PBE as compared to women in the control group. The presence of elevated oxidative stress in women was investigated measuring capillary blood plasma free radicals. Oxidative stress was significantly lowered after four weeks ($P<0.05$) and eight weeks ($P<0.022$) in the PBE group while no significant changes were observed in the control group at any time [35].

Finally, the results on the beneficial effects on perimenopause and menopause symptoms are encouraging and seems to tackle most of the health modifications that can occurred during this period of woman life.

7.6 OPCs in men health

OPCs from pine bark extract were tested in several clinical studies to evaluate its effect on erectile dysfunction. A double-blind study aims to evaluate the effect of 120 mg per day of PBE or placebo on erectile function in 21 patients suffering from erectile dysfunction. After three months of administration, PBE significantly improved erectile dysfunction ($p < 0.05$) from moderate to mild stage determined with International Index of Erectile Function (IIEF-5). Placebo had no effect [36]. Another study shows that PBE leads in improvement of erectile function in patients with erectile dysfunction by 45% even if they presented diabetes mellitus [37], as hyperglycemia can be associated with erectile dysfunction.

Other clinical studies have tested the co-administration of PBE and L-arginine. Three clinical studies were carried out with a blend of PBE and L-arginine aspartate) for men with mild form of erectile dysfunction. All the three clinical studies uniformly showed that male sexual function was permanently restored during supplementation with a combination of L-arginine and PBE. Moreover, in none of the studies side effects were reported, nor cases of hyper-stimulation, nor priapism [38]. The combination has also demonstrated positives results on oligoasthenozoospermia in mean suffering from erectile dysfunction. The mechanism of action behind the effect of both PBE And L-arginine was investigated in that study. It seemed that L-arginine acts to increase the production of nitric oxide and PBE activates the endothelial nitric oxide synthase, and it is a potent antioxidant and inhibitor of inducible nitric oxide synthase. This study suggests that the combination of PBE and L-arginine is helpful for infertile men to ameliorate simultaneously quality of sperms as well as erectile functions [39].

Based on these clinical studies, it seems that PBE associated or not with L-Arginine appeared as an effective and safe options in helping men with erectile dysfunction but also oligoasthenozoospermia.

8. CONCLUSIONS

Polyphenols including OPCs are important secondary metabolites for the health of plants. These OPCs from grape seed and pine bark extracts tested in preclinical and clinical studies have demonstrated beneficial effects - through trans-kingdom actions as they are able to alter most of the health conditions encountered during life of a human being. Their protective effects described, per os or by topically, are linked to their powerful antioxidant and anti-inflammatory activities in human cells and tissues. Modulation of the microbiota via a prebiotic effect is another way recently deciphered explaining their potential action in the gut but also outside the gastrointestinal tract. The use of OPCs in the nutraceuticals or cosmetics world to cope with increasing chronic or ageing disorders in humans will be of great interest today and in the future.

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