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VANILLIN: A COMPREHENSIVE REVIEW OF PHARMACOLOGICAL ACTIVITIES

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Abstract

Vanillin is the chief constituent of the vanilla bean extract obtained from the seed pods of *Vanillus planifolia* belonging to the family Orchidaceae. Nowadays, synthetic vanillin is being preferred as a flavouring agent in foods, beverages and pharmaceuticals. Chemically, it is a phenolic aldehyde with the molecular formula $C_8H_8O_3$. Over years it has been used as a flavor in sweet foods like chocolates & ice creams, in cosmetics like perfumes, and in pharmaceuticals to mask the unpleasant odor and tastes in medicines. Also, vanillin-HCl is extensively used a visualizing agent in Thin Layer Chromatography. Quite recently, vanillin has been studied by researchers all over the world for its pharmacological effects. The compound has exhibited remarkable effects in treatment and management of several pathological conditions. This review focuses on the different reported pharmacological activities of vanillin.

***Keywords*:** Antioxidant, Alzheimer's disease, flavouring agent, neuroprotection, pharmacological effects, vanillin

Introduction

Recently, there has been increasing research in the field of natural foods, specifically with respect to the additives such as flavouring agents and preservatives. Amidst the variety of flavouring agents of natural origin being used today, vanilla encompasses a prominent place in the market. It has been extensively used for the preparation of cakes, soft drinks, ice creams, chocolates, liquors, perfumes, pharmaceuticals, and nutraceuticals (Ranadive, 1992). Natural vanilla is a concoction of components extracted from the cured pods of different Vanilla species: *Vanillus planifolia* and *Vanillus tahitensis* (Ramachandra Rao & Ravishankar, 2000). However, due to its pod quality and yield *V. planifolia* is valued the most (Sinha, Sharma, & Sharma, 2008).

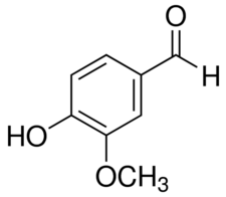

Fig. 1: Chemical structure of 4-Hydroxy-3-methoxybenzaldehyde (Vanillin) (CAS No. 121-33-5)

The flavour profile of vanilla comprises of more than 200 constituents, only 26 of which occur in amounts greater than 1 mg/kg. The aroma and flavour of vanilla extract is attributed mainly to presence of vanillin (Figure 1), which occurs in a concentration of 1-2% w/w in vanilla pods (Bettazzi, Palchetti, Sisalli, & Mascini, 2006; Sinha et al., 2008; Westcott, Cheetham, & Barraclough, 1993)

1.1 Physical and Chemical Properties

Table 1: Various properties of vanillin

Parameter	Description	Reference
Molecular weight	152.149 g/mol	(PubChem, 2017)
Appearance	White or very slightly yellow needles	(PubChem, 2017)
Odour	Pleasant aromatic vanilla odor	(The Merck Index Online, 2013)
Taste	Pleasant vanilla taste	(The Merck Index Online, 2013)
Boiling point	285 deg C	(The Merck Index Online, 2013)
Melting point	81-83 deg C	(Sigma-Aldrich, 2017)
Flash point	153 deg C	(Sigma-Aldrich, 2017)
Solubility	125 parts of water, 20 parts of glycerine, 2 parts of 95% alcohol, chloroform and ether	(PubChem, 2017)
Density	1.056	(The Merck Index Online, 2013)
Vapour pressure	1.18 X 10^{-4} mm Hg at 25 deg C	(PubChem, 2017)
Partition coefficient	log $K_{o/w}$ = 1.37	(PubChem, 2017)
Stability	Photosensitive, gradually oxidizes in presence of moisture	(The Merck Index Online, 2013)
Auto ignition	>400 deg C	(PubChem, 2017)
Decomposition	Emits acrid smoke and irritating fumes	(PubChem, 2017)
pH	Acidic to litmus	(The Merck Index Online, 2013)

(i) Safety and Toxicology

Table 2: Safety and Toxicological Profile of Vanillin

Parameter	Description
LD_{50} (Oral) Acute	1580 mg/kg (*Rattus norvegicus*), 3925 mg/kg (*Mus musculus*), 1400 mg/kg (*Cavia porcellus*)
LD_{50} (Dermal) Acute	5010 mg/kg (*Oryctolagus cuniculus*)
Health hazards (Acute)*	Hazardous if comes in contact with eyes, if ingested, or if inhaled. Slightly harmful in case of dermal contact
Health hazards (Chronic)**	Slightly harmful in case of dermal contact. No data available for carcinogenicity, mutagenicity, teratogenicity, developmental toxicity

* It may lead to irritation in eyes, mucous membrane, respiratory tract and skin. It may be absorbed dermally. Ingestion may lead to irritation in gastrointestinal tract and may also adversely influence the cardiovascular system, respiratory system, liver (causing jaundice), urinary system, nervous system (causing muscle weakness, somnolence, coma).

** Repeated or prolonged inhalation may ensue undesirable effects on the brain and blood (alterations in the count of white and red blood cells). Repeated or prolonged ingestion may adversely influence the urinary system, liver, heart, and metabolism (causing weight loss) (NLM Toxnet Toxicity Data Network, 2015).

(ii) Pharmacokinetics

Pharmacokinetics of vanillin following p.o. administration have been established by a study involving rats. The parameters are listed in Table 2.7 (Beaudry, Ross, Lema, & Vachon, 2010).

Table 3 : Pharmacokinetic parameters of vanillin (p.o.)

Parameter	Value
C_{max}	290.24 ng/mL
T_{max}	4h
Relative clearance	62.17 L/h/kg
$t_{1/2}$	10.3h
Bioavailability	7.6%

Reported Pharmacological Properties

(i) Parkinson's disease

Parkinson's disease (PD) is a major neurodegenerative disease, second only to Alzheimer's disease (AD). It generally affects the geriatric population. The characteristic symptoms of PD are TRAP i.e. tremors, rigidity, akinesia, postural instability. It occurs due to a significant degeneration of the dopaminergic neurons in Substantia Nigra Pars Compacta (Depboylu *et al*., 2011). Vanillin has been reported to have neuroprotective effect on rotenone induced PD in male Wistar rats. Rotenone model is advantageous over other animal models of PD as it mimics both kinds of symptoms – motor and non-motor (Barbiero *et al*., 2011; Lima, Reksidler, & Vital, 2009). The study reported that oral administration of vanillin alleviated motor and non-motor impairments, oxidative stress, neurochemical deficits and apoptosis due to rotenone. Vanillin elicited a remarkable neuroprotective activity by inhibiting the peroxynitrite induced reactions and lipid peroxidation due to reactive oxygen species. It also exhibited an enhancement in activities of the innate enzymatic antioxidant mechanisms. Additionally, it also crosses the Blood Brain Barrier (Dhanalakshmi, Manivasagam, Nataraj, Justin Thenmozhi, & Essa, 2015a).

(ii) Alzheimer's disease

AD is the most common form of dementia which is associated with significant decline in memory and cognitive processes (Anand, Khurana, Chawla, Sharma, & Khurana, 2017). It is one of the top five causes of mortality in the US (Centers for Disease Control & Prevention, 2017). The disease involves deterioration of cholinergic system in brain, increased activity of glutamate leading to excitotoxicity, deposition of amyloid beta plaques and tau neurofibrillary tangles in brain (Allen & Dawbarn, 2011; Francis, 2005). The current pharmacotherapy of AD (acetylcholinesterase inhibitors, NMDA glutamate antagonist) is based on providing symptomatic relief only (Anand, Patience, Sharma, & Khurana, 2017). Recently, in an *in vitro* study, vanillin has been reported to have a disintegratory effect on amyloid beta plaques (Song *et al*., 2016). It suggests that vanillin may have a disease modifying effect in AD. Additionally, vanillin has been reported to have antioxidant effects *in vivo* (Dhanalakshmi, Manivasagam, Nataraj, Justin Thenmozhi, & Essa, 2015b). Oxidative stress plays a major role in pathology of AD (Huang, Zhang, & Chen, 2016). Also, vanillin has been reported to possess an acetylcholinesterase inhibitory activity. It could thereby lead to restoration of levels of acetylcholine in brains of patients suffering from AD, causing an improvement in memory and cognitive abilities (Kundu & Mitra, 2013). Therefore, vanillin could have multifactorial effects in delaying or halting the progression of AD.

(iii) Huntington's disease

Huntington's disease (HD) is a form of dementia that is generally seen in very young age (30-50). However, it may also appear at 2 years of age or even at 80 years. It occurs due to a single defective gene on fourth chromosome. It involves a remarkable decline in reasoning and thinking, abnormal involuntary actions, mood swings, depression and irritability (Alzheimer's Association, 2017). Vanillin has been reported to have an ameliorating effect in HD as a combination therapy with agomelatine. It has been shown that vanillin has mitochondrial protective effects. Also, the protective mechanism of vanillin may be attributed to its activating effect on antiapoptotic pathways via mitochondria (Gupta & Sharma, 2014). The beneficial effect of vanillin in HD are also reported to be by the virtue of its anti-inflammatory and antioxidant effects (Dhanalakshmi *et al*., 2015b). Treatment with vanillin ameliorated 3-nitropropionic acid induced impaired mitochondrial enzyme complexes (I, II, and IV) in experimental model of Huntington's disease. Also, it led to inhibition of singlet oxygen-induced protein and lipid oxidation (Dhanalakshmi, Manivasagam, Nataraj, Justin Thenmozhi, & Essa, 2015c).

(iv) Depression

National Institute of Mental Health (NIMH), a unit of National Institute of Health (NIH) defines depression as a common but serious mood disorder. The symptoms affect the way the patient feels, handles routine chores (such as sleeping, working or eating), and thinks (National Institute of Mental Health, 2016). Vanillin has been reported to have an anti-depressant activity comparable to the marketed drug fluoxetine. The anti-depressant effect has been attributed to the agonistic action on α2 adrenergic receptors and opioid receptors. Also, the antioxidant property of vanillin has been reported to contribute to the effect (Shoeb, Chowta, Pallempati, Rai, & Singh, 2013). A study also reported that vanillin elevates the levels of monoamine neurotransmitters i.e. dopamine and serotonin in brain, thereby alleviating chronic depressive symptoms (Xu, Xu, Liu, He, & Li, 2015). Vanillin has also been reported to restore the behavioural and biochemical alterations linked with stress (Abo-youssef, 2016).

(v) Antimutagenic Effect

Mutations refer to alterations in the genetic sequence, on various levels, in the cells of an organism. Often, these mutations lead to cancers and other genetic disorders (Loewe, 2008). Vanillin has been reported to have an inhibitory effect on chromosomal aberrations due to mitomycin C and hydrogen peroxide (Keshava, Keshava, Ong, & Nath, 1998). Also, it has been proven to inhibit the mutations on the hprt locus due to UV and X-rays. Another study suggested that vanillin can inhibit the DNA repair process thereby killing the potential mutants while enhancing the DNA repair mechanisms. It has been reported that vanillin has an inhibitory effect on mutations on CD59 locus, induced by hydrogen peroxide and N-methyl-N-nitrosoguanidine and mitomycin C (Gustafson *et al*., 2000). Vanillin may exhibit its antimutagenic effect by inducing or inhibiting certain enzymes. It induces cytosolic glutathione S-tranferase, inhibits the metabolism of 4-(methylnitosoamino)-1-(30pyridyl)-1-butanone and inhibits human liver sulfotransferases (Aboobaker, Balgi, & Bhattacharya, 1994; Bamforth, Jones, Roberts, & Coughtrie, 1993; Morse, Kresty, & Toburen, 1995). A study proposes that vanillin exhibits its antimutagenic effect by enhancing recombination and DNA repair at homologous sites in damaged cells (Tamai, Tezuka, & Kuroda, 1992).

(vi) Antineoplastic Effect

Neoplasm may be defined as an abnormal mass of tissue which occurs either when cells divide at rate faster than normal or do not die when they should. Neoplasms may be benign (non-cancerous) or malignant (cancerous). These are also known as tumours (National Cancer Institute, 2017). Natural products and bioactive phytoconstituents play a major role in antineoplastic drug development (Carvalho *et al*., 2015; Sobral, Xavier, Lima, & de Sousa, 2014). The antimutagenic and ant carcinogenic effects of vanillin may be attributed to its antioxidant activity. On the other hand, its anti-metastatic, antiangiogenic and cytotoxic activities may be due to the prooxidant vanillin radicals. Ontologically, the genes downregulated by vanillin could be classified into three categories i.e. regulation of cell cycle, cellular process and death. A majority of the genes downregulated by vanillin were those linked with progression of cancers (Bezerra, Soares, de Sousa, & Pergentino, 2016). Vanillin has been reported to have remarkable antineoplastic effects in several systemic malignancies (Kapoor, 2013). It has exhibited antitumerogenic effects in gastrointestinal cancers. Vanillin at high concentrations leads to arrest of G2/M phase of cell cycle, while at lower concentrations it causes the arrest of G0/G1 phase (Ho, Yazan, Ismail, & Ismail, 2009). Vanillin has also been reported to have an inhibitory effect on tumour growth in hepatocellular carcinomas by attenuating the expression of Matrix Metalloproteinase-9 within the neoplasm (Liang, Wu, Lo, Hsiang, & Ho, 2008). Vanillin has also been reported to enhance TRAIL-induced apoptosis in cancerous cells by inhibiting the activation of NF-kappaB (Lirdprapamongkol *et al*., 2010).

Conclusion

Plants and derived phytoconstituents provide a vast avenue for pharmacological research. In the modern age, adjunct plant based therapy is being adopted along with allopathic treatment for better results. Vanillin is such a versatile phytoconstituent that has been in use since ages as a flavouring agent in foods, beverages, cosmetics, etc. In the recent past, it has been subjected to rigorous research and it has proven its potential to be a pharmcotherapeutic agent in several diseases. Apart from the known antioxidant activity of a majority of compounds of the class vanillin belongs to i.e. phenolic compounds, it has been reported to act at molecular levels as well. Vanillin is a substantial candidate to be put under more structured and elaborate research. It may emerge as a promising candidate for treatment of a wide array of serious diseases.

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References

Abo-youssef, A.M. (2016). Possible antidepressant effects of vanillin against experimentally induced chronic mild stress in rats. Beni-Suef University Journal of Basic and Applied Sciences, 5(2): 187–192.

Aboobaker, V.S.; Balgi, A.D. and Bhattacharya, R.K. (1994). In vivo effect of dietary factors on the molecular action of aflatoxin B1: role of non-nutrient phenolic compounds on the catalytic activity of liver fractions. In Vivo (Athens, Greece), 8(6): 1095–8.

Allen, S.J. and Dawbarn, D. (2011). ONL Alzheimer's Disease. (Waldemar G & B. A, Eds.), Oxford Medicine Online. Oxford Medicine Online.

Alzheimer's Association. (2017). Huntington's Disease. Retrieved from http://www.alz.org/dementia/huntingtons-disease-symptoms.asp

Anand, A.; Khurana, P.; Chawla, J.; Sharma, N. and Khurana, N. (2017). Emerging treatments for the behavioral and psychological symptoms of dementia. CNS Spectrums, 1–9.

Anand, A.; Patience, A.A.; Sharma, N. and Khurana, N. (2017). The present and future of pharmacotherapy of Alzheimer's disease: A comprehensive review. European Journal of Pharmacology.

Bamforth, K.J.; Jones, A.L.; Roberts, R.C. and Coughtrie, M.W. (1993). Common food additives are potent inhibitors of human liver 17 alpha-ethinyloestradiol and dopamine sulphotransferases. Biochemical Pharmacology, 46(10): 1713–20.

Barbiero, J.K.; Santiago, R.M.; Lima, M.M.S.; Ariza, D.; Morais, L.H.; Andreatini, R. and Vital, M.A.B.F. (2011). Acute but not chronic administration of pioglitazone promoted behavioral and neurochemical protective effects in the MPTP model of Parkinson's disease. Behavioural Brain Research, 216(1): 186–192.

Beaudry, F.; Ross, A.; Lema, P.P. and Vachon, P. (2010). Pharmacokinetics of vanillin and its effects on mechanical hypersensitivity in a rat model of neuropathic pain. Phytotherapy Research, 24(4): 525–30.

Bettazzi, F.; Palchetti, I.; Sisalli, S. and Mascini, M. (2006). A disposable electrochemical sensor for vanillin detection. Analytica Chimica Acta, 555(1): 134–138.

Bezerra, D.P.; Soares, A.K.N.; de Sousa, D.P. and Pergentino, O. (2016). Overview of the Role of Vanillin on Redox Status and Cancer Development. Oxid Med Cell Longev, 2016,

Carvalho, A.A.; Andrade, L.N.; de Sousa, É.B.V.; de Sousa, D.P.; de Sousa, D. and Pergentino, O. (2015). Antitumor Phenylpropanoids Found in Essential Oils. BioMed Research International, 1–21.

Centers for Disease Control, & Prevention. (2017). Leading Causes of Death. CDC. Retrieved from https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

Depboylu, C.; Schäfer, M.K.-H.; Arias-Carrión, O.; Oertel, W.H.; Weihe, E. and Höglinger, G.U. (2011). Possible Involvement of Complement Factor C1q in the Clearance of Extracellular Neuromelanin From the Substantia Nigra in Parkinson Disease. Journal of Neuropathology & Experimental Neurology, 70(2): 125–132.

Dhanalakshmi, C.; Manivasagam, T.; Nataraj, J.; Justin Thenmozhi, A. and Essa, M.M. (2015a). Neurosupportive Role of Vanillin, a Natural Phenolic Compound, on Rotenone Induced Neurotoxicity in SH-SY5Y Neuroblastoma Cells. Evid Based Complement Alternat Med, 1–11.

Dhanalakshmi, C.; Manivasagam, T.; Nataraj, J.; Justin Thenmozhi, A. and Essa, M.M. (2015b). Neurosupportive Role of Vanillin, a Natural Phenolic Compound, on Rotenone Induced Neurotoxicity in SH-SY5Y Neuroblastoma Cells. Evid Based Complement Alternat Med, 1–11.

Dhanalakshmi, C.; Manivasagam, T.; Nataraj, J.; Justin Thenmozhi, A. and Essa, M.M. (2015c). Neurosupportive Role of Vanillin, a Natural Phenolic Compound, on Rotenone Induced Neurotoxicity in SH-SY5Y Neuroblastoma Cells. Evidence-Based Complementary and Alternative Medicine, 1–11.

Francis, P.T. (2005). The interplay of neurotransmitters in Alzheimer's disease. CNS Spectrums, 10(11 Suppl 18): 6–9.

Gupta, S. and Sharma, B. (2014). Pharmacological benefits of agomelatine and vanillin in experimental model of Huntington's disease. Pharmacol Biochem Behav, 122: 122–135.

Gustafson, D.L.; Franz, H.R.; Ueno, A.M.; Smith, C.J.; Doolittle, D.J. and Waldren, C.A. (2000). Vanillin (3-methoxy-4-hydroxybenzaldehyde) inhibits mutation induced by hydrogen peroxide, N-methyl-N-nitrosoguanidine and mitomycin C but not (137)Cs gamma-radiation at the CD59 locus in human-hamster hybrid A(L) cells. Mutagenesis, 15(3): 207–13.

Ho, K.; Yazan, L.S.; Ismail, N. and Ismail, M. (2009). Apoptosis and cell cycle arrest of human colorectal cancer cell line HT-29 induced by vanillin. Cancer Epidemiology, 33(2): 155–160.

Huang, W.-J.; Zhang, X. and Chen, W.-W. (2016). Role of oxidative stress in Alzheimer's disease. Biomedical Reports, 4(5): 519–522.

Kapoor, S. (2013). Multiorgan Anticarcinogenic Effects of Vanillin. Journal of Medicinal Food, 16(9): 777–777.

Keshava, C.; Keshava, N.; Ong, T.M. and Nath, J. (1998). Protective effect of vanillin on radiation-induced micronuclei and chromosomal aberrations in V79 cells. Mutation Research, 397(2): 149–59.

Kundu, A. and Mitra, A. (2013). Flavoring Extracts of Hemidesmus indicus Roots and Vanilla planifolia Pods Exhibit *In vitro* Acetylcholinesterase Inhibitory Activities. Plant Foods for Human Nutrition, 68(3): 247–253.

Liang, J.-A.; Wu, S.-L.; Lo, H.-Y.; Hsiang, C.-Y. and Ho, T.-Y. (2008). Vanillin Inhibits Matrix Metalloproteinase-9 Expression through Down-Regulation of Nuclear Factor-κB Signaling Pathway in Human Hepatocellular Carcinoma Cells. Molecular Pharmacology, 75(1).

Lima, M.M.S.; Reksidler, A.B.B. and Vital, M.A.B.F. (2009). The Neurobiology of the Substantia Nigra Pars Compacta: from Motor to Sleep Regulation. Journal of Neural Transmission. Supplementum, 73(73): 135–145.

Lirdprapamongkol, K.; Sakurai, H.; Suzuki, S.; Koizumi, K.; Prangsaengtong, O.; Viriyaroj, A.; … Saiki, I. (2010). Vanillin enhances TRAIL-induced apoptosis in cancer cells through inhibition of NF-kappaB activation. *In Vivo* (Athens, Greece), 24(4): 501–6.

Loewe, L. (2008). Genetic Mutation. Retrieved from https://www.nature.com/scitable/topicpage/genetic-mutation-1127

Morse, M.A.; Kresty, L.A. and Toburen, A.L. (1995). Inhibition of metabolism of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone by dietary benzaldehydes. Cancer Letters, 97(2): 255–61.

National Cancer Institute. (2017). Neoplasm. Retrieved from https://www.cancer.gov/publications/dictionaries/cancer-terms?cdrid=46264

National Institute of Mental Health. (2016). Depression. Retrieved from https://www.nimh.nih.gov/health/topics/depression/index.shtml

NLM Toxnet Toxicity Data Network. (2015). VANILLIN - National Library of Medicine HSDB Database. HSDB.

Retrieved from https://toxnet.nlm.nih.gov/cgi-bin/sis/search/a?dbs+hsdb:@term+@DOCNO+1027

PubChem. (2017). Vanillin. Retrieved July 4, 2017, from https://pubchem.ncbi.nlm.nih.gov/compound/vanillin

Ramachandra Rao, S. and Ravishankar, G. (2000). Vanilla flavour: production by conventional and biotechnological routes. Journal of the Science of Food and Agriculture, 80(3): 289–304.

Ranadive, A.S. (1992). Vanillin and related flavor compounds in vanilla extracts made from beans of various global origins. Journal of Agricultural and Food Chemistry, 40(10): 1922–1924.

Shoeb, A.; Chowta, M.; Pallempati, G.; Rai, A. and Singh, A. (2013). Evaluation of antidepressant activity of vanillin in mice. Indian J Pharmacol, 45(2): 141–144.

Sigma-Aldrich. (2017). Vanillin (Vanillic aldehyde). Retrieved July 4, 2017, from http://www.sigmaaldrich.com/catalog/product/sigma/v2375?lang=en&region=IN

Sinha, A.K.; Sharma, U.K. and Sharma, N. (2008). A comprehensive review on vanilla flavor: Extraction, isolation and quantification of vanillin and others constituents. International Journal of Food Sciences and Nutrition, 59(4): 299–326.

Sobral, M.V.; Xavier, A.L.; Lima, T.C. and de Sousa, D.P. (2014). Antitumor Activity of Monoterpenes Found in Essential Oils. The Scientific World Journal, 1–35.

Song, S.; Ma, X.; Zhou, Y.; Xu, M.; Shuang, S. and Dong, C. (2016). Studies on the interaction between vanillin and β-Amyloid protein via fluorescence spectroscopy and atomic force microscopy. Chemical Research in Chinese Universities, 32(2): 172–177.

Tamai, K.; Tezuka, H. and Kuroda, Y. (1992). Different modifications by vanillin in cytotoxicity and genetic changes induced by EMS and H_2O_2 in cultured Chinese hamster cells. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis, 268(2): 231–237.

The Merck Index Online. (2013). Vanillin. Retrieved from https://www.rsc.org/Merck-Index/monograph/m11390/vanillin?q=unauthorize

Westcott, R.J.; Cheetham, P.S.J. and Barraclough, A.J. (1993). Use of organized viable vanilla plant aerial roots for the production of natural vanillin. Phytochemistry, 35(1): 135–138.

Xu, J.; Xu, H.; Liu, Y.; He, H. and Li, G. (2015). Vanillin-induced amelioration of depression-like behaviors in rats by modulating monoamine neurotransmitters in the brain. Psychiatry Research, 225(3): 509–514.