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Polyphenolic Treatment and Prevention of Alzheimer's Disease

Prevención y tratamiento de la enfermedad de Alzheimer por medio de polifenoles

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Resumen

Las enfermedades mentales son una de las mayores aflicciones del mundo, ya que afectan a casi 60 millones de personas en todo el planeta. La enfermedad de Alzheimer es una de las formas de demencia más prevalentes registradas y su progresión no puede revertirse, ya que degenera el sistema neuronal e impide la recuperación. Si bien se han desarrollado tratamientos para ralentizar la progresión de la enfermedad, suelen ser agresivos para el paciente, muy costosos y no garantizan su eficacia. Por ello, la prevención es el punto central del tratamiento del Alzheimer y los compuestos polifenólicos han demostrado su capacidad de actuar como antiinflamatorios para detener la inflamación neuronal, que es la principal aflicción en la patogenia del Alzheimer. Esta revisión se centrará en el efecto preventivo de diferentes compuestos polifenólicos y cómo pueden ser un tratamiento potencial para prevenir y ralentizar la progresión del Alzheimer.

Palabras clave: enfermedad de Alzheimer, Elagitaninos, Flavonoides, Neurodegenerativo, Polifenoles.

Abstract

Mental illness is one of the world's greatest afflictions as it affects nearly 60 million people around the world Alzheimer's Disease is one of the most prevalent forms of dementia that is registered, and its progression can never be reversed as it degenerates the neuronal system making it impossible to recover. Treatments have been developed to slow down the progression of the disease, but they tend to be aggressive on the patient, very expensive, and can't guarantee their efficiency, prevention is the main focal point in the treatment of Alzheimer's, and polyphenolic compounds have shown their capacity to act as an anti-inflammatory compound to stop neuronal inflammation which is the main affliction on the pathogenesis of Alzheimer's. This review will focus on the preventive effect of different polyphenolic compounds and how they can be a potential treatment for preventing and slowing the progression of Alzheimer's.

Keywords: Alzheimer's Disease, Ellagitannins, Flavonoids, Neurodegenerative, Polyphenols.

INTRODUCTION

Mental illness as stated by the World Health Organization (WHO) is characterized by the alteration in the mental capacity of a person, more specifically in thinking, perception, emotions, conduct, and memory. Among these diseases, we can find depression, bipolarity, schizophrenia, psychosis, Alzheimer's disease (AD), and Parkinson's. The improvements in the health services around the world and the pharmacological industry have led people to have a better life quality adding years of lifespan to people which has also caused the increase in neurodegenerative disorders, as previously mentioned.

One of the main problems of health systems worldwide is AD, which is the most prevalent mental illness in the world. Discovered in 1901 by Alois Alzheimer, studied a case of a female patient named Auguste D., who was observed and investigated at the Frankfurt Psychiatric Hospital in Germany. Auguste started with paranoid symptomatology that could not be treated and only deteriorated over time until she became an inpatient of the hospital until she died in 1906.

Alzheimer described this unusual disease very thoroughly through symptomatology, progression, and course of the illness since Auguste was admitted at the beginning of the illness until

her death. Shortly after her death, an autopsy was ordered and Alzheimer was able to investigate Auguste's brain, both histologically and morphologically (Hippius y Neundörfer, 2003).

As of 2022 Alzheimer's disease is the most common form of dementia with 60-70% of the total cases of dementia all over the world, and currently there are more than 55 million cases of dementia worldwide, with nearly 10 million cases adding up every year and by the year 2050 it is expected that this number rises to 150 million (WHO, 2022).

It is not known why Alzheimer's disease happens, but several risk factors prompt the apparition in each person, the most common are: Age, family history, physical activity, diet, alcohol consumption and even maybe the environment are some of the factors that can be associated with the appearance of AD (CDC, 2020).

AD symptoms vary from patient to patient and one may experience multiple symptoms over the course of the years, in the first stages of the disease the patient will be able to do most activities on its own but may require assistance from a caretaker or family member in some other activities, in middle stages of the disease the patient will have difficulty in their routines, become confused about where they are and may begin wandering in confusion. Final stages of AD the patient will always needing a caretaker or a family member to help in their daily basis, activities such as brushing their teeth, taking a shower, dressing and even communicating with others may represent a challenge for the patient (Association, 2018).

Treatment for AD currently focuses on reducing the apparition of symptoms, at the moment only four drugs are FDA-approved for the treatment of AD, AChE inhibitors such as donepezil, galantamine, and rivastigmine and memantine which is an NMDA antagonist (Vaz y Silvestre, 2020). As mentioned before, current treatment does not modify the progression of AD, so new treatments are needed and being investigated, one of those alternatives is polyphenolic supplementation. Galantamine and rivastigmine act as acetylcholinesterase inhibitors by binding to the peripheral site preventing acetylcholine at the synapse, helping to enhance cholinergic transmission and neurotransmission by acetylcholine, preventing or slowing the onset of Alzheimer's disease (Arya y col., 2021). On the other hand, donepezil is also an acetylcholinesterase inhibitor and has minimal effects on butyrylcholinesterase and a long-lasting action (Burns y col., 1999) and memantine, acting as NMDA receptor blocker (Silva y col., 2022).

Many studies all over the world, show the importance of a good and balanced diet in the prevention of AD, one of the best dietary approaches is the Mediterranean diet which consists of but is not limited to ingredients such as grapes, wines, berries, and olive oil which are known for their polyphenolic content. Polyphenols as an AD treatment have several properties such as the ability to interfere with Aβ accumulation, polyphenols have scavenging properties against reactive oxygen species (ROS) protecting the neurons from oxidative stress and their subsequent death, some polyphenols able to increase the expression of the heat shock protein (HSP) 70 and insulin-like growth factor 1 which protect from kainite-induced cell damage and support learning and memory functions (Ravi y col., 2019). Some of the major challenges modern medicine faces nowadays with the treatment of Alzheimer's disease are the prompt diagnosis and the delay of the appearance of the symptoms once diagnosed. This literature review covers how the use of polyphenols can help in the treatment and prevention of Alzheimer's disease.

Neuropathogenesis of AD

Alzheimer's disease is characterized by the loss of memory in the short and mid-term in the worst cases it can be complete memory loss, the main treatment consists of medicine that helps slow down the advance of the disease, but current medicine is not able to reverse, prevent or stop the disease progression. AD is caused by the accumulation of extracellular amyloid plaques, which are known as senile plaques, these plaques are also associated with neuroinflammatory changes and neurofibrillary tangles that can affect the process that is essential in maintaining neuronal health (Kommaddi y col., 2018, Parent y col., 2017). One possible path for the apparition of the neuropathology of AD consists of the extracellular and blood vessel accumulation of amyloid-β peptide (Aβ) and intraneuronal aggregation of tau protein in the form of neurofibrillary tangles. Aβ is derived by the proteolytic cleavage of amyloid precursor protein (APP) by the γ- secretases, β-secretases, presenilin 1, and presenilin 2 (PS1 and PS2 encoded by PSEN1 and PSEN2 respectively) (Calderon-Garcidueñas y Duyckaerts, 2018, Masters y col., 2015). Neurotoxicity and neuroinflammation in AD are caused by the aggregation and deposition of Aβ25-35 as this peptide has been recognized as responsible for neuronal dysfunction in AD.

Another hallmark stablished for the pathogenesis of AD is the apparition of neuronal inflammation, which at large is caused by the macrophages of the brain, the microglia cells, these cells are very important in the constant well-being of the brain as they can detect toxic components in the nervous system and eliminate the threat. Microglia can switch from M2 which "passively" watches over the brain's health to M1 which is the more "active" form when it recognizes a pathogen-associated molecular pattern or damage-associated molecular pattern (Merighi y col., 2022, Zindel & Kubes, 2020).

Once the M1 recognizes a threat like the toll-like receptors (TLRs) the system activates and it commences an inflammatory cascade which results in the release of several pro-inflammatory cytokines like tumor-necrosis factor-α (TNF-α), interferon-γ (INF-γ) and various interleukins such as 1β, 6 and

18. This reaction mechanism was triggered for the sole purpose of stopping and neutralizing the toxic agents found in the central nervous system (Tang y col., 2016).

In a healthy system the microglia go back to normal secreting anti-inflammatory cytokines like interleukins 4. 10 and 18, but under pathological conditions this is not the case, the microglia do not go back to M2 resting state therefore causing a state of chronic inflammation, The pro-inflammatory cytokines eventually cause irreparable damage to the neuronal matrix causing neurodegeneration.

The neurological degeneration caused by the chronic inflammation can be the starting point for the apparition of many dementia states like AD (Sánchez-Sarasúa y col., 2020).

As previously stated, the best course of action on the treatment of neurological diseases is the prevention of the appearance of the named disease, inflammation-mediated neurodegeneration and microglia are implicated in the appearance of AD. The inhibition of microglial activation can function as a therapy in the treatment of AD as bacterial component lipopolysaccharide (LPS) causes microglia to secrete inflammatory molecules including tumor necrosis factor α (TNF-α), interleukin-6, interleukin-1β, nitric oxide and inductive nitric oxide synthase (Farbood y col., 2015, Harikrishnan y col., 2018).

Polyphenolic supplementation in the prevention of Alzheimer's disease.

Research has intended to lower the dependence on psychiatric medicine, to take a big step in a new way to treat mental illness, coining a new term called "psychiatric nutrition" having as a base that the brain is an organ that uses a great amount of energy and nutrients, which can lead to possible causes of mental illness with a bad nutritional intake, as neuronal development and repair mechanisms are also bonded with nutritional factors (Martínez y González, 2017).

One of the most important factors to take into consideration for the treatment of AD is the targeting neuroinflammation, which certain polyphenolic compounds are known to reduce the inflammation in the human body.

Polyphenols have a beneficial role in the prevention and treatment of the disease as they are functional ingredients that may help prevent memory loss; epigallocatechin-3-gallate, 4-O-methyl honokiol, resveratrol, and ginkgolide A are just some of the examples of polyphenols that have been analyzed for the treatment of AD (Choi y col., 2012, Obrenovich y col., 2010). This preventive mechanism may be attributed to the antioxidant and anti-inflammatory properties capable of diminishing the inflammation caused by oxidative damage and the alteration of the brain's microglia.

The consumption of phenolic compounds can selectively target the microglia, compounds like quercetin are able to inhibit the expression of interleukin 12 and IFN-γ, which are known pro-inflammatory released by the M1 function of the microglia. Resveratrol is another compound known by its anti-inflammatory effect which acts in the microglia by stopping the phosphorylation of the inhibitor of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). This action causes the disruption of the expression of interleukin-6 and TNF-α also released by the M1 function of the microglia (Rangaranjan y col., 2016).

Epigalocathequin gallate (EGCG)

EGCG is a polyphenolic flavonoid that can be found abundantly in green tea and it has the potential to positively affect human health and disease, along with those great beneficial effects, it can prevent memory impairments caused by amyloid-beta peptide (Lee y col., 2009). This can be attributed to the inhibition of the NF-κB pathway, in in vivo studies it has been shown that rats reduced the amount of hippocampal lipid peroxide in the brain when supplemented with EGCG (Haque y col., 2008, Weinreb y col., 2004).

EGCG at concentrations of 10 mg/mLin drinking water and an oral application of 36.1 ± 1.6 mg/kg/day is one of the best mitochondria protective compounds as they observed in their experiment the restorative effects of EGCG specifically the treatment with this polyphenol restored mitochondrial respiratory rates, mitochondrial membrane potential, ROS production, and ATP levels by 50-85% in mitochondria obtained from the hippocampus cortex and striatum (Dragicevic y col., 2011). The protection that these compounds grant can be greatly attributed to the up-regulation of antioxidant protective enzymes including superoxide dismutase and catalase (Man del y col., 2008). Mitochondria dysfunction is a pathophysiological process that occurs in the brain of an AD patient.

One of the most important factors in the development of AD is the misfolding and self-assembling of amyloid-beta (Aβ) peptides and a study has shown that EGCG has inhibitory effects on the conformational transition of Aβ42 peptide, also reduces the ratio of β-sheet secondary structures of Aβ42 peptide while inducing random coil structures (M. Fang y col., 2022).

Another path in the prevention of AD that EGCG at concentrations of 0.1 to 100 μM exhibits is that this molecule can form inter-molecular hydrogen bonds with each of IAPP and Aβ40. It can also reduce the hetero-aggregate formation which resulted in lowering β-sheets content and higher unordered structures in IAPP-Aβ40-EGCG samples. It has also been shown that EGCG is highly effective in reducing the toxicity of IAPP-Aβ40 hetero aggregates in both cell models (Al Adem y col., 2022).

Quercetin

Quercetin is another polyphenol member of the family of flavonoids that have been reported to possess great effects against the progression of AD, as some studies show that concentrations as low as 5-10 µM can reduce cell damage and death caused by treatments with H_2O_2 and amyloid β peptides (Aβ) in cell models of PC12 cells and primary neuronal cultures (Gupta y Prakash, 2015). In other studies, it has been shown that quercetin can reverse the pathological processes of the disease such as β-amyloidosis, tauopathies, astrogliosis, and microgliosis, this test carried out in a murine design also showed that there was a significant increase in memory and learning (Khan y col., 2020, Maccioni y col., 2022)

Another study in a mice model has successfully shown that the consumption of quercetin in the form of nanoencapsulation in zein nanoparticles (NPQ), improved the cognitive status of senescence-accelerated mice (SAMP8). This was carried out in the lapsus of 2 months where they were given an amount of 25 mg/kg every 2 days, and the results of cognitive improvement were directly related to the decrease in the expression of the hippocampal astrocyte marker GFAP (Bartekova y col., 2016).

Geraniin

Geraniin is a polyphenolic compound member of the ellagitannins family which is known to possess high antioxidant activity as demonstrated by various previous studies (Cheng y col., 2017, Estrada-Gil y col., 2022, Mendez-Flores y col., 2018) it can be obtained from various food sources but also from some plants that can be deemed medicinal such as Geranium spp. Thanks to its important biological activity this compound has been studied in various models of AD with various favorable results.

Due to its great anti-inflammatory properties and capacity to modulate macrophage polarization a study was able to determine that geraniin could be a great coadjutant at concentrations of 25, 50 and 100 µM in the treatment of neuroinflammation which is part of the neuropathogenesis of cognitive diseases such as AD (Wang y col., 2019). The main mechanism of action that makes geraniin a potential treatment for AD is that it can suppress LPS-induced inflammation at concentrations of 10, 20 and 40 mg/kg by inhibiting NF-κB signaling pathways and the production of pro-inflammatory cytokines (Zhu y col., 2017).

Specific neuroprotective mechanisms of geraniin at concentrations of 0.1, 1 and 10 µM were studied to demonstrate the protective effect of geraniin on oxidative damage and neuroinflammation in beta-amyloid peptides (Aβ25-35) induced rat pheochromocytoma12 cells. Due to its high antioxidant activity geraniin was able to suppress Aβ25-35-dependent injury by decreasing the oxidative stress and restoring cell cycle dysregulation (Youn y Jun, 2020).

Ellagic Acid

Ellagic acid (EA) is another polyphenol member of the family of ellagitannins this compound can be found in the peel of many fruits and the leaves of some plants . This phenolic compound has been of great importance in the pharmaceutical and food industries due to its high antioxidant activity, although this is the most reported activity, EA is also known for being anti-inflammatory, antimicrobial, anticarcinogenic, and antiproliferative (Baradaran Rahimi y col., 2020, P. Gupta y col., 2019, Phuong y col., 2020). This anti-inflammatory activity takes importance in the treatment of AD, due to the main pathogenesis is caused by neuronal inflammation.

A study recorded the effects of EA in a concentration of 50 mg/kg on the entorhinal cortex (ERC) in an AD rat model; EA was found to possess a therapeutic effect due to the upregulation of superoxide dismutase expression diminishing amyloid precursor protein and caspase-3 expression both associated in the neurodegenerative changes and plaque formation in the brain, thus diminishing the effects of AD on the ERC tissue (Ramadan & Alkarim, 2021, Bradshaw y col., 2013).

A study by Ismail y col., (2020) investigated the effects of EA in concentrations of 0.5 to 10 µM over neuroinflammation in a murine model, the findings show that EA blocks the expression of MyD88 genes which are directly involved in controlling the inflammatory response and the development of pro-inflammatory cytokines, this induced by LPS.

Corilagin

Corilagin is another one of the members of the family of ellagitannins. Its presence can be found in many ethnopharmacological plants such as *Phyllanthus niruri L*., *P. emblica L*., and *P. uirinaria L*. (Li y col., 2018) and certain fruit peels such as rambutan (Hernández-Hernández y col., 2020). Corilagin as well as the previous ellagitannins possesses anti-inflammatory activity which grants the compound the correct properties to be able to treat AD.

Studies about PC12 neurotoxicity and neuroinflammation were investigated in PC12 cells against Aβ25-35 induced damage and apoptosis. A pretreatment with corilagin at varying concentrations of 0.1, 1 and 10 µM was able to protect these cells from TNF-α, nitric oxide, and prostaglandin E2 attenuating also the Aβ25-35 inflammation response downregulating NF-κB signaling pathway (Youn y col., 2016).

Resveratrol

Studies carried out in murine designs have reported that resveratrol at a concentration of 500 mg/day acts as an activator of SIRT1 which when expressed inhibits NF-κB signaling by decreasing Aβ-induced toxicity. SIRT1 is responsible for the

maintenance and well-being of neuronal systems and behavior including the memory processes. The absence of expression of this protein is directly correlated with loss of cognitive capacity as it could directly affect short-term memory (Gomes y col., 2018, Herskovits y Guarente, 2014, Michan y col., 2010); this way the activation of the expression of the protein SIRT1, resveratrol may be a potential polyphenolic supplementation alternative in the prevention of AD.

Resveratrol is capable of inhibiting lipopolysaccharide-induced activation of murine RAW 264.7 macrophages and microglial BV-2 cells at concentrations of 25-100 μM and it also prevented the proinflammatory effect of Aβ on macrophages by inhibiting activation of STAT1 and STAT3 and NFκB activation by interfering with IKK and IκB phosphorylation (Capiralla y col., 2012, Rege y col., 2014).

A treatment of resveratrol was used in a model of 3xTg-AD in which mice were treated with different variables such as; exercise trained (ET) mice, ET and resveratrol-treated mice, and mice supplemented with resveratrol-only, this was achieved by adding 4 g/kg of resveratrol to processed food pellets. Results stated that ET by itself does not make a difference in decreasing neuroinflammation markers such as NF-κB, GFAP, and PARP, however when resveratrol is mixed with ET the results showed a significant decrease in such neuroinflammation markers. The study states that resveratrol in combination with ET can decrease the accumulation of Aβ oligomers, and decrease apoptosis, autophagy, endolysosomal degradation, and ubiquitination in the brains of 3xTg-AD mice (Broderick y col., 2020).

Sinensetin

In studies where sinensetin supplementation was done, it was found that it can inhibit BACE1 with an IC50 value of 6.3 × 10–5 M to lower Aβ generation in a dose-dependent manner (Han Jie y col., 2021, Youn y col., 2017). Sinensetin supplementation was evaluated in a murine design where it showed that it could prevent memory impairment at a dose of 25 mg/kg/day which was compared to nobiletin (50 mg/kg/day) and got even better results, also sinensetin restored mid-brain dopaminergic function in aged animals when supplemented in long-term (Sun y col., 2017).

Absorption

The process of absorption of polyphenols begins in the mouth with the secretion of saliva and microbiota, converting them to simpler forms. When they reach the colon, oxidation-reduction reactions, hydrolysis, methylation, glucuronidation, etc. take place to transform them into aglycones by microbial action and enzymes. Once they have been absorbed by enterocytes and colonocytes, the polyphenols circulate in the blood by binding with proteins, to be transported to the brain and thus the polyphenols can permeate the blood-brain barrier as aglycones or conjugation products and interact with neurotransmitters (Arias-Sánchez y col., 2023; Prakash Reddy y col., 2020)

Table 1. Natural sources where the compounds can be found.

Compound	*Dietary source*	*Reference*
EGCG	*Black tea* *White tea* *Green tea* *Oolong tea*	*Markowska y col., 2023; Pedro y col., 2020*
Geraniin	*Rambutan* *Geranium*	*Estrada-Gil y col., 2022, Cerda-Cejudo y col.,2023 Cheng y col., 2020*
Corilagin	*Rambutan* *Longan fruit* *Myrobalan*	*Estrada-Gil y col., 2022, Cerda-Cejudo y col.,2023, Hassan Bulbul y col., 2022 Li y col., 2018*
Ellagic Acid	*Rambutan* *Oak bark* *Valonia* *Pomegranate* *Divi-Divi* *Myrobalan* *Algarrobilla*	*Cerda-Cejudo y col.,2023, Izábal-Carvajal y col., 2023 Sharifi-Rad y col., 2022, Estrada-Gil y col., 2022,*
Resveratrol	*Legumes* *Blueberry* *Bilberry* *Cranberry* *Peanuts* *Grapes* *Red wine*	*Tian y Liu 2020; Chiang Chan y col., 2019*
Quercetin	*Apples* *Berries* *Cauliflower* *Onion* *Peppers*	*Meresman, Götte, y Laschke 2021*
Sinensetin	*Clementine* *Java tea* *Mandarin* *Shiikwaasa*	*Weiss et al. 2020; Han Jie et al. 2021*

Adverse effects of polyphenols

Studies on the toxicity or safety of polyphenols are still scarce, however, green tea consumption has consistently been reported to be safe, being abundant in epicatechin gallate (Shen y col., 2017; Silva y col., 2022). On the other hand, the use of resveratrol was observed with minimal toxicity, as well as high bilirubin levels at doses greater than 1000 mg/kg per day in in-vivo studies (Johnson y col., 2011). Sergides y col., (2016) reported in patients dosed with 500 mg resveratrol tablets were tolerated and showed no harm. Quercetin has also been found to be safe at concentrations ranging from 30 to 3000 mg/kg body weight per day (Ruiz y col., 2009), furthermore, quercetin has been reported to be non-genotoxic at concentrations of 2000 mg/kg body weight (Utesch y col., 2008). For polyphenols such as geranin, it has been established in a previous study that no adverse effects are observed at concentrations of less than 2000 mg/kg body weight (Moorthy y col., 2019). Other studies with corilagin showed tolerance in mice at concentrations of 3500 and 5000 mg/kg and did not affect liver histology (Reddy y col., 2018; Zhang y col., 2013).

Future trends

Polyphenolic supplementation has garnered attention as a potential breakthrough in modern medicine. These naturally occurring metabolites can be extracted and integrated into various products. WHO data from 2023 reveals that an estimated 55 million individuals above the age of 60 worldwide are afflicted with Alzheimer's disease. These compounds have properties which can be transferred to a functional product which facilitates the intake of these compounds. Previous studies have demonstrated the ability to create products with polyphenol additives such as grape pomace cookies, which are rich in resveratrol (Fontana y col., 2022). Other examples of innovations in the industry are the cosmeceuticals which have gained strength, with enough studies this type of products could become an assistant for the prevention of several diseases not only AD (Dias y col., 2021). Dietary treatments such as the Mediterranean diet are important as adjuvants for the prevention of this disease, due to the high polyphenolic content of this diet (Ballarini y col., 2021). Nevertheless, with the implementation of polyphenolic supplementation as a preventative measure, it may be possible to mitigate the number of Alzheimer's patients in the future.

CONCLUSIONS

Polyphenols are a diverse group of compounds with a wide range of biological properties, including antioxidant, anti-inflammatory, and neuroprotective effects. As a result, polyphenolic supplementation is a promising approach for the prevention and treatment of Alzheimer's disease. Several studies have shown that polyphenols can reduce the production and accumulation of amyloid-β peptide (Aβ), one of the hallmarks of Alzheimer's disease. Polyphenols can also protect neurons from oxidative damage and inflammation, two other key factors in the progression of the disease. In addition, polyphenols have been shown to improve cognitive function and memory in animal models of Alzheimer's disease. These findings suggest that polyphenolic supplementation may be a viable strategy for delaying the onset or slowing the progression of Alzheimer's disease in humans. More research is needed to determine the optimal dosage and formulation of polyphenols for the prevention and treatment of Alzheimer's disease. However, the current evidence suggests that polyphenolic supplementation is a safe and effective way to reduce the risk of developing Alzheimer's disease and improve cognitive function in people with the disease.

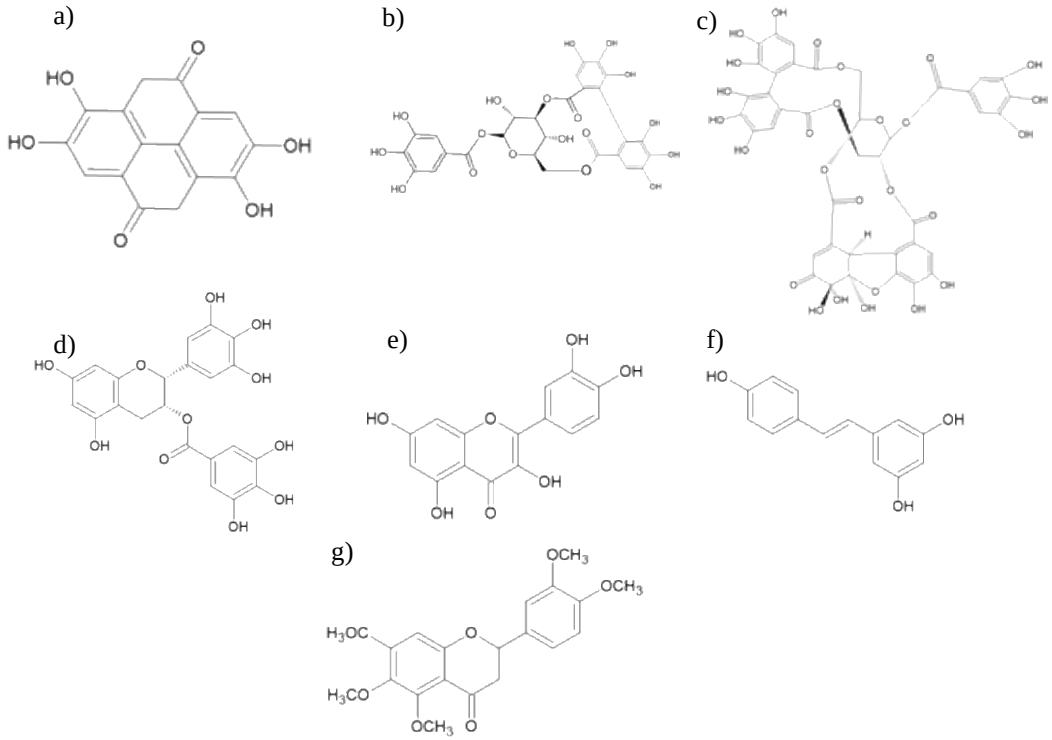

Figure 1. Chemical structure of a) ellagic acid, b) corilagin, c) geraniin, d) EGCG, e) quercetin, f) resveratrol, g) sinensetin.

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