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A REVIEW ON PHARMACOLOGICAL BENEFITS OF POTENTIAL FLAVONOIDS – VICENIN-2

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ABSTRACT

Many traditional medicinal plants contain vicenin-2, which has been shown to have therapeutic properties. Vicenin-2 (apigenin-8-C-glucoside) has recently grown a lot of interest because of its diverse array of pharmacological actions, which include anti-oxidant, anti-cancer, anti-inflammatory, anti-hyperalgesic, and neuro-protective benefits, to highlight a few. Vicenin-2 has been recommended as a viable substitute therapy for a variety of disorders, as well as adjuvants for health supplements, according to recent research. This review compiled recent discoveries on vicenin-2's pharmacological actions and associated signalling pathways to serve as a resource for future research and therapeutic applications.[2]

KEYWORDS: Vicenin-2, Anti-inflammatory, Anti-cancer, Labiate, Flavonoids.

INTRODUCTION

Vicenin-2 (apigenin-8-C-glucoside) is a component found in a variety of traditional medicinal herbs. It's a c-glycosylated flavone found in Artemisia capillaries,[1] Urtica circularis,[2] Ocimum sanctum[3] among other therapeutic plants. Since flavonoids tending to show multiple pharmacological activities, Vicenin-2 has recently received increased attention due to its wide range of pharmacological effects, including anti-cancer,[4] anti-oxidant,[5] anti-inflammatory activities.[6-7] The effects are linked to multiple systems such as the central nervous system, the heart and vascular system, the endocrine system, et al.

Yet, due to a lack of understanding of their side effects and metabolism, as well as complex pharmacological actions and molecular mechanisms, the most of research is still in the pre-clinical phase. To serve as a reference for future clinical applications, this study gives a complete explanation of Vicenin-2 's pharmacological activities and mechanisms.

Phytochemical features of Vicenin-2

Flavones are a class of flavonoids, which name after their common yellow colour, that is, flavus. Flavones are based on the backbone of 2- phenylchromen-4-one (2-phenyl-1-benzopyran-4-one) (flavone).[8] Apigenin (4, 5,7-trihydroxyflavone) is one of typical natural flavones.[12] Vicenin-2 whose structures are shown in Fig. 1, belong to the class of flavones and are as derivatives of apigenin with 8/6-C-glucoside.[9] vicenin-2 is chemically known as 6,8-di-C-glucosyl-4',5,7-trihydroxyflavone or 8-D- Apigenin 6,8-di-C-glucoside 6,8-di-c-glucosylapigenin,[23] with molecular formula $C_{21}H_{30}O_{15}$, and molecular weight 594.5g/mol.[10-11]

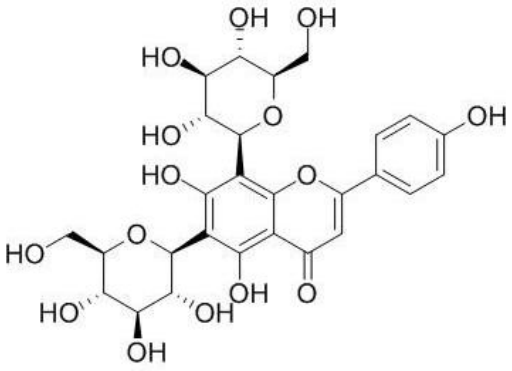

Fig. 1: Vicenin-2.

Plant resources distribution

Vicenin-2 was found in various plant families but mainly seen in flavonoid rich labiate family. Few members rich in Vicenin-2 in the family are Ocimum sanctum,[3] and Perilla frutescens, Teucrium fruticans L, Teucrium polium, Ocimum americanum, Mentha longifolia, Thymus piperella, Phlomis aurea.[11] The flavonoid is present in other family plats such as Artemisia capillaries, Perilla frutescens, Urtica circularis.[1-7]

Pharmacological properties

1. Anti-inflammatory effects

Inflammation is linked to the pathophysiology of a variety of clinical disorders. Because of their high efficacy in the treatment of pain, fever, and inflammation, no steroidal anti-inflammatory medications (NSAIDs) are among the most widely prescribed medicines.[13] The usage of NSAIDs, on the other hand, is linked to the emergence of side effects. Flavanoid class of compounds have been demonstrated to have an important part in the process of creation of novel treatment techniques for issues connected to Inflammation and

discomfort**.** Vicenin-2 was isolated and identified using a crude ethanol extract of Urtica circularis aerial parts. This crude extract was found to have a significant anti-inflammatory effect (41.5 % inhibition at a dose of 300 mg/kg; ip) in a carrageenan-induced rat hind paw edoema model. Vicenin-2, and a mixture of swertisin and iso-swertisin were detected in Cayaponia tayuya, Cucurbitaceae extract, which was identified as a mixture of flavonoids.[6] The anti-inflammatory action of flavonoids derived from tayuya roots is thought to be due to their suppression of COX-2 and iNOS production. It is widely established that secretory group IIA phospholipase A2 (sPLA2-IIA) expression is increased in inflammatory disorders, and that lipopolysaccharide (LPS) increases sPLA2-IIA expression in human umbilical vein endothelial cells (HUVECs). The medicinal herb Cyclopia subternata is often used in traditional medicine to reduce discomfort in biological processes. Vicenin-2 and scolymoside, two structurally related active compounds discovered in C. subternata, were tested for their impact on the expression and activity of sPLA2-IIA in HUVECs and mice. LPS-induced expression and activity of sPLA2-IIA were reduced by pre-treatment of cells or mice with vicenin-2 and scolymoside. LPS activation of cytosolic phospholipase A2 (cPLA2) and extracellular signal-regulated kinase (ERK) 1/2 was inhibited by each drug. As a result of the decrease of cPLA2 and ERK 1/2, vicenin-2 and scolymoside reduced LPS-mediated production of sPLA2-IIA.[7-8]

2. Antiseptic effects

HMGB1 (high-mobility group box protein) is a nuclear chromosomal protein that aids in the preservation of nucleosomal structure and stability, as well as the regulation of gene expression, by enabling transcription binding. Many studies in both experimental and clinical settings have recently revealed the role of extracellular HMGB1 in the pathophysiology of many inflammatory diseases, including sepsis. When organ failure, hypo perfusion, or hypotension are present, sepsis is a systemic reaction to a major infection with a bad prognosis. Studies proved that treatment with VCN and SCL would result in reduced mortality in our CLP induced sepsis mouse mode factors to their cognate DNA sequences.[12-13]

3. Hepato - Protective effects

Damage to the liver can result in a variety of liver illnesses, including liver failure. Hepatic fibrosis, cirrhosis, and cancer are all common complications of chronic hepatic dysfunction. Bacterial lipopolysaccharide (LPS), which is found in the outer membrane of all Gram-

negative bacteria, causes systemic inflammation and septic shock, as well as various organ failure. Liver failure due to severe hepatic damage characterises LPS-induced mortality. In animals, LPS has been used to imitate endotoxin-induced liver injury. LPS enhanced mortality, serum levels of alanine transaminase, aspartate transaminase, and inflammatory cytokines, as well as toll-like receptor 4 (TLR4) protein expression, all of which were significantly reduced by VCN or SCL. It also inhibited LPS-induced activation of the myeloid differentiation primary response gene and TLR-associated activator of interferon-dependent TLR signalling pathways. Vicenin-2 (VCN) and scolymoside (SCL), two structurally related flavonoids identified in Cyclopia subternata, inhibited LPS-induced liver failure in mice., suggesting that it could be used to treat liver disorders.[14]

4. Osteoporosis and Bone associated disorders

Osteoporosis has become one of the most serious public health problems in the world, with over 200 million people impacted by soreness and fissures at some point in their lives. Low bone density, deterioration of bone tissue, and disruption of bone micro-architecture are all symptoms of osteoporosis, which increase the risk of fractures. It affects a huge number of people, but its frequency may grow as people get older. Vicenin-2 was found to be an excellent option for treating bone-related illnesses. Vicenin-2 reduces osteoporosis in ovariectomized rats by raising body weight, maintaining uterine index, and restoring lipid levels, according to research. It also aided in the enhancement of ACP, BGP, and E2 expression in OVX rats. In the presence of Vicenin-2, serum inflammatory indicators, creatinine, phosphorus, TRAP, and calcium levels were also restored in OVX rats. In rats with OVX, vicenin-2 has a favourable influence on femoral stretch and other biomechanical parameters. Overall, the findings suggested that Vicenin-2 is an excellent candidate for treating bone-related illnesses.[15]

5. Renal protective effects

Despite recent breakthroughs in critical care, sepsis is a deadly infection that induces significant inflammatory reactions and is associated with a high rate of mortality. Although cytokine activation is a necessary aspect of the host's fight against infection, excessive cytokine production can result in significant damage and multiple organ failure. Related flavonoids found in Cyclopia subternata—vicenin-2 (VCN) and scolymoside (SCL)—could modulate renal functional damage in a mouse model of sepsis, Studies report that the

expression of plasma BUN and creatinine and urine protein levels were increased by CLP, but decreased by Vicenin-2 and SCL treatment.[16]

6. Anti- glycation properties

Diabetes mellitus (DM) is a metabolic endocrine illness in which the pancreatic hormone insulin fails to regulate carbohydrate and lipid metabolism appropriately, resulting in an elevated blood glucose level. Vicenin 2, a 6,8-di-C-glucoside of apigenin isolated from the traditional medicinal plant Artemisia capillaris, has been tested for anti-diabetic potential using a-glucosidase, protein tyrosine phosphatase 1B (PTP1B), rat lens aldose reductase (RLAR), and advanced glycation end products (AGE) formation inhibitory assays. In the similar experiments, vicenin 2 substantially inhibited a-glucosidase, PTP1B, and RLAR. Vicenin 2 also prevented the development of both fluorescent and nonfluorescent AGEs, such as CML, as well as the amount of fructosamine in glucose–fructose-induced BSA glycation. Vicenin 2 inhibited glycation-induced protein oxidation in the test system by reducing the production of protein carbonyl groups and decreasing the alteration of protein thiol groups. Vicenin 2 was also discovered to be a powerful inhibitor of glycation-induced amyloid cross-b structure formation in BSA. Vicenin 2 may be a promising lead for the development of a variety of target-oriented therapy methods for the treatment of diabetes and diabetes-related complications.[17]

7. Antithrombotic and antiplatelet activities of vicenin-2

The medicinal herb Cyclopia subternata is often used in traditional medicine to reduce discomfort in physiological processes. Vicenin-2 (VCN), an active component in C. subternata, was tested for anticoagulant and antiplatelet properties. Monitoring activated partial thromboplastin time (aPTT), prothrombin time (PT), and the activities of thrombin and activated factor X revealed anticoagulant activity (FXa). In TNF-activated human umbilical vein endothelial cells, the effects of VCN on the expression of plasminogen activator inhibitor type 1 (PAI-1) and tissue-type plasminogen activator (t-PA) were investigated (HUVECs). In HUVECs, VCN treatment resulted in prolonged aPTT and PT, suppression of thrombin and FXa activities, and inhibition of thrombin and FXa generation. VCN also stopped platelet aggregation and thrombin-catalyzed fibrin polymerization. In mice, VCN had an anticoagulant effect. Furthermore, VCN therapy resulted in a considerable decrease in the PAI-1 to t-PA ratio. VCN, taken as a whole, has antithrombotic properties and could be used to produce a new anticoagulant.[18-20]

8. Trypanocidal activity

The hemoflagellate protozoan Trypanosoma cruzi causes human Chagas disease (American trypanosomiasis), which can be transmitted congenitally or by blood transfusion by blood-sucking triatomine bugs. This is a devastating parasitic disease that affects Latin America and has significant social and economic consequences. In vitro testing of crude extracts of Lychnophora pohlii against trypomastigote forms of Trypanosoma cruzi revealed that the dichloromethane and methanol crude extracts from leaves and inflorescences have trypanocidal activity. In the methanol extract, bioassay-guided fractionation produced seven active compounds, including vicenin-2.[20]

9. Healing effect

Chronic wounds are a major health-care and economic concern worldwide, particularly for people with hyperglycaemia. Surprisingly, a sophisticated wound dressing containing a synthetic medicinal molecule embedded in a natural polymer compound that works as a drug release carrier has shown promise in treating wounded wounds. Low concentrations of Vicenin-2 (VCN-2) compound greatly increased HDF cell proliferation and migration, according to studies. In wound repair, it also controlled the production of pro-inflammatory cytokines such IL-6, IL-1, and TNF-. The expression of TGF-1 and VEGF wound repair maker was also aided by VCN-2 treatment in a dose-dependent manner. A hydrocolloid film based on sodium alginate (SA) and VCN-2 synthetic molecule was successfully produced and optimised for its physiochemical properties with the goal of promoting wound healing, particularly in diabetes patients.[22]

10. Anti-oxidant effects

Oxidative stress at the cellular or subcellular level is a deleterious process that can be an important mediator of damage to cell structures and, consequently, various disease states. In addition, reactive oxygen radicals induced lipid peroxidation in cellular membranes and generate lipid peroxides, which caused extensive damage to membranes and Membrane - mediated chromosomal damage. Thus, the anti-oxidant effects of some medicinal plants have garnered scientific interests; analysing their ingredients for bioactive chemical, a wide range of studies including classical in vitro chemical-based assays and cellular assays, which have comprehensively described their anti-oxidant properties in various aspects. Comparatively, chemical-based assays are more economical, high-throughput and comparable. The effect of orientin and vicenin on radiation-induced lipid peroxidation in vivo and their antioxidant

activity in vitro were proved. The antioxidant activity of orientin/vicenin (10–500 μM) was studied by measuring inhibition of hydroxyl radicals generated by the Fenton reaction.[3]

11. Antineoplastic effects

Anticancer drugs, often known as antineoplastic agents, are a wide and diverse class of medications. They have a limited but crucial utility, and they frequently cause hepatotoxicity. Prostate cancer (CaP) is the second largest cause of cancer death in men in the United States, trailing only lung cancer. The fact that one out of every three men develops prostatic intraepithelial neoplasia is alarming (PIN). CaP is characterised by the beginning of precancerous PIN, followed by the loss of the basal lamina and transformation to locally invasive carcinoma, which proceeds to metastatic CaP. Vicenin- 2 in combination with docetaxel synergistically inhibited the growth of prostate tumors in vivo with a greater decrease in the levels of AR, pIGF1R, pAkt, PCNA, cyclin D1, Ki67, CD31, and increase in E-cadherin.[24]

The anticancer effect of vicenin-2 was assessed with three different hepatocellular carcinoma cell lines and their effect of induction of apoptosis was also assessed with immune blotting analysis. To confirm the anticancer effect of vicenin-2, the xenografted hepatocellular mice model was treated with vicenin-2 and analysed for tumour size reduction and apoptotic induction. Vicenin-2 significantly inhibited the STAT3 protein expression even in the presence of IL-6 and EGF induction.[25]

NSCLC is a type of lung cancer that has a high incidence and is resistant to chemo- and radiation. VCN-2 flavonoid derived from Ocimum has been shown in studies to be a potential chemotherapeutic and radio sensitizing agent in NSCLC.[26]

Helicobacter pylori (H. pylori), a Gram-negative bacteria that causes stomach cancer, has been identified as the leading cause of human gastric cancer (GC). Vicenin-2 inhibits H. pylori-induced gastric carcinogen signalling in human stomach epithelial cells, according to research (GES-1). According to in vitro cytotoxicity experiments, 40 μM of vicenin-2 protects gastric cells dramatically, and this concentration also exhibits 85 % cell survival while causing no toxicity. Furthermore, vicenin-2 protects H. pylori-infected individuals against enhanced antioxidant depletion caused by reactive oxygen species, DNA damage, malondialdehyde, and nuclear fragmentation.[27]

12. Anti-viral and Anti-microbial effects

Ocimum sanctum has Vicenin-2 as an important active ingredient and possess several pharmacological properties. Essential oils and extracts of Ocimum species possess the compounds involved in antiviral and antimicrobial properties. In addition, this plant contains certain nutrients which boost the immune system.[29-30]

DISCUSSIONS

Flavonoids were discovered to have a wide range of bioactivities, including anti-oxidant and anti-inflammatory characteristics, anti-neoplasia effects, cognitive effects, cardiovascular disease protection, anti-diabetic effects, and many more. Structure of phenolic hydrogen in their molecules, especially o-tri- or o-dihydroxyl structure in the A or B ring, may be the active group, based on the structure of flavonoids and known evidences for their bioactivities. There may also be skeleton structure fit for certain proteins, based on the structure of flavonoids and known evidences for their bioactivities. They have common bioactivities as 8/6-C-glucoside derivatives of apigenin, a well-known flavone, and their unique properties are attributable to their chemical structure. Their common o-di-hydroxyl structure in the A ring, for example, has been shown to contribute to the effective radical scavenger, and the presence of C-8 glucoside boosts vicenin-2's antioxidant efficacy by decreasing the negative charge on the oxygen atom at C-. Research on the biological activity of flavonoids is significant not only because of its uses, but also because it adds to our understanding of the link between flavonoids and human health. Apoptosis signalling pathway; inflammatory cytokines network, MAPK pathway, and HIF-1, P53, Ca2+ signalling pathway, as well as other possible molecular targets related to free radicals, -glucosidase and -amylase, cytochrome P450, and others have been proposed in the literature to explain their pharmacological effects. However, the findings should be viewed with caution because many of them are based on small studies, and further research is needed to validate and verify those chains. The anti-inflammatory actions of vicenin-2 include inhibition of pro-inflammatory cytokines such as IL-1, IL6, IL-8, TNF-, and others, as well as an increase in anti-inflammatory cytokines such as IL-10. These findings could indicate possible therapeutic effects in inflammatory illnesses.

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