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Review Paper

## A Review of the Pharmacological Characteristics of Vanillic Acid

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### Abstract

A dihydroxybenzoic acid analog used as a flavoring agent is vanillic acid (4-hydroxy-3-methoxybenzoic acid). It's a form of vanillin that has been oxidized. It's also a step in the process of making vanillin from Ferulic Acid. Vanillic acid has seen a lot of press because of its many uses in the cosmetics, fruit, flavorings, cigarettes, alcohols, drinks, and polymer sectors. It's said to have effective antioxidant, anti-inflammatory, and neuroprotective properties. The pharmacological impact on oxidative stress-induced neuro-degeneration, on the other hand, have not been thoroughly examined. The pharmacological properties of vanillic Acid lead to its possible use in the treatment of various diseases.

**Keywords:** Vanillic acid, Pharmacological Potential, wound healing, Antioxidants

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## 1. INTRODUCTION

Vanilla beans contain the largest concentration of vanillic acid (4-hydroxy-3-methoxybenzoic acid). It can be present in a variety of species, including the Chinese medicinal plant *Angelica sinensis*, benzoin, soybeans, olives, among many others.<sup>1</sup> It occurs as a white/yellow powder or crystals with a good creamy odor, and is thus used as a fragrance and flavoring agent.<sup>2</sup> Natural vanillic acid can be found in a variety of foods, including oranges, guava, sherry, rice grains, brandy, bourbon, scotch, and Canadian whisky, as well as red and white wines. Vanillic acid has seen a lot of press because of its many uses in the cosmetics, fruit, flavorings, cigarettes, pharma, alcohols, drinks, and polymer sectors. However, separating it from fermentation broths and wastewater from olive oil mills, as well as the paper and pulp industries, remains a difficult task.<sup>3</sup> The isolation of vanillic acid from aqueous sources was studied in this paper using liquid-liquid extraction. Calculating the partition coefficient, dimerization constant, distribution coefficient, and extraction efficiency are used to determine equilibrium.<sup>4</sup> The extraction ability is given in terms of extraction efficiency and distribution coefficient followed a trend: 1-octanol (54.07%) > isobutanol (51.73%) > toluene (45.23%) > xylenes mix (35.47%) > petroleum ether (31.54%) > benzene (30.44%). The obtained results were discussed with help of acid properties, type of solvent used, and their physicochemical properties such as dipole moment (Dm), dielectric constant ( $\epsilon$ ), solvent polarity parameter (ET), solubility in water, octanol-water partition coefficient (log Kow), etc.<sup>5</sup> This is the first research to use the extractive separation approach to isolate or recover vanillic acid from aqueous solutions using the solvents described above.<sup>6</sup>

## 2. PHARMACOLOGICAL ACTION

### 2.1 Sedative activity:

The ethanol extract of *Vernonia patula* (VP) aerial parts demonstrated strong antinociceptive behavior when examined in acetic acid-induced writhing and formalin-induced paw-licking experiments.<sup>7</sup> It also significantly delayed the onset of sleep, increased the length of sleeping time, and significantly decreased locomotor activity and exploratory behavior in mice in neuropharmacological studies.<sup>8</sup> Following HPLC-DAD study, five phenolic compounds were found in VP: gallic acid, vanillic acid, caffeic acid, quercetin, and kaempferol. The presence of these phenolic compounds in VP lends credence to the antinociceptive and sedative effects observed.<sup>9</sup> The cannabinoid type 1 (CB1) receptor binding affinity of gallic acid, vanillic acid, caffeic acid, quercetin, and kaempferol was predicted using a statistical analysis.<sup>10</sup> The most likely ligand efficiency indices against the CB1 target is caffeic and vanillic acid. Vanillic acid has the highest estimation score for blood-brain barrier penetration. These results support the long-held belief that VP can be used to relieve pain.<sup>11</sup>

### 2.2 Antidepressant effects:

Depression is a common psychological ailment that affects up to 20% of the global population. Traditional Chinese medicine (TCM), with its unusual curative role in the treatment of depression, is gaining popularity as pharmaceutical firms rush to produce new antidepressant drugs.<sup>12</sup> This article reviews studies on TCM natural products that have been reported to have antidepressant effects in the last two decades, and which can be categorized

based on different pathways such as increasing monoamine synaptic concentrations, alleviating hypothalamic-pituitary-adrenal (HPA) axis dysfunctions, decreasing neuroplasticity impairment, and battling depression.<sup>13</sup> Saponins, flavonoids, alkaloids, polysaccharides, and other antidepressant active ingredients have all been reported.<sup>14</sup> Albiflorin, Baicalein, Berberine chloride, beta-Asarone, cannabidiol, Curcumin, Daidzein, Echinocystic acid (EA), Emodin, Ferulic acid, Gastrodin, Genistein, Ginsenoside Rb1, Ginsenoside Rg1, Ginsenoside Rg3, Hederagenin, Hesperidin, Honokiol, Hyperoside, Icariin, Isoliquiritin, Kaempferol, Liquiritin, L-theanine, Magnolol, Paeoniflorin, Piperine, Proanthocyanidin, Puerarin, Quercetin, Resveratrol (trans), Rosmarinic acid, Saikosaponin A, Senegenin,

Tetrahydroxystilbene glucoside and Vanillic acid are Specified in this review. Simultaneously, chemical structures of the active ingredients with antidepressant activities are listed and their sources, models, efficacy and mechanisms are described.<sup>15</sup> Antidepressant Chinese compound prescriptions and extracts are now added, which may serve as a source of inspiration for future study.<sup>16</sup> According to the findings of this review, some TCMs have an antidepressant effect that is positive and motivating. However, much work continues to be done in order to ascertain the precise medicinal effects and pathways of certain active ingredients, especially in order to create a unified standard for diagnosis and assessment of curative action.<sup>17</sup>

**Table 1: Plant Contain Vanillic Acid and Its Reported Activity**

Sr.No	Activity	Plant Name	family	Extract of plant	Part of plant	Reference
1	Sedative activity	Vernonia patula	<i>Asteraceae</i>	Ethanol extract	Aerial part	[7][8][9][11]
2	Antidepressant effects	Panax ginseng	<i>Araliaceae</i>	methanolic extracts	Root	[12][13][14][15][16][17]
3	Antinociceptive effects	Lithraea molleoides	<i>Anacardiaceae</i>	Dichloromethane extract	Leaves,bud,& Stems	[18][19][20][21][22][23]
4	Hypertension	Angelica sinensis	<i>Apiaceae</i>	ethyl acetate extract	Root	[24][25][26][27][28]
5	ulcerative colitis effects	Angelica sinensis	<i>Apiaceae</i>	ethyl acetate extract	Root	[29][30][31][32]
6	Anticancer effects	Camellia sinensis	<i>Theaceae</i>	Ethanol extract	Leaves	[33][34][35][36][37]
7	Antifungal activities	Thecacoris annobonae Pax	<i>Phyllanthaceae</i>	methanol extract	Stems bark	[38][39][40]
8	Hepatoprotective activity	Lentinula edodes	<i>Marasmiaceae</i>	seed extracts	Whole plant	[41][42][43][44][45]
9	Wound healing activity	Panax ginseng	<i>Araliaceae</i>	methanolic extracts	Root	[46][47]
10	Antioxidant activity	Cyathobasis fruticulosa	<i>Amaranthaceae</i>	methanol extract	Plant tissues	[48][49][50][51][52]

### 2.3 Antinociceptive effects:

Many plants used in herbal medicine contain high levels of vanillic acid. It has been linked to a number of pharmacologic effects, including carcinogenesis inhibition, apoptosis, and inflammation, but it is well known for its pleasant creamy odor.<sup>18</sup> Since there are few studies on this phenolic compound's antinociceptive function, the aim of this research was to investigate it in vivo animal models.<sup>19</sup> The intraperitoneal administration of vanillic acid resulted in dose-dependent suppression of the acetic acid-induced writhing reaction (ED50:9.3mg/kg).<sup>20</sup> Pretreatment with ondansetron and yohimbine inhibited the antinociceptive function, suggesting that the serotonin ergicandad renergicsy stems could be involved in the pathway underlying vanillic acid's analgesic activity.<sup>21</sup> In vivo, this compound was shown to interact with ASICs (Acid-sensing Ion Channels) as well as TRPV1, TRPA1, and TRPM8 receptors. Additionally, vanillic acid has little effect on locomotory activity or muscle control.<sup>22</sup> The t<sub>1/2</sub> and AUC of plasmatic phenolic content were 0.123 and 1.38g•h/mL, respectively, as determined by HPLC. Finally, vanillic acid

could be a promising medicinal alternative for the management of pain.<sup>23</sup>

### 2.4 Hypertension:

In adult male albino Wistar rats treated with N-Nitro-L-arginine methyl ester hydrochloride (L-NAME), the antihypertensive and antioxidant ability of vanillic acid (VA) was examined.<sup>24</sup> In contrast to the control group, rats given L-NAME (40 mg/kg Bw for 30 days) had a persistent rise in systolic (SBP) and diastolic (DBP) blood pressure, as well as a substantial decrease in nitrite/nitrate (NO<sub>x</sub>) concentration in plasma.<sup>25</sup> SBP and DBP in rats treated with VA were restored to normal levels, although plasma NO metabolites concentrations were maintained. Furthermore, VA greatly recovered enzymatic antioxidants (superoxide dismutase, catalase, and glutathione peroxidase), non-enzymatic antioxidants (vitamin C, vitamin E), and lipid peroxidation products (thiobarbituric acid reactive compounds, lipid hydroperoxides, conjugated dienes).<sup>26</sup> Hepatic and renal function indicators were assessed to see if VA therapy caused any toxicity. The effect of 50 mg/kg Bw VA was more pronounced than the other two doses, 25 and 100 mg/kg

Bw, according to our findings. (#27) Hepatic and renal function indicators were assessed to see if VA therapy caused any toxicity. The effect of 50 mg/kg Bw VA was more pronounced than the other two doses, 25 and 100 mg/kg Bw, according to our findings. <sup>27</sup> Histopathology research backed up these findings. In L-NAME-induced hypertensive rats, VA has antihypertensive and antioxidant properties. <sup>28</sup>

## 2.5 Ulcerative colitis effects:

Vanillic acid is a benzoic acid derivative that is used as a flavoring agent. It is an oxidized form of vanillin. The aim was to see if vanillic acid could help people with ulcerative colitis caused by dextran sulfate sodium (DSS). <sup>29</sup> Our findings revealed that vanillic acid decreased the severity of DSS-induced colitis clinical symptoms, such as weight loss and colon length shortening, as well as the disease activity index. Vanillic acid inhibited the expression of cyclooxygenase-2 and the activation of transcription nuclear factor- $\kappa$ B p65 in DSS-treated colon tissues, according to the findings. <sup>30</sup> Furthermore, plasma levels of interleukin (IL)-6 were higher in the DSS-treated group than in the control group, but these higher levels were decreased by vanillic acid administration. <sup>31</sup> These results indicate that vanillic acid has a protective effect against DSS-induced ulcerative colitis, suggesting its utility in the management of chronic intestinal inflammation. <sup>32</sup>

## 2.6 Anticancer effects:

Hypoxia-inducible factor 1 (HIF-1) is a significant factor in tumor tolerance to microenvironmental hypoxia, as well as angiogenesis and tumor growth. <sup>33</sup> Vanillic acid is a phenolic compound found in foods that has been shown to have anticancer properties. The mechanisms by which vanillic acid inhibits tumor development, however, remain unknown. The effect of vanillic acid on HIF-1 activation was investigated in this study. <sup>34</sup> In different human cancer cell lines, vanillic acid inhibits HIF-1 expression caused by hypoxia. Vanillic acid prevented the synthesis of HIF-1 protein, according to further research. Vanillic acid had no effect on the rate of HIF-1 protein degradation or the steady-state levels of HIF-1 mRNA. <sup>35</sup> Vanillic acid also inhibited HIF-1 expression by suppressing the rapamycin/p70 ribosomal protein S6 kinase/eukaryotic initiation factor 4E-binding protein-1 and Raf/extracellular signal-regulated kinase (ERK) kinase (MEK) kinase (ERK) kinase (MEK) kinase (ERK) kinase (ERK) Vanillic acid inhibited VEGF and EPO protein expression and disrupted tube formation in a dose-dependent manner, according to our findings. <sup>36</sup> The findings indicate that vanillic acid prevents angiogenesis effectively. Vanillic acid significantly induced G1 phase arrest and prevented the proliferation of human colon cancer HCT116 cells, according to flow cytometry study. Vanillic acid therapy inhibited tumor growth substantially in a xenografted tumor model, according to in vivo studies. These findings show that vanillic acid is an important HIF-1 inhibitor and shed light on the mechanism of its antitumor activity. <sup>37</sup>

## 2.7 Antifungal activities:-

Mitsunobu technique was used to synthesize four castor oil fatty acid-based novel lipoconjugates of phenolic acids. The phenolic moieties are ferulic and vanillic acid, and the lipid component is made up of methyl ricinoleate and its saturated analogue, methyl-12-hydroxystearate. <sup>38</sup> Synthetic compounds are compared to three commonly used antioxidants in the food industry, BHT, atocopherol, and dodecyl gallate, in three in vitro assays (DPPH radical scavenging assay, DSC tests for oxidative induction temperature of linoleic acid, and autoxidation of linoleic acid

in Tween 20 micellar medium). <sup>39</sup> The antiradical activity of synthesised compounds has been discovered to be very good. These compounds also had a lot of antifungal activity against the fungal strains that were tested. All of these findings indicated that the synthesized compounds could be used as effective lipophilic antioxidants in the fight against oxidative stress. <sup>40</sup>

## 2.8 Hepatoprotective activity:-

The edible mushroom *Lentinula edodes*' mycelia can be cultured in lignin-rich solid medium, and the hot-water extracts (L.E.M.) are commercially available as a dietary supplement. During cultivation, the lignin-degrading peroxidase secreted by *L. edodes* mycelia formed phenolic compounds such as syringic acid and vanillic acid. <sup>41</sup> We investigated their protective effect on oxidative stress in mice with CCl<sub>4</sub>-induced liver injury because these compounds have radical scavenging activity. On CCl<sub>4</sub>-induced chronic liver injury in mice, the hepatoprotective effects of syringic acid and vanillic acid were investigated. <sup>42</sup> The serum levels of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) increased after CCl<sub>4</sub> was injected into the peritoneal cavity. The levels of transaminases were substantially reduced when syringic acid and vanillic acid were administered intravenously. Four weeks of CCl<sub>4</sub> therapy resulted in a reasonable amount of collagen fibril deposition. <sup>43</sup> Syringic acid and vanillic acid clearly suppressed collagen aggregation and significantly decreased hepatic hydroxyproline content, which is a quantitative marker of fibrosis, according to Azan-stained liver parts. <sup>44</sup> Both of these compounds held hepatocyte viability while inhibiting the activation of cultured hepatic stellate cells, which play a key role in liver fibrogenesis. These results indicate that syringic and vanillic acid administration may minimize hepatic fibrosis in chronic liver injury. <sup>45</sup>

## 2.9 Wound healing activity:

Skin care products containing Panax ginseng C.A. Meyer are commonly used. The phenolic acids in ginseng root extract (GRE) have been shown to inhibit melanogenesis in a previous study. Vanillic acid, the most abundant portion of phenolic acids in GRE, suppressed the expression of microphthalmia-associated transcription factor (MITF) and melanogenic enzyme *sin3B16F10* cells and decreased tyrosinase activity and melanin levels with or without -MSH stimulation. <sup>46</sup> NOS activity, nitric oxide (NO) content, cGMP level, guanylate cyclase (GC) and protein kinase G (PKG) activity, and the phosphorylation of cAMP-response element-binding protein (CREB) were all reduced by vanillic acid, while arbutin had no effect on the NO/PKG pathway. These findings suggest that vanillic acid in GRE inhibited the NO/PKG signaling pathways, thus suppressing melanogenesis. This research reveals a possible mechanism for ginseng's melanogenesis inhibitory effect. <sup>47</sup>

## 2.10 Antioxidant activity:

Diabetes has become much more common across the world as a result of widespread behavioral and dietary changes. In humans and animals, high-fat diets are closely linked to the development of obesity and can cause insulin resistance. <sup>48</sup> Obesity is undeniably a risk factor for the onset of type 2 diabetes. Using a rat model, we explored the therapeutic potential of vanillic acid on diabetes-related complications in this report. Rats were given a high fat diet (HFD) for 20 weeks and then given vanillic acid (50 mg/kg bw) for the last eight weeks to make them diabetic and hypertensive. <sup>49</sup> The effects of vanillic acid on glucose, plasma insulin, systolic and diastolic blood pressure, thiobarbituric acid

reactive substances (TBARS), hydroperoxides as a lipid peroxidation marker, and the activities of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), reduced glutathione (GSH), vitamin C and vitamin E as an antioxidant marker, AST and ALT as a liver function marker, urea, uric acid and creatinine as a kidney function marker were investigated.<sup>50</sup> The histopathology of the liver and kidney was also looked at as part of the diabetes pathology. When diabetic rats were given oral vanillic acid at a dosage of 50 mg/kg/body weight for 8 weeks, their fasting plasma glucose, insulin, and blood pressure levels were significantly lower than in the diabetic control group.<sup>51</sup> In diabetic hypertensive rats treated with vanillic acid, antioxidant activities were significantly improved and lipid peroxidation markers were significantly reduced. These findings indicate that vanillic acid has a modulatory impact on diabetic hypertension regulation by lowering blood glucose, insulin, and blood pressure while also combating oxidative stress via tissue activation.<sup>52</sup>

### 3. CONCLUSION

In the treatment of vascular dementia and cerebrovascular insufficiency states, vanillic acid is a promising, affordable, and novel neuroprotective agent. It has recently been the focus of extensive studies, and it has shown its effectiveness as a pharmacotherapeutic agent in a variety of diseases. Aside from the antioxidant action of the majority of compounds in the vanillic acid class, i.e. phenolic compounds, it has also been stated to function at the molecular level. Vanillic acid is an excellent candidate for more systematic and detailed analysis. It may be a potential treatment option for a variety of severe diseases.

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