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Procyanidin and Its Benefits on Aging: A Literature Review

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ABSTRACT

Procyanidin is an oligomeric compound composed of catechin and epicatechin. Procyanidin can be found in many foods that can be found easily in Indonesia. In contrast, many people might not know that procyanidin can be found innatural plantations like fruits and cultivation crops. It can be found in grapes, apples, cranberries, cherries, strawberries, kiwis, apricots, and mangoes. Also in barley, sorghum, red rice, soybeans, and cocoa. Even nuts like almonds, hazelnuts, and peanuts. Many studies found that it has medicinal properties. Famous for its antioxidant and anti-inflammatory properties, procyanidin also has many other benefits. Aging is a definite process. It cannot be stopped. Lately, researchers have been trying to slow the process of aging. This literature review discusses the benefits of procyanidin for aging.

KEYWORDS: procyanidin, polyphenol, aging, osteoporosis, cardioprotective, neuroprotective, chondroprotective

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INTRODUCTION

Procyanidin is an oligomeric compound composed of catechin and epicatechin monomers. It could be found in foods and can have significant medicinal properties. Although much is already known about their biological activities, research concerning their medicinal benefits is continuing (1).

People are living longer, and the number of older in the population is growing. As people age, their bodies experience some changes. There are many health problems associated with aging, which attracts health researchers to investigate large natural compounds to prevent aging.

Procyanidins are promising in the treatment of chronic diseases such as cancer, diabetes, and cardiovascular disease, as they prevent cell damage related to oxidative stress. Therefore, it is necessary to study the advantages of procyanidins in aging. In this review, advances in the mechanisms of procyanidins on aging prevention were presented, which includes its activity on antioxidant, anti-inflammatory, cardioprotection, neuroprotection, generative disorder, hormonal, and muscle strength (2).

MAIN BODY

Procyanidin

Polyphenols can be found naturally in medicinal plants and food (2), and they can be found in plant-based food products (3). Procyanidin, known as condensed tannins, is derived from proanthocyanidin(2). Procyanidin is a naturally found polyphenol composed of flavan-3-ol units, epicatechins, and catechins. They can be classified as polymers or oligomers according to their degree of polymerization. It is found in fruits, vegetables, grains, legumes, leaves, tea, coffee, wine, chocolate, and cereal. Some fruits rich in procyanidin are blueberries, strawberries, grapes, apples, kiwis, cherries, cranberries, apricot, and mangoes. It also can be found in pears and bananas. Chocolate, cocoa powder, barley, sorghum, red rice, and soybeans are also rich in procyanidin. (2–4).

Antioxidant

Aging is an unavoidable process that affects all populations and results in the development of diseases and leads to death. Oxidative stress is a primary cause of cellular injury, even in normal physiological conditions. Several antioxidants have been studied to discover their beneficial effect against

oxidative stress, including flavonoids and polyphenols (5). Procyanidins have been endorsed to possess significant antioxidant capacities. It scavenges free radicals through a robust inhibitory effect against lipid oxidation (6). Procyanidins also maintain a normal cell cycle and regulatethe antioxidant enzyme system by protecting macrophages against oxidative stress produced by H_2O_2, inhibiting intracellular ROS production by reducing the chelated metal ions,and inducing the overexpression of antioxidant enzymes (7–11). Oligomeric procyanidins also presented antimicrobial activity against gram-positive bacteria and *Candida albicans* due to their high antioxidant capacity (9). The antioxidant effects of cocoa polyphenols are more evident in people with physical conditions or a significant antioxidant deficiency (12). However, the effects of procyanidins are dose-dependent and organ-dependent(8,13). Furthermore, Tapariareported that the procyanidin-rich extract of natural cocoa powder could elevate intracellular ROS levels. This prooxidant effect was beneficial as it could diminish the invasive potential of epithelial ovarian cancer cells (14).

Generative disorder:

- Neuroprotective

Alzheimer's disease (AD) is an age-related and progressive neurodegenerative disease with memory impairment in later life. AD is diagnosed by accumulation of amyloid, observed as a deposition in the cerebral cortex and hippocampus, called a senile plaque, composed of amyloid β-proteins. A study using procyanidin extracted from apples found that it inhibited amyloid β-proteins aggregation and neurotoxicity (15). Two mechanisms contributing to Alzheimer's disease pathogenesis are neuroinflammation and oxidative stress. A recent study using *Chrysophyllumperpulchrum* extract reported restoring spatial learning deficits and recognition memory. It also reduces oxidative stress status in the brain. Using the extract containing procyanidin P2 and P3, the study reported an approximately 3-fold decrease of NO level in different brain areas, suggesting its repressive action on the Aβ-induced iNOS activity and the release of cytokine via downregulation of NF-KB expression. It also reported a reduction of activated microglia in hippocampal and CPF areas (16).

Parkinson’s disease (PD) is an irreversible degenerative disorder caused by the premature death of dopaminergic neurons and dopamine deficiency in the nigrostriatal system. Some symptoms are tremors, rigidity, postural instability, and slow voluntary movement. Mitogen-activated protein kinases (MAPKs) are a type of serine/threonine protein kinases consisting of the extracellular, signal-regulated kinase (Erk) 1 and 2 (Erk1/2), P38 isoforms, and c-Jun N-terminal kinase (JNK). Research suggests that abnormal regulation of MAPKs may contribute to the pathogenesis of PD. Using cinnamon procyanidin oligomers (CPOs) was reported to have a neuroprotection effect against 1-methyl-4-phenylpyridinium (MPP+)-induced cytotoxicity. It was found to activate Erk1/2 phosphorylation, attenuate an intracellular level of reactive oxygen species, enhance the ratio of Bcl-2/Bax expression and inhibit caspase-3 activity (17). Another study found that proanthocyanidin (PC) prevented mitochondrial apoptosis, reactive oxygen species (ROS) production, and c-Jun N-terminal kinase (JNK) activation in neurons. It reported that PC could reduce cell apoptosis in vitro and inhibit striatal dopamine depletion in vivo (18).

Grapeseed procyanidin (GSP) was reported to have a potential protective effect on cognitive dysfunction in mice. Procyanidin has a strong antioxidant effect and stabilizes NR2B/CREB pathway, which is essential for memory processes and formation. GSP enhanced antioxidant enzyme activities, increasing superoxide dismutase (SOD) total activity. Superoxide dismutase can scavenge free radicals (19). In another setting, an ethanol-induced hippocampal neuronal toxicity, grapeseed procyanidin was also reported to increase superoxide dismutase (SOD) activity and decrease the levels of malondialdehyde (MDA) and lactate dehydrogenase (LDH). GSP also increases the number of dendrites and total dendritic length per cell (20). Another study found that procyanidin has neuroprotective effects via activating the nuclear factor-erythroid 2-related factor 2/antioxidant response element (Nrf2/ARE) pathway. It improved the levels of antioxidant enzymes, including glutathione,peroxidize (GSH-Px), catalase (CAT), and superoxide dismutase (SOD) but decreased the levels of ROS and MDA(21)**.** A study using procyanidin B2 found that it has neuroprotective effects in the primary culture of rat cerebellar granule neurons. It protects from oxidative and nitrosativestressors and glutamate-induced endotoxicity (22).

- Chondroprotective

Osteoarthritis (OA) is a degenerative disorder of the joints that causes significant pain and functional disability. OA involves the articular cartilage, subchondral bone, ligaments, synovial membrane, and periarticular muscle. The cause of OA is unknown, but some studies have suggested that it results from the combination of biochemical factors and mechanical stress, mainly reactive oxygen species (ROS) and matrix metalloproteinases (MMPs) (23).

Grapeseed proanthocyanidin extract (GSPE) has an antioxidant effect, decreasing the chondrocyte damage and proteoglycan loss by scavenging ROS and MMPs. It also reduced MMP-13-producing cells in arthritic joints. The antioxidant activity of GSPE also decreasesnitrotyrosine production in cartilage and synovium; it may contribute to the antinociceptive effect. GSPE also has anti-inflammatory activity by reducing synovial inflammation (synovitis) and suppressingosteoclastogenesis(23).

Proanthocyanidin from red jasmine rice crude has also shown chondroprotective potential. It inhibited the IL-1β-induced NF-KB activation signaling pathway, resulting in the reduction of proinflammatory cascades and thus the production of cartilage-degrading enzymes (24).

An olive-grape seed extract containing hydroxytyrosol and procyanidins was found to exert anti-IL-1β effects in chondrocytes in vitro. It also reduces the severity of post-traumatic OA in mice and rabbit models (25). In another study using human articular chondrocytes cultures, both in vitro and ex vivo, hydroxytyrosol and procyanidins showed anti-IL-1β activities (26).

Extract of *Croton palanostigma* was riched in proanthocyanidins, has antioxidant activity, and prevents the catabolic breakdown of the human cartilage matrix. Its chondroprotective actions are associated with direct inhibition of MMP activity and enhanced chondrocyte expression and production of IGF-1 (Insulin-like Growth Factor), an anabolic growth factor known for cartilage repair (27). Procyanidin was also found to suppress VEGF-mediated signaling (Vascular Endothelial Growth Factor) in OA chondrocytes by reducing phosphorylation of VEGF-receptor 2 in human OA primary chondrocytes (28)

Apple procyanidin (procyanidin B2) was found to protect against articular cartilage degeneration and prevent the development of knee osteoarthritis in mice because of the modulation of mitochondrial biogenesis and proteoglycan biosynthesis in chondrocytes (29).

Cardioprotective

Several studies have shown the cardioprotective effects of procyanidins. Possible beneficial effects on cardiovascular include vasodilators, anti-inflammation, anti-thrombotic, and anti-atherogenic.

Vasodilation: vasodilation is beneficial in angina and hypertension (30). Procyanidins increase NO synthesis (31)and induce endothelium-dependent vasodilatation (32), resulting in reducing heart rate (33), thus reducing systolic and diastolic blood pressure (34,35). Some studies showed that dietary intake of procyanidins was significantly associated with reducing renin and Angiotensin II plasma levels and the risk of hypertension induced by a high-fat diet (36,37). Another study also reported that low-dose procyanidins (<245 mg/day) could significantly reduce SBP, DBP, PP, and MAP, while no significant effect was reported on the higher dose (38).

Antioxidant: Procyanidins improve antioxidant defenses (34) and decrease oxidative stress in endothelial cells (39).

Anti-inflammation: Procyanidins alleviate inflammatory responses (34), decrease NF-kB activation, decrease COX, LPO, and monocyte adhesion, and attenuate proinflammatory cytokines and chemocytokines release (31).

Anti-thrombotic: Procyanidins suppressed platelet aggregation (33), increased PGI2, and decreased TXA2(31).

Anti-atherogenic: anthocyanin-rich extract supplementation affected the expression of genes involved in essential processes underlying atherosclerosis(40). Procyanidins work in the regulation of lipid metabolism(41) by significantly decreasing total cholesterol, LDL-C, and triglycerides and increasing HDL levels with four weeks of flavanol-rich treatment (13,42).Moreover, it blocks the oxidation of low-density lipoprotein (LDL) (34), improves endothelial function, improves antioxidant defenses, alleviates inflammatory responses (43), and protects VSMCs against oxidative stress and apoptosis(44). In 2018, Rong, in his study using ApoE-KO mice fed with a western-type diet, showed procyanidins intake could alleviate the lipid disorder and ameliorate atherosclerosis via regulating gene expression involved in hepatic lipid homeostasis effectively (45).

Lately, Dalgaard found that the inverse association between flavonoid intake and atherosclerotic cardiovascular disease was more potent in current smokers and individuals who consume high quantities of alcohol (46).

In conclusion, many studies above show that procyanidins treatment was dose and time-dependent.

Osteoporosis

Bone diseases are caused by disharmony in the bone remodeling process, which is mediated by bone-formative osteoblasts and bone-resorbing osteoclasts. Excessive activation of osteoclasts leads to excessive bone destruction. It is associated with low concentration levels of estrogen in postmenopausal women or excessive inflammatory responses in pathological circumstances (47). Osteoporosis is characterized by an increased bone turnover with insufficient bone formation relative to bone resorption, leading to increased bone fragility and increased risk of fracture (48)

Many studies found that procyanidin can attenuate bone loss. Using Grape Seed Proanthocyanidin Extract (GSPE), Tofani et al. in 2004, found that GSPE induces bone formation in low-calcium feeding rats. The effects were more significant in trabecular bone than cortical bone (49). Di et al. also reported that GSPE promotes proliferation and inhibits osteoclast differentiation and apoptosis in vitro. It also protects against lipopolysaccharide (LPS)-induced inflammatory bone loss in vivo. (47)Another study in 2014 using GSPE found that proanthocyanidinsprotect MC3T3-E1 osteoblastic cells from H_2O_2-induced mitochondrial dysfunction and apoptosis by improving mitochondrial function and inhibiting mitochondrial dysfunction and inhibiting the activation of p53 signaling(48).

Orsolic et al. in 2018 reported that proanthocyanidin demonstrated a significant antioxidant and antiosteoporotic effect in retinoic acid-induced osteoporotic rats. It maintains calcium and phosphorus homeostasis and increases antioxidative enzymes that increase bone markers formation and mineral density while reducing lipid peroxidation. Proanthocyanidins also inhibit the production of proinflammatory cytokines, including TNF-α and IL-1β (50). Chen et al. reported that proanthocyanidin protected osteoblasts against dexamethasone-induced oxidative stress, mitochondrial dysfunction, and osteogenic impairment by activating the antioxidant Nrf2 pathway. It subsequently decreased ROS accumulation and mitochondrial superoxide levels in osteoblasts (51). Supporting the previous study, Tenkumo et al. also reported that proanthocyanidin could

prevent bone loss and facilitate bone healing in ovariectomized animals due to its antioxidative and anti-inflammatory properties. (52)

Muscle Strength

Low muscle strength is associated with mortality, presumably due to low muscle mass (sarcopenia) and physical inactivity.Sarcopenia is the loss of muscle mass that occurs with aging(53). A study on 32-week-old senescence-accelerated mice which supplemented a diet containing procyanidins improves mitochondrial quality via regulating molecular signals involved in mitochondrial biogenesis, mitochondrial fusion and fission, and autophagic flux. Optimized mitochondrial quality by oligonol led to a positive protein turnover via increased muscle protein synthesis, decreased muscle protein degradation, and mitochondria-mediated apoptosis (54). Furthermore, five consecutive weeks of administration of dark chocolate mixture (mainly containing procyanidins) to obese middle-agedmice showed 2.38 times increase in body weight and significantly improved physical performance evaluated with the hang-wire, inverted-screen, weight-lifting tests, and dynamometry compared with the performance of the controls consistent with the modulation of the muscle biomarkers for sarcopenia (55).

Hormone Regulation

As most of the population ages, hormonal issues such as osteoporosis, insulin resistance, metabolic syndrome, and hormonal-related cancer become medical attention. The use of alternative and complementary products is rapidly expanding (56). Procyanidins were one of the most likely compounds found in fruit and vegetable. One of the procyanidins'benefits ison preventing bone aging. A study on 43 postmenopausal women with osteopenia receiving standardized procyanidins supplementation for 12 weeks showed a beneficial effect through improving the antioxidant defense system in the plasma and peripheral blood mononuclear cells (PBMCs) that was accompanied by an increase in indicators of bone marrow (57).

Procyanidins also have some roles in improving insulin resistance. As we know, α-Glucosidase is a critical enzyme in the human intestine.Inhibiting its activity can lower blood sugar levels to prevent hyperglycemia-induced tissue damage. Procyanidins intervene in the progression of type-2 diabetes by inhibiting α-glucosidase. A study on different structures of procyanidins showed that the α-glucosidase was lower than that of acarbose. A-type procyanidins might have better inhibitory activity than B-type procyanidins (58).

Moreover, thestudy of polyphenol-enriched cocoa extract administration on insulin-resistant rats showed sucrose-induced insulin resistance, hepatic carbohydrate and lipid dysmetabolism, oxidative stress, and inflammation were effectively disrupted. Dietary administration of cocoa flavanols (mainly containing procyanidins) may effectively prevent or reverse prediabetes (59). Furthermore, Montagut, in his *in vitro* study, showed that grape seed procyanidins extract (GSPE) differed from insulin in how it stimulated glucose uptake in insulin-resistant adipocytes. This suggests that GSPE is partly dependent on Irs1 when stimulating glucose uptake but also suggests that GSPE has a direct effect on Glut4 transporter activity. These mechanisms could be responsible for slightly improving plasma IR parameters (mainly by reducing insulinemia) (60). A study on *streptozotocin-induced diabetic rats* showed that procyanidins mimic and influence insulin effects by directly acting on specific components of the insulin-signaling transduction pathway (61). Kawakami stated that ingestion of 25 g of cacao polyphenol-rich chocolate before a 50 g OGTT could enhance early insulin and GLP-1 secretion in healthy participants and illustrates the potential of cacao polyphenol-rich chocolate in managing postprandial glucose excursions (62). Castell-Auvi, in his *in vivo* experiment, reported that different doses of procyanidins affected insulinemia in different ways by modifying β-cell functionality and insulin degradation.In addition, insulin gene expression, insulin synthesis, and expression of genes related to insulin secretion were all down-regulated. In vitro studies revealed that GSPE decreased the ability of β-cells to secrete insulin in response to glucose. GSPE increased glucose uptake in β-cells under high-glucose conditions, but impaired glucose-induced mitochondrial hyperpolarization decreased adenosine triphosphate (ATP) synthesis and altered cellular membrane potentials. GSPE also modified Glut2, glucokinase, and Ucp2 gene expression and altered the expression of hepatic insulin-degrading enzyme (Ide), thereby altering insulin degradation (63).

Cocoa flavanols which are rich in procyanidins, appear to alleviate metabolic syndrome, and specifically, derangements in glucose homeostasis, by several mechanisms: cocoa may reduce glucose excursion after a meal by inhibiting digestive enzymes, inhibiting glucose transporters, and promoting an incretin response (64).

Rosenberg et al. reported the effect of natural products on steroid hormone-regulated gene expression. Procyanidin extracts exhibited weak estrogenic and progestin activity but only at the highest concentrations tested. This has been demonstrated to have antiproliferative and anticarcinogenic activities in cell culture and animal studies (56).

Cell senescence

Aging is an inevitable process that causes functional decline progressively in organisms. (65). Several studies reported that procyanidin has anti-aging effects. In degenerative retinal disorders, GSPE was reported to improve impaired mitochondrial function in the aging retinal pigment epithelium, increasing NAMPT expression and improving NAD+ contents in aging mice via NAMPT/SIRT1/NLRP3 pathway. NAD+ promotes SIRT1 expression and then inhibits the activation of the inflammasome complex. (66).

Previous study in 2008 using persimmon peel also reported that proanthocyanidin elevated SIRT1 expression and decreased oxidative DNA adducts, 8-Hydroxy-2'-deoxyguanosine (8OH-dG) (67). In a recent study, procyanidin C1 was reported to be a broad-spectrum senolytic compound. It also can act as a xenomorphic agent, minimizing senescence-associated secretory phenotype (SASP) expression in lower concentrations (65).

CONCLUSIONS AND RECOMMENDATION

Procyanidin, an oligomeric compound composed of catechin and epicatechin, can be found in many foods in Indonesia. Many studies found that it can be beneficial for the human body. While aging cannot be stopped, we can try to slow the process of aging using procyanidin.

Competing Interest

The authors declare that there are no competing interests related to the study.

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