



AN OVERVIEW OF THERAPEUTIC EFFECTS OF VANILLIC ACID

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Abstract

Vanillic acid (VA) is a derivative of benzoic acid which is used as a flavouring agent, preservative, and food additive in the food industry. VA is phenolic molecule that is oxidized molecule of vanillin. VA is obtained from the several cereals such as whole grains; herbs; fruits; green tea; juices; beers and wines. It is known to have various pharmacological properties such as antioxidant, anti-inflammatory, immuno-stimulating, neuroprotective, hepatoprotective, cardioprotective, and antiapoptotic. It is reported that Vanillic acid have the potential to attenuates A β 1-42-induced cognitive impairment and oxidative stress therefore contributes to treatment of Alzheimer's disease. Now days, work is going on to investigate that how the vanillic acid produces neuroprotective effect via acting on oxidative stress. Vanillic acid is found in abundance in Black sesame pigment which is used as a food supplement for the prevention of Alzheimer's Disease. In this review, we reviewed the neurological effects of vanillic acid.

Keywords : Vanillic acid, therapeutic effects, neuroprotective, antioxidant.

Introduction

Natural compound are always prime choice for the treatment of various diseases. Various researchers explore natural compounds in in-vitro and in-vivo studies. Researchers also use PASS software to predict the therapeutic activity of the phytochemicals (Kumar *et al.*, 2018; Kumar *et al.*, 2018). These are basically phenolic compounds or standardized extracts of particular plant like: Hesperidine (Habibyar *et al.*, 2016), Boswellic acid (Mehta *et al.*, 2018), INM-176 (Kumar *et al.*, 2017), Extract of sida cordifolia (Khurana *et al.*, 2017a, 2017b, 2016), Withania somnifera (Jassal and Kaur, 2016), Alpinia galangal (Malik *et al.*, 2016), Plumbago auriculata (Jaryal and Kaur, 2017), Artemisia indica (Nahid *et al.*, 2017), Moringa oleifera (Kumar *et al.*, 2012), Psidium guajava (Mehta *et al.*, 2011), Paris polyphylla (Mayirnao and Bhat, 2017), Heracleum afghani kitamura (Amini *et al.*, 2017), Betain (Kaur *et al.*, 2019), Fisetin (Kumar *et al.*, 2019) Gallic acid (Manshare *et al.*, 2018; Pandey *et al.*, 2015) Sinomenium (Gupta *et al.*, 2019) Curcumin (Busari *et al.*, 2017; Garg *et al.*, 2019; J. Kaur *et al.*, 2017; M. Kaur *et al.*, 2017; Kaur *et al.*, 2018; Som *et al.*, 2020; Y.S. *et al.*, 2015; Khursheed *et al.*, 2019) Quercetin (Chellappan *et al.*, 2019; Khursheed *et al.*, 2020; Singh Joshan and Singh, 2013) Epigallocatechin gallate (Anand *et al.*, 2017) etc. VA is a naturally occurring phenolic acid (conjugated acid of vanillate). It is obtained from plant *Angelica sinensis* used in the traditional chinese medicine (Imming *et al.*, 2010). It has a solid appearance, melting point of 211.5 degree Celsius, solubility of 1.5 mg/ml at 14 degree Celsius. Vanillin widely used in food industry, cosmetics and pharmaceuticals as a flavouring agent (Imming *et al.*, 2010). As per research outcomes, VA is the intermediate compound after bioconversion of ferulic acid (FA) to vanillin. When vanillin gets oxidized, it produces chlorogenic acid. VA is also produced when caffeic

acid get metabolised (Overington and Al-Lazikani, 2012). It is a monohydroxybenzoic acid substituted by methoxy group at position 3. It possesses antioxidant, hepatoprotective, cardioprotective, and antiapoptotic activities. Some phenolic compounds such as hispidulin and nepetin were found to possess immunosuppressive property whereas vanillic acid in the same study was found to possess immunostimulating potential. It has a pleasant and creamy odour therefore used as a flavouring agent. VA is known to selectively and specifically inhibit 5' neucleotidase activity. The anti-inflammatory effects and action on oxidative stress of vanillin, vanillin acid and vanillyl alcohol are well established (Calixto-Campos *et al.*, 2015). VA has role in neurological disorders. It attenuates β -amyloid that is pathogenesis of Alzheimer's disease in oxidative stress induced model (DeCS, 2018 ; Amin *et al.*, 2017). It along with other metabolites is used for establishing prognosis in Parkinson's Disease. (Han and Sapkota, 2017).

Source

It is obtained from plant *Angelica sinensis* used in the traditional chinese medicine. The presence of VA is also reported in many research that VA is obtained from the various cereals such as whole grains; herbs; beers; wines; fruits; herbs; green tea and juices (Overington and Al-Lazikani, 2012; Amin *et al.*, 2017)

Synonyms

Benzoic acid; m-Anisic acid; 4-Hydroxy-3-methoxybenzoic acid; 3-Methoxy-4-Hydroxybenzoic acid; 4-Hydroxy-3-methoxybenzoic acid; 4-hydroxy; Protocatechuic acid; 3-methyl ester; p-Vanillic acid; NSC 3987; NSC 674322; and Acidevanillique (Overington and Al-Lazikani, 2012; Amin *et al.*, 2017)

Formula and Molecular weight

Formula: C₈H₈O₄ (Overington and Al-Lazikani, 2012; Amin *et al.*, 2017)

Molecular weight: 168.1467 (Overington and Al-Lazikani, 2012; Amin *et al.*, 2017) Structure

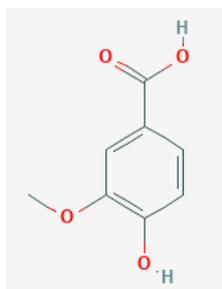


Fig. 1 : Structure of Vanillic Acid
(Overington and Al-Lazikani, 2012)

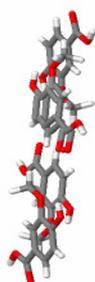


Fig. 2 : 3D structure of Vanillic acid (Overington and Al-Lazikani, 2012)

Therapeutic Effects

Oxidative stress and inflammatory response regulation

A research literature reported that VA and its metabolite vanillyl have various pharmacological activities. As it is known that inflammation is hall mark of various known as well new diseases those are having less therapeutic options, for fighting with these all there is a need to develop and search molecules/drug those have the capability to modified the inflammatory process. Therefore, in this review we made an attempt to collect the information regarding the reported therapeutic activities of vanillin and its main metabolites for the treatment of inflammatory diseases (Bezerra-Filho CSM *et al.*, 2019).

At present, it is not known that with which mechanism VA exerts its anti-inflammatory effects. An attempt has been made to evaluate that how the VA attenuate the lipopolysaccharide (LPS) induced inflammatory response in the peritoneal macrophages of the mouse. The results showed that VA inhibits the creation of tumor necrosis factor (TNF- α) and interleukin (IL-6) which was increased the existence of LPS (Kim *et al.*, 2011).

Behaves similar to oestrogen over MAP kinase-mediated ER signaling pathway

Since thousands of years, VA is used to cure the bone and joint disease *Sambucus williamsii* Hance (SWH) in China. A research study was conducted on SWH extract that is bioactive fraction. SWH can effectively treat the bone loss ovariectomized, induced model of oestrogen deficiency in mice. A study postulated that VA was observed to have substantial stimulation in proliferation, alkaline phosphatase

(ALP) actions which simultaneously transformed the mRNA expression of genes that involved in osteoblast functions and osteoclastogenesis in UMR 106 cells. (Xiao *et al.*, 2014). The findings of the study were:-

Attenuation of obesity via activation of the AMPK pathway

Obesity, is known for years as the cause of many health-related problems. It leads to the incidence of hepatic steatosis, type 2 diabetes, inflammation and various types of cancer. The obesity epidemic has steadily increased in recent years. Approximately 70% of American adults are overweight. As a result, the quality of life is decreasing while morbidity and economic damages are increasing. It is reported that administration of VA in induced High-fat diet (HFD) mice model showed suggestively attenuated body weight. The peroxisome markers and adipogenic proliferator level activated receptor γ (PPAR γ). The CCAAT/enhancer-binding protein α (C/EBP α); get decreased; while the level of AMPK α enhanced in the white adipose tissue after VA administration. From these results it can be concluded that VA has the potential to activate the AMPK α - and to act as thermogenesis compound in treating obesity. Adipogenesis is related to the aetiologies of obesity and other obesity-related metabolic disorders. Adipocytes (in mammals) are divided into 2 types, white and brown, which have opposite functions. White adipocytes store excess energy in the form of triglycerides, while brown adipocytes release energy through thermogenesis (Jung *et al.*, 2018).

Vanillic acid exerts ER-dependent actions in ligand-independent non-genomic manner

Bone protective effects of vanillic acid.

Vanillic acid exerts Oestrogen like effects.

Fig. 2 : Investigated activities of VA (Xiao *et al.*, 2014)

Lipogenesis is an important mechanism for fat accumulation. The most important causes of liver fat accumulation is the inhibition of AMPK. AMPK is an enzyme that acts as an energy homeostasis maintainer in cells. It is involved in the energy metabolism of organs including liver, muscle, and fat tissue.

Activation of AMPK causes phosphorylation of the enzyme acetyl-CoA carboxylase (ACC). The ACC enzyme for synthesizing malonyl-CoA which is an important

precursor in fatty acid synthesis as it potentially inhibits its oxidation in mitochondria. To study in detail the mechanisms of hepatic steatosis, human HepG2 cells were treated with free fatty acids including palmitic acid and oleic acid, the main FAs in the human body in order to develop a cellular hepatic model. A study showed that VA caused inhibition of intracellular TG in 3T3-L1 adipocytes. The purpose was to evaluate the antiobesity and thermogenic potential of VA and to confirm the mechanisms regarding the AMPK pathway *in vivo* and *in vitro* (Jung *et al.*, 2018).

Effect on antioxidant status in diabetes and hypersensitivity

A study was reported in which research evaluate the effect of VA on diabetes. High fat diet model of rat obesity was used. Diet was given to animals for 20 weeks. The VA was administered in a dose of 50 mg/kg for the last 8 weeks. They estimate the different biological parameters like: level of glucose, plasma insulin, blood pressure, oxidative stress parameters, antioxidant enzymes, liver and kidney function. Their result showed a positive effect of VA on these all parameters when compared to the disease control animals. The results of histopathology study also favour the VA for treating the obesity. These results suggest that VA have a good potential in the treatment of diabetes. (Vinothiya and Ashokkumar, 2017)

Inhibition of inflammatory pain

Phenolic compounds are mostly used for their antioxidant effect, these compounds are present in various plants. As these compounds have the potential to treat various kinds of human diseases, they received a good attention. But, the actual mechanism by which they treat the diseases is still unknown. From a study which done using murine model of inflammation it was concluded that VA exerts anti-inflammatory and analgesic action by reducing manufacture of pro-inflammatory cytokines (Calixto-Campos *et al.*, 2015).

Role of VA in various disorders

Cytoprotective effects on methylglyoxal induced apoptosis in Neuro-2A cells

In a study, chlorogenic acid; phenolic acids; syringic acid and vanillic acid were evaluated in methylglyoxal induced mouse model in which neuro-2A neuroblastoma (neuro-2A) cell apoptosis was under the progression of diabetic neuropathy. In research, it was found that methylglyoxal induces cell apoptosis in mice Neuro-2A neuroblastoma (Neuro-2A) cell by altering membrane potential of mitochondria and Bax/Bcl-2 ratio (Huang *et al.*, 2008).

Effect on mutants of COQ6 identified in patients with coenzyme Q₁₀ deficiency

CoQ is performed by monooxygenase enzyme which is encoded by Human COQ6. Deficiency of CoQ occurs whenever there is Mutations in COQ6. To treat this condition oral CoQ₁₀ supplementation is given. As the CoQ₁₀ have the poor bioavailability so the treatment I problematic. As per the research review, it was speculated that "*S. cerevisiae*" is lacking the orthologous gene was used to characterize the two different human COQ6 isoforms. This study also suggested that COQ6 isoform *a* can moderately complement

the defective yeast. But, isoform *b* lacks part of the FAD-binding domain (Doimo *et al.*, 2014).

Protection against benzo(a)pyrene induced lung cancer

In a study it is reported that VA have the potential to protect the benzo pyrene induced lung cancer. They use Swiss albino mice for the study. B(a)P (50 mg/kg body wt.) was administered o the mice in order to produce lung cancer. VA was used at dose of 200mg/kg along with B(a)P. it was observed that when VA is given to the mice along with disease inducing agent a significant recovery from the disease was there when compared to the animals in which only disease inducing agent is give. From this study it is also concluded that VA represents its effect by acting as a free radical scavenging compound (Velli and Sundaram, 2019).

Mitigation the ovalbumin (OVA)-induced asthma

VA also reported to have the anti-asthmatic activity. In the study asthma was induced in the rats by using ovalbumin (OVA). VA was used at two dose level that is 25 and 50 mg/kg body weight orally. The study was performed for 28 days. It was observed that VA treat the manifestations of asthma in a dose-dependently manner. The potential of VA to treat the manifestations of the asthma may be due to its potential to suppress the oxidative stress parameters and pro-inflammatory cytokines in the lung airway inflammation (Bai *et al.*, 2019).

Role of VA in neurological disorders

Neuroprotective role

VA reported to have various neuroprotective effects (Anand *et al.*, 2019). Ischemia is one of the leading causes of the neurological disturbance. Many of the neuroprotective strategies have been investigated in order to decrease ischemia induced cognitive deficits. In a study, animal model (Bilateral Common Carotid Artery Occlusion and Reperfusion) was explored to estimate the neuroprotective potential of VA. It was observed that the spatial memory restored when treatment with VA was given for 14 consecutive days. The level of inflammatory marker that TNF and IL-6 was found to decreased in treatment animals. In a study data, VA can better serve for hopeful, accessible and novel neuroprotective agent in treatment of vascular dementia and cerebrovascular insufficiency states (Khoshnam *et al.*, 2018; Koshnam and Farbood, 2018).

Clerodendrum petasites S. Moore is a Thai traditional medicine, prescribed to treat asthma, fever, inflammation, vomiting, cough, and also dermal conditions since 30 years. In this study, flavones, phenolic acids, flavone glycosides, glycosides and diterpenoid phenylpropanoid are the main phytoconstituents of this herbal plant. In its ethanolic extract hispidulin was discovered as a predominant constituent followed by verbascoside, nepetin, apigenin and vanillic acid. Hispidulin, being responsible for curing cancer, neurological diseases and osteolytic bone diseases on the other hand other compounds including VA that was found to treat inflammation and also in neurodegenerative disorders (Brimson *et al.*, 2019).

The millions people around the world are affected from neuroinflammation. This interference of stress as well as injury. It acquaintances neurodegenerative diseases such as Parkinson disease (PD); Alzheimer's disease (AD); and multiple sclerosis (MS). These all types of neurological

diseases is characterised by the synaptic loss and demyelination. The neuroinflammation response is propagated by modulation of extracellular matrix proteins and the activation of glial cells. In a study, an anti-inflammatory effect of GA (1.0 μM) and VA (0.2 μM) on lysolecithin (LPC, 0.003%) induced model were studied. The hippocampal neurons were isolated and co-cultured with glial cells. Morphometry software was used to measure neurite outgrowth. Immunostaining and western blotting methods/techniques were used to determine the level of myelination and demyelination. In order to observe the repetitive firing pattern of whole-cell patch clamp recordings. The result exhibited that gallic acid (GA) and VA increased the neurite outgrowth in culture after 48 hours. The both of them significantly reduced the expression of, NF κ B, COX-2, tenascin-C. The myelin protein was upregulated by VA and GA treatment (Khoshnam *et al.*, 2018; Koshnam and Farbood, 2018).

The treatment of Alzheimer's Disease

AD is the most basic type of dementia and it occurs among elderly people (Sharma *et al.*, 2017). During AD level of acetylcholine (ACh) in the brain get decreased. Due to this metabolism of metals get disturbed, level of oxidative reactive species get increased and accumulation of β -amyloid (A β) protein starts. The accumulation of β -amyloid (A β) is the hall mark of AD. In general, A β is found to be the main culprit of a cascade process followed by synaptic dysfunction, aggregation and tau protein hyperphosphorylation, oxidative stress and neuroinflammation would then follow eventually leading to neurotransmitter deficits and neuronal death. Black Sesame Pigment (BSP) is a extract of black seasame seeds reported to have anti-oxidant and metal binding properties. Using HPLC analysis it was observed that BSP under the simulated gastrointestinal digestion at particular pH it get converted into another molecule. When, that molecule was analysed it found that the new molecule was the VA. From, this study we can conclude that if we use BSP as food supplement prevention of AD can be done (Panzella *et al.*, 2018). VA released form BSP upon simulated gastrointestinal digestion reported to have AChE and BChE activity (Khoshnam *et al.*, 2018; Koshnam and Farbood, 2018) as well as it also reported to inhibit the aggregation of A β 1-40 protein (Panzella *et al.*, 2018).

In neurodegeneration and neuroinflammation

In a study, it was observed that VA have the potential to treat the streptozotocin induced neurodegeneration in mice. During study the researcher evaluate the various behavioural and biochemical parameters. They reported that VA produces a dose dependant positive effect on behavioural and biochemical parameters which are in the favour of VA to treat the neurodegeneration (Singh *et al.*, 2015).

In cerebral hyperemia and anxiety

A study was conducted in order to check the effect of VA in ischemia reperfusion induced injury in brain of the rats. This model was used for the study "transient bilateral common carotid artery occlusion" (tBCCAO) and followed by reperfusion. For testing of the VA certain physiological parameters were analysed like cerebral hyperemia; anxiety behaviour; neurological deficits and blood-brain barrier (BBB) interruption induced by bilateral occlusion of the

basic carotid arteries and reperfusion. This study revealed that VA have the potential to treat the reactive hyperemia and can prevent the disruption of BBB (Khoshnam and Farbood, 2018).

Summary and Conclusion

VA is a promising, accessible and novel neuroprotective agent in treatment of vascular dementia and cerebrovascular insufficiency states. It also has an significant role in the treatment of inflammation and also in neurological diseases. Neuroinflammation, as a result of stress or injury affects the people around the world. It represents almost all types of diseases related to neurological disorders like Alzheimer's disease and Parkinson's Disease. This shows that VA can be used as the ingredient of functional food and as a food supplement for the prevention of neurological disorders. It can also treat vascular dementia and cerebrovascular insufficiency states.

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