Biological and Pharmacological Activities of Esculetin

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Abstract

Esculetin is a natural flavonoid and derivative of coumarin found in various plant species such as citrus fruits, green tea, and chicory. It exhibits a variety of biological effects, including anticancer, antioxidant, and anti-inflammatory properties. It can scavenge free radicals and prevent oxidative stress. In addition, esculetin has been shown to have anti-apoptotic effects by inhibiting caspase activation and protecting against cellular damage. This compound has several positive effects against oxidative, inflammatory, and apoptotic stress. Esculetin has also been studied for its potential therapeutic applications in the treatment of cardiovascular and neurological diseases. The compound was found to penetrate the blood-brain barrier, making it an attractive candidate for drug development against various diseases such as cancer, renal failure, cardiovascular disease, Alzheimer's disease, and Parkinson's disease. Oxidative stress is a risk factor for cardiovascular disease, and antioxidants protect the circulatory system against oxidative stress caused by free radicals. Additionally, it has been shown to have neuroprotective effects by protecting against ischemia-reperfusion brain injury, a common cause of stroke. Overall, esculetin exhibits a variety of pharmacological properties and may be useful in the treatment of a variety of diseases.

Keywords: Flavonoid, Coumarin, Anticancer, Antioxidant, Anti-inflammatory, Cardiovascular diseases, Anti-apoptotic

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Introduction

Flavonoids are a significant class of natural compound; they specifically belong to a group of secondary plant metabolites with polyphenolic structures that are widely reported in various beverages, fruits and vegetables. Flavonoids is a class of plant metabolites that are hypothesized to provide medical benefits through anti-oxidant properties and cell signaling pathways. Foods rich in flavonoids are responsible for flavor, color, vitamin and enzyme protection as well as fat oxidation prevention (Yao et al., 2004). In plants flavonoids have several roles including control cell growth, luring insects and pollinators shielding against stresses both biotic and abiotic. Flavonoids are active food components that may promote health and many chronic diseases. A diet full of flavonoids can help to prevent from neurological, cardiovascular and autoimmune conditions as well as metabolic diseases like diabetes mellitus (Birt and Jeffery, 2013). Clinical experiments shown that eating food rich in antioxidant anthocyanin (which were present in berries) and flavan 3-ol (which can be found in beverages such as green tea and cocoa) offer a degree of defense against cardiovascular diseases and type 2 diabetes (Corcoran et al., 2012). These biological process is influenced by the bioavailability of possible mechanism of action and the type of flavonoid. The group of natural compounds extracted from plants, flavonoids are used by vegetables for their growth and defense against plaques. They belong to a class of low-molecular-weight phenolic compounds that are widely distributed in the plant kingdom. These natural products are well known for their positive effects. Many flavonoids are easily recognized as flower pigments in most angiosperm families. Despite being commonly associated with flowers; flavonoids are ubiquitously present throughout various plant parts. Moreover, they are abundantly found in a range of food and beverage sources derived from plants, such as fruits, vegetables, lea, cocoa, and wine. Thus, they are referred to as dietary flavonoids. These flavonoids can be classified into distinct subgroups, which include chalcones, flavones, flavonols, and isoflavones, each having unique primary sources (Panche et al., 2016). Flavonoids exert diverse biological activities across plants, animals, and bacteria. In the plant kingdom, flavonoids are synthesized in specific locations and are responsible for conferring color and aroma to flowers and fruits, respectively. In fruits, they play a critical role in attracting pollinators and subsequently aiding in fruit dispersion, seed, and spore germination, as well as seedling growth and development. Flavonols and flavones are notably abundant in onions and lea, making these two sources major contributors of these dietary flavonoid subgroups. Flavonoids also help to protect plants against various biotic and abiotic stresses by serving us unique UV fillers and functioning as signal molecules.

Use in Chinese Medicine

Chinese medicine with herbs has been widely utilized to treat a wide range of disorders for ages. Esculetin, a flavonoid is essential part of herbal medicine. In many circumstances it is referred to as aesculetin; It is the main bioactive component of the commonly used herbal medicine *Fraxinus rhychophylla Hance* of the Oleaceae family (Kim et al., 2018). Esculetin is abundant in many therapeutic herbs, including *Artemisia capillaries, A scoparia, Ceratostigma* and *Citrus limonia willmottianum* (Subramaniam and Ellis, 2011). It displays anti-proliferative, anti-tumor, anti-oxidant, anti-inflammatory, anti-bacterial, anti-apoptotic, neuroprotective as well as vascular protective effects (Shabanov and Vislobokov,

2013). Esculetin protects the cells from DNA damage induced due to oxidative stress (Liang et al., 2017) Oxidative stress is caused by free radicals, which leads to inflammation, arthritic conditions diabetes, fatty liver disease, cancer, and other disorders. This reduces the effectiveness of anticancer medications even further, activates inflammatory signaling pathways, alters the glycemic index, interferes with normal liver enzyme activity and destroys cartilage and joints. It depends on the basic mode of action for the therapeutic and bioactivities of coumarin compounds and their derivatives. In the development of many diseases free radicals are involved however, Esculetin has hydroxyl groups it is more efficient as an anti-oxidant by reducing oxidative stress in circumstances related to diseases (Kostova et al., 2011). The hydroxyl group on phenolic substances enable them to successfully bind with free radicals. Short lived metals such as copper and iron can also chelate in phenolic compounds due to hydroxyl group (Zhu & Jiang, 2018). Esculetin dual apoptotic modulation as well as its ability to control diabetes and reduced inflammation may be partially explained by its anti-oxidant characteristics (Najmanova et al., 2015).

Anti-oxidant Properties

Many plant species contain esculetin, a powerful antioxidant. The goal of this study was to see how esculetin prevents reactive oxygen species damage in human hematoma cells induced by H202. Cell viability, cellular oxidative stress and response lo reactive oxygen species have been evaluated by measuring the health of cells, cell integrity, intracellular glutathione levels, reactive oxygen species generation, and antioxidant enzyme expression. Maintain cell integrity after being exposed to 0.9 milliM of hydrogen peroxide (Subramaniam and Ellis, 2011). A rise in ROS production that follows hydrogen peroxide therapy was dramatically reduced by treating the material for 8 hours with esculetin. Esculetin also prevented the loss of exposure to hydrogen peroxide decreases glutathione levels intracellularly, NADPHI was also elevated alter eight hours of exposure to 25 M esculetin quinine oxidoreductase by a factor of 12 und 15, respectively, in protein and mRNA expression. The esculetin also resulted in an X-fold increase in nuclear Nriz accumulation indicating that the upregulation of NQO1 expression is mediated by Nr/2. The data show that esculetin induces protective enzymes as part of an adaptive response mediated by nuclear Ni2 accumulation, protecting human hematoma HepG2 cells from hydrogen peroxide-induced oxidative injury.

Anti-inflammatory Properties

Esculetin's anti-inflammatory properties are shown by a number of reports on the molecular mechanisms that explain them. In one sense, esculetin decreases the secretions of Nitric Oxide to regulate circulation and stop organ tissue damage brought on by inflammation. However, esculetin suppresses the release of a soluble intercellular adhesion molecule (sICAM1) that can lessen leukocyte and endothelial cell adhesion reactions to reduce inflammation (Duan et al., 2007). Esculetin may delay the first signs of osteoarthritis, lower PGE2 and NO levels in synovial fluid (SF), and drastically diminish cartilage's ability to produce matrix metalloproteinase-1 (Lu et al., 2017). The Heme Oxygenase-I indicates that esculetin has anti-inflammatory characteristics by lowering the release of cytokines that are pro-inflammatory when adipocytes and macrophages interact. Inflammation of adipose tissue, which is a chronic disease associated with obesity. Esculetin has the ability to decrease chronic pain in obese individuals (Kim et al., 2014).

Natural coumarin compounds, are used in medicine as anticoagulants. Esculetin serves as the therapeutic potential for stroke therapy (Wang and Xia, 2011). Vascular smooth muscle cell growth (VSMC) brought on by damage to the intima of an artery, such as atherosclerosis and restenosis, is one of the main causes of vascular proliferative diseases. Esculetin can effectively inhibit VSMC growth in vitro in a dose- and time-dependent manner. Esculetin's ability to block the activation of the signaling pathways Ras-Raf-MEK-ERK/MAPK and Ras-PI3K-Akt has provided information about the anti-proliferative effect (Dai et al., 2009). In particular, esculetin inhibits cell proliferation by mediating both the upstream and downstream effects of Ras signaling, including the activation of p42/44 MAIK, PI3K, and early gene expression, as well as the activation of NF-kappa and AP-I.

Anti-bacterial Properties

The anti-bacterial impacts of the effects of a plant's coumarin esculin and its aglycone esculetin on a strain of E. coli 0157's ability to survive in the gut have been investigated. It is thought that *E. coli* 0157:H7, a human pathogen, can spread by direct or indirect contact with animal or human waste (Duncan et al., 2004). In human fecal sludge and in vitro continuous flow fermenter models, these substances drastically reduced the survival of an acquired strain of *E. coli* 0157 that reflected situations in the rumen and colon of humans. Four calves that had been fed the esculin and experimentally contaminated with *E. coli* 0157 had the pathogen found in five of 28% (eighteen percent) stool samples that were examined post-inoculation. Compared to five control calves not given esculin, thirteen of thirty-five (37 percent) stool samples were examined. The chemical coumarin compounds have probably reduced E. coli 0157's ability to survive in the stomach. That is present in the food or found organically in diet vegetation (Lee et al., 2014).

Anti-cancer Properties

Esculetin has strong anti-cancer and anti-proliferative effects. Esculetin is capable of inducing apoptosis in various types of cancer cells, including but not limited to human colorectal carcinoma, gastric carcinoma, malignant melanoma, and breast carcinoma (Kim et al., 2015; Chang et al., 2016). Additionally, esculetin may significantly increase cell death in human hematoma (HepG2) cells when combined with chemotherapy, as opposed to chemotherapy alone. According to a prior study, esculetin causes the mitochondrial permeability transition pore to open, which can cause the death of human gastric cancer cells. (Pan et al., 2015). In the xenograft mouse model, esculetin leads to the death of stomach cancer cells through a signaling pathway, but its effects on these cells have not been investigated.

Cell lines include squamous cell carcinoma of the oral cavity, HSC4, HN22, human monocyctic leukemia U937, and human cancer of the melanoma G361 are a few of the human cancer cell types in which phenolic esculetin significantly causes tumor death (Jeon et al., 2015). Another study used immunocytochemistry and overexpression of apoptotic-related DRS proteins to evaluate esculetin's anti- proliferative impact on factor-related apoptosis, Tumor necrosis and ligand-induced apoptosis. The inhibition of Spl transcription factor, as well as

downstream target regulatory genes like p21, p27, and cyclin D1, in a time- and dose-dependent manner, esculetin also has strong antiproliferative effects on HIMM cells, HSC4, HN22 and triggered death. Additionally, in G361 HMM cells, esculetin causes apoptosis. Signaling molecules such as the ERK pathway, PARP and caspase-3 are activated. (Yang et al., 2010). In particular, all the studies indicated that esculetin could be a potential chemotherapeutic option in medical care of malignant skin cancer, acute promyelocytic leukemia and other carcinomas.

Glycemic Index (GI)

The glycemic index (G1) variations have been shown to be reduced by esculetin; as a result, it aids in the maintenance of blood sugar levels (Zhang et al., 2021). The accumulation of fat in the liver is a sign of non-alcoholic fatty liver disease. Risk factors for accumulating liver fat include elevated cholesterol levels, elevated blood pressure, obesity, and diabetes (Tomah et al., 2020). Esculetin's therapy has been confirmed to be effective in treating hepatic failure, diabetes, neurological problems, cardiovascular disorders, arthritis, atherosclerosis, and kidney failure. As a result of deficiencies in insulin action or secretion, diabetes is a met abolic condition that causes alterations in plasma glucose levels (Singh et al., 2022). Esculetin is only one of the many organic and man-made substances that have been used to mitigate oxidative stress. In such circumstances, it is discovered that diabetes-induced oxidative stress is caused by the down regulation of a number of antioxidant enzymes (Asmat *et al.*, 2016). Oxidative stress caused by hyperglycemia is a major factor in diabetes complications.

Esculetin inhibits serving three signaling pathways: p42/44 MAPK stimulation as well as a result of e-jun and c-fos immediate early genes (NF-kB), nuclear factor-kB and activator protein-1 activation, and cell cycle progression. It inhibits the tumor-necrosis treated factor vascular smooth muscle cells from migrating and invading, while also suppressing MMP-9 synthesis through NF-kappa B inhibition and AP-I binding activity without causing any harm (Lee et al., 2011). The results presented esculetin's medicinal potential in the treatment of atherosclerosis and cardiovascular disease.

Neurological Disorder

Esculetin has been revealed to cure neurological conditions by modulating a variety of physiological systems (Delogu and Matos, 2017). The G2019S mutation, which is associated 10 increased kinase activity, is more common than the LRRK2 mutation, which is the most common cause of familial Parkinson's disease. Esculetin has significant kinase inhibitory activity according to in vitro study the range of doses from 0.001 to 10 M, and is capable of preventing oxidative dysfunction, dopaminergic neuron loss, and locomotor abnormalities in neurons expressing G2019S. These results may be advantageous in the treatment of LRRK2-linked Parkinson's disease; moreover, esculetin may be used to treat Parkinson's disease, which is brought on by mitochondrial dysfunction, according to an in vivo study.

In Alzheimer's disease, esculetin activates Nr/2, raises glutathione levels, and shields cell damage caused by free radicals from oxidative stress and amyloid proteins (Lee et al. 2007). It has been found that H2O2 upregulates the production of MMP-1, producing oxidative stress and premature aging of the skin via initiating the MAPK or API signaling cascades. The method involves upregulation of intracellular Ca2+ levels induced by H2O2, inhibition of phosphor-SEK11, phosphor-MEK1, phosphor-ERK1/2, and phosphor-JNK 1/2 expression (Zhen et al., 2019). Esculetin has also been shown to protect human fibroblasts from DNA damage caused by oxidative stress, linoleic acid hydroxide, and iron (II) ions (Kaneko et al., 2003).

Renal Disease

High creatinine levels, microalbuminuria, and hyperuricemia are signs of renal disease. Esculetin is used to treat kidney failure since hyperuricemia and renal function frequently operate together (Hu et al., 2013). The oxonate-induced animal model is used to evaluate medications or potential treatments that reduce the total amount of uric acid in the plasma has been helpful. Hyperuricemia, which has previously been related to kidney injury, is the primary biochemical cause in gout (Dehghan *et al.*, 2008). Esculetin and its glycosylation product, esculin, were employed in an experimental setup, wherein the organic anion transporter 1, organic cation transporters (mOCTI and mOCT2), and carnitine transporters (mOCTN1 and mOCTN2) were examined for their expression levels.

Folklorie is used in the traditional Chinese remedies Bougainvlira and Cichorium intybus spectabillis, both of which contain esculetin, which includes long-term liver damage. This long-term use is beneficial and demonstrates that esculetin has anti-hepatotoxic effect based on animal research (Dong-Kug Choi and Palanivel Ganesan 2017). According to the histological investigation, esculetin was found to lowers oxidative stress in Tertiary-Butyl hydro peroxide induced rat liver lesion model by lowering liver cell edema, necrosis und leukocyte infiltration. Consequently, esculetin also act as a preventive measure by combining radical-producing substances to release hepatotoxicity.

Anti-inflammatory Effect

The basic root causes of atherosclerosis are the activation of inflammatory cells and a number of oxidative stress events caused by endothelial cell damage (Fuentes et al., 2017). Esculetin was considered to regulate the lipopolysaccharide-induced inflammation of intestinal micro vascular endothelial cells (Roman el al., 2020). Esculetin decreased the release of tumor necrosis factor, interleukin-1. Nitric Oxide that is produced by endothelial cells in the vascular system and has the ability to inhibit platelet adhesion as well as aggregation is essential for maintaining vascular homeostasis (Karnewar et al., 2016). Esculetin was found to significantly increase AMPK activity in H2O2-oxidized human umbilical vein endothelial cells. By increasing response to this stimulation, endothelial nitric oxide synthase is phosphorylated and NO levels were raised to minimize the HUVEC damage. Esculetin can be made in a variety of ways, is reliable and safe to use, and is easily absorbed by the body. Even though there hasn't been much clinical study on esculetin's ability to prevent atherosclerosis, tests conducted in vivo have shown that the substance has a high bioavailability. The most recent studies show that esculetin has a favorable and attractive anti-atherosclerotic activity. Despite the fact that there is still much to be done in this field, it is necessary to elucidate esculetin's molecular mechanism in the cure of atherosclerosis (Wang et al., 2022).

Conclusion

Human food includes flavonoids, which are helpful in chemicals that are bioactive in nature. The ways in which bioactive dietary components affect health. There is increasing evidence that flavonoids present in natural diet can play a role in disease prevention. Flavonoids' anti-inflammatory, antioxidant, and anti-carcinogenic effects are especially beneficial for the liver, pancreas, adipocytes, and brain cells. The development and disease resistance of plants are greatly influenced by flavonoids. They are a common in plant compound with a low molecular weight phenolic structure. Esculetin is a flavonoid extracted from certain herbal medicines such as Cortex Fraxini. Numerous studies have been conducted on the biochemical and pharmacological potentials of coumarin compounds specifically esculetin. This coumarin molecule protects against a wide range of ailments, including diabetes, inflammation and cancer, by Scavenging free radicals produced during oxidative stress. A variety of biological modes of action with an emphasis on cancer, oxidative stress, and fatty liver. Flavonoids are already being utilized to treat many different viral and degenerative illnesses, and future developments will definitely bring in a new era of pharmacological medicines based on flavonoids.

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