Original Article

Vanillin- More Than A Flavouring Agent: A Review On Its Bioactive Properties

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Abstract

Vanillin, the white crystalline aromatic component of Vanilla orchid, renowned to be its the primary flavour component, has wide ranging lucrative applications not only in the food industry, but also in the perfumery, cosmetics, metal plating and most essentially, in the pharmaceutical industry. Vanillin has been recognised to have various medicinal properties like antioxidant, antitumor, anticancer, antiviral, antibacterial, antifungal, neuroprotection, anti-quorum sensing activity, etc., and have extensive applications in the treatment of Parkinson's disease; hypertension, upper respiratory tract infections and venereal diseases etc. In this review, we have attempted to focus on the bioactive properties of vanillin considering its potentially emerging pharmacological significance.

Keywords: Vanillin, Bioactive properties, Antioxidant activity, Anticancer activity, Antibacterial activity.

INTRODUCTION

Vanillin, an aromatic compound, also known with various names like- 4-hydroxy-3-methoxybenzaldehyde, vanillic aldehyde, vanillaldehyde, 3-methoxy-4-hydroxybenzaldehyde, methyl-protocatechualdehyde and *p*-vanillin [1,2], is found widely in nature, especially in the seed pods of the plant genus *Vanilla*, viz., *Vanilla planifolia*, *Vanilla pompona* and *Vanilla tahitensis* [3]. It is the primary component among about 200 other flavour components found in vanilla beans [4]. This white needle-like crystalline powder possesses the aldehydic, etheric and phenolic functional groups and has molecular formula $C_8H_8O_3$, analogous to a molecular weight of 152.15 [1]. It has a characteristic pleasant aromatic vanilla odour and an intensively delicate and mellow flavour which are the main factors behind its worldwide demand as one of the most popular flavouring material in the food industry. It is extensively used as an additive in many processed foods like chocolates, ice creams, maple syrups, confectionery, coffee, raspberry ,olive oil, oatmeal, clove oil, baked goods and beverages, etc., with normal concentrations ranging from 50 to 1000 ppm, depending on the product category. In addition, it has wide applicability as an ingredient in perfumes, cosmetics and in the pharmaceutical and metal plating industry. It has also become an imperative deodorant to disguise unpleasant odours of various medicines, cleaning products, and many other manufactured goods, like plastics, rubber goods and paper products, etc., [5-8].

Vanillin has applications in various drugs like - L-dopa used for the cure of Parkinson's disease; Aldomet, used as anti-hypertension and Trimethoprim, used for the cure of infections related to upper respiratory tract and different types of venereal ailments [9]. Besides, other miscellaneous uses of vanillin are – as antioxidant in linseed oil, anti-foaming materialfor lubricant, attractant for insecticides, brightener for zinc coating baths, catalyst in polymerization of methyl methacrylate, neutralizing agent for tobacco induced mouth dehydration, solubilising material for riboflavin, commonly used stain for TLC plate development, radiocarbon dating agent and in the investigation of the tannin localization in cells. A vigilant assessment of vanillin levels in lignin artefacts may assist in revealing its age [10-12]. However, only 0.2% of the total universal market place necessity of vanillin is obtained from vanilla orchid, and most of the commercial vanillin are obtained from other sources like, various lignin waste materials, clove oil eugenol, guaiacol, ferulic acid, etc., [7, 13].

From various studies, it has been observed that vanillin exhibits quite a range of medicinal properties, like antioxidant, antitumour, anticancer, antiviral, antibacterial, antifungal, neuroprotective and anti-quorum sensing ability etc., and its medicinal properties may be further advantageous for human wellbeing and healthiness than that had been formerly believed [10, 11, 14-18]. Because of the potentially emerging reports of wide ranging applicability of vanillin as a curative agent along with its addition as a food preservative on the GRAS material list, it becomes a superlative compound for medicinal purposes [15, 19]. Thus, considering the significance of vanillin in its wide spectrum of applicability and therapeutic potentials, we have primarily focused on the bioactive properties of vanillin in this review.

METHODOLOGY

In order to extract the literature for this review, an assortment of research papers, review papers, research book articles, and conference proceedings were collected and studied. Searches have been executed in the scientific databases that includes Web of Science, Google Scholar, ScopeMed, Scopus, PubMed and Science direct using different keywords like - vanillin, vanillin derivatives, toxicity, antioxidant, antitumor, bioactivity, anticancer, anti-inflammatory, antiviral, anti-sickling, anti-fungal, neuroprotective, antibacterial, anti-quorum sensing ability, antibiotic property, wound healing, etc.

BIOACTIVITIES

The bioactivity studies on vanillin showed that vanillin displayed a LD_{50} (fatal dose for killing half of an experimented populace) of 4333 mg/kg in case of mouse and in case of rats, 4730 mg/kg [20]. Toxicological experiments of vanillin on rats by means of oral and intra-peritoneal administration validated that vanillin is harmless to a potentially higher concentration of 300 mg/kg depicting no noxious effect on blood cells, liver and kidney. In addition, it exhibited blood and neuro-shielding characteristics [21].

ANTIOXIDANT AND ANTI-INFLAMMATORY POTENTIAL

Vanillin showed new possibilities for its utilization in the food manufacturing business as a food preservative in cakes, butter, fruit juice, ice-creams, chocolate, chips, cookies, etc. as it exhibits antioxidant activity towards foods that are highly enriched with polyunsaturated fatty acids [5]. It is reported to be an effective scavenger of reactive oxygen species and depicted good antioxidant potential in various antioxidant assays like ABTS assay, ORAC assay, Hydroxyl radical scavenging assay [22-23] and oxidative haemolysis inhibition assay, in which it works through its own-dimerization leading to superior stoichiometric ratio[20]. Vanillin exhibited little superoxide anion scavenging activity and very feeble antioxidant power against lipid peroxidation in case of mouse liver microsomes [24], and weak potential for DPPH radical scavenging [25-26], β-carotene decolorization method [27], linoleic acid and cholesterol oxidation methods [28]. Again, vanillin, with concentration 2.5mM, prevented photosensitization induced lipid peroxidation and protein oxidation in liver mitochondria of rats [29]. In vivo antioxidant activity studies via plasma ORAC method; it depicted highest antioxidant potential, when 100 mg/kg of vanillin was given to mice, orally [20]. Vanillin also has anti-inflammation potential and has prospective applicability in the manufacture of medicines for reducing arthritis, rheumatology, allergies, etc. For illustration, vanillin prevented the of nitric oxide escalation in the lipopolysaccharide stimulated RAW264.7 macrophages. In addition, RT-PCR experiments depicted the suppression of nitric oxide synthase and mRNA induction in lysophosphatidic acid activated macrophages by vanillin [29]. Moreover, vanillin exhibited hepato-protective effect on pre-treatment against CCl_4- initiated hepatotoxic affects, through prevention of the protein and lipid oxidation by inhibiting inflammation mediators along with augmentation of the antioxidant enzymes activities [30]. Defensive impact of vanillin was also reported against oxidative stress caused by $KBrO_3^-$[26]. Vanillin weakened histopathological alterations in $KBrO_3^-$ led kidney and renal oxidative stress by preventing production of reactive oxygen species and by overturning antioxidant enzyme actions in kidney [31].

ANTIMUTAGENIC ACTIVITY

Vanillin (150μg/mL), was found to inhibit mutagenesis caused by 4-nitroquinoline-1-oxide, furylfuramide, ormethylglyoxal and captan, in *Escherichia coli* WP2s and vanillin was recognised to boost DNA injury restoration by means of re-combinational pathways of repair [32–34]. It slowed down the occurrence of unprompted mutations of *S. typhimurium* TA102 and TA104, and the strain NR9102 of *E. coli*, wild type [35-37]. In case of the germ cell line of *Drosophila melanogaste*, it reduced both unprompted and mitomycin led ring X-loss [38]. Again, in case of *D. melanogaster* somatic cells, vanillin weakly slowed down mitomycin C induced mutations but enhanced recombination in mitomycin C treated lesions and also, vanillin induced a synergistic impact, in its somatic cells with ethyl methanesulfonate or bleomycin [39-40]. Conversely, its co-treatment with vanillin provided momentous safeguard against the damages of genetic information in cells caused by methanesulfonate, *N*-ethyl-*N*-nitrosourea, *N*-methyl-*N*-nitrosourea, and bleomycin. Vanillin augmented toxicity of mitomycin C and ethyl methanesulfonate and yet, it safeguarded against the lethality of *N*-ethyl-*N*-nitrosourea in case of repair-deficient flies. This complicated antimutagenic property arouse out of the vanillin led inhibition against oxidative stress, along with stimulatory function on detoxification enzymes [41, 42]. In experiments executed on ovary fibroblast CHO K-1 cells of Chinese hamster, vanillin successfully promoted an amplification of the sister-chromatid exchange frequencies in cells treated with *N*-ethyl-*N*'-nitro-*N*-nitrosguanidine, mitomycin C, ethyl methanesulfonate, *N*-ethyl-*N*-nitrosourea and *N*-methyl-*N*-nitrosourea. In contrast, on post treatment with vanillin, the occurrence of chromosome abnormalities were reduced in mitomycin C- introduced cells in phase G2 [43, 44]. In investigations executed by using lung fibroblast V79 cells of Chinese hamster, it lessened the occurrences of 6-thioguanine-resistant mutagenesis caused via UV ray, X-ray and ethyl methanesulfonate [45]. Hydrogen peroxide created cytotoxicity and chromosomal abnormality were reduced on post-treatment of V79 with vanillin [46]. Also, vanillin was found to reduce methotrexate, UV and X-ray induced micro-nucleated and bi-nucleated aberrant cells [47, 48]. Also, when in vivo anti-mutagenic outcomes were explored in X-ray and mitomycin C treated micronuclei of mouse bone marrow cells, it was observed that post-treatment with vanillin led to reduction in the occurrence of X-ray and mitomycin C treated micro-nucleated polychromatic erythrocytes [49, 50]. Again, it was found that three consecutive introduction of vanillin (500mg/kg, orally), dwindles the *N*-ethyl-*N*-nitrosourea-induced occurrence of recessive carrier pups, in case of mouse spot assessment for male and female mice [45]. Vanillin successfully inhibited the mutagenesis, caused by hydrogen peroxide, mitomycin C and N-methyl-N'-nitro-N-nitrosoguanidine, in case of the *CD59* locus in human-hamster hybrid AL cells [51]. It can obstruct DNA modifications by non-homologous DNA end-combination and can prevent DNA-protein kinase action in lymphoma

GM00558 cells and interrelated gene insufficient cells of individuals [52]. The protective power of vanillin against $KBrO_3$ caused bone, liver and blood related ailments in mice has been extensively studied and observed that co-administration of vanillin to $KBrO_3$ appreciably reduced DNA injury, hepatic lipid peroxidation, hepatic cell variation, diminution of enzymatic and non-enzymatic antioxidants, plasma transaminases increases and manifestation of pro-inflammatory cytokines. The antimutagenic effect of vanillin might be attributable to its influence on cell redox and DNA fixing pathway [53, 54].

ANTI-CANCER ACTIVITY

For the first time, the anticancer property of vanillin was investigated during the starting phase of animal hepatocarcino genesis where it exhibited inhibition properties against hepatocancer initiation caused via food carcinogen IQ [55]. Later on, quite a number of experiments on vanillin confirmed about its anticarcinogenic and anticlastogenic activities. *Ramadoss and Sivalingam* observed that vanillin (1000 µg/mL) can successfully slow down the proliferation induced in the Colon cancer (HT-29) cells, in cases where considerable cell capture observed throughout G0/G1 stage and amplification of cell apoptosis during the sub-G0 stage occurred [56]. Molecular docking study of vanillin discloses that combination of vanillin with CAMKIV enzyme is related to neuro-degenerative and carcinogenic problems. Vanillin monodimer reduced the metastasis of HepG2 cells via *FAK/PI3K/Akt* signal prevention [57]. In vitro study by *Naz et al*, indicated about the vanillin caused apoptosis in neuroblastoma cells and hepatocancer cells of human [58]. Besides, a vanillin derivative exhibited prevention of escalation, incursion and movement of HT-29 and HCT116 cells through its interaction and combination with a Wnt/β-catenin signal receptor [59]. According to this reported work by *Ma et al.*, vanillin reduced proteasome genes response in colon tissues and extensively repressed proteasome actions. Also, it slowed down the mitogen-induced protein kinase phosphorylation by decreasing granulocytes quantity of colon tissue, cell proliferation and p65-positive cells. Anticarcinogenic property of vanillin might be linked to reduction is response of the proteasomes, mitogen-activated protein kinase signal pathways and NF-κB signalling [18]. VND3207, another vanillin derived compound, exhibited very good radio-shielding power against intestinal damage of mice caused by radiation. VND3207 was found to enhance the catalytic activity of protein kinase, an indispensable element in the repair pathway of DNA double-strand breakage and thereby improve the radiation induced damage of human lymphoblastoid cells [60].

ANTI-INVASION, ANTIANGIOGESIS AND ANTIMETASTATIC ACTIVITIES

Vanillin also exhibits Anti-invasion, Antiangiogesis and Antimetastatic activities in various experiments. In vitro investigations disclose that non-cytotoxic concentrations of vanillin prevents the expansion and penetration of cancer cells in case of adenocarcinoma 4T1 cells of mouse, prevents the activity of metalloproteinase 9 [61]; diminish invasive capacity and also suppresses the level of mRNA in HepG2 cells, caused by metalloproteinase-9, that takes place through down-regulation of the NF-κB signal pathway [62]. In addition, vanillin also depicts preventive activity towards migration of lung A549 cancer cells of humans, led by hepatocyte growth [63]. The result of vanillin treatment was analysed in case of augmentation of mouse 4T1 cells and found that oral administration of vanillin on female mice displayed significant reduction in numbers of metastasized lung colonies [61].

CYTOTOXIC ACTIVITY

Vanillin has been found to have cytotoxic potential against fibroblast 3T3 cells of mice [64, 65], colorectal cancer HT-29 cells, ovarian cancer A2780-SC1 cells [54], cervical cancer HeLa cells [66], HepG2 cells [67] and colorectal cancer SW480 cells [68] of human. The analyses of vanillin-treated gene expression [67] in HepG2 cells resulted that genes, correlated to cancer development were slowed-down by vanillin. Investigation of activator protein-1 transcription factor demonstrated inhibition of the activator protein-1 action by vanillin, while dwindling the extracellular signal-regulated kinase phosphorylation. In another experiment, [65], in HT-29 cells, vanillin induced cytolytic and cytostatic potential and caused fatality in cell via apoptosis. Cell cycle investigations demonstrated that, at low concentration around 200μg/mL, vanillin led to G0/G1 capture and at high concentration (1000 μg/mL), it induced G2/M arrest. Pre-treatment of vanillin with HeLa cells improved tumour necrosis related apoptosism, leading to ligand caused cell death via prevention of NF-κB activation [66].

NEUROPROTECTIVE POTENTIAL

According to the reported works by *Gupta and Sharma*, and *Kim et al.*, vanillin was observed to be a neuro-protective agent in Huntington's disease well as in global ischemia of animals [69, 70]. It demonstrates appreciable impact on 3-nitropropionic acid induced Huntington's disease in rats by controlling motor coordination, locomotor disabilities, biochemical problems, etc., [69]. *Lan et al.*, reported that, in case of rats after hypoxic-ischemic injury, vanillin promotes early neuro-functional development, brain infarct volume, ameliorates histomorphological damage and brain edema [71]. Vanillin demonstrated neuroprotective ability in case of hippocampal CA1 neuron cell injury [70]. This neuroprotective activity was reported to be mediated by scavenging reactive oxygen species and thereby decreasing lipid peroxidation and apoptosis, and attenuating mitochondrial dysfunction [72]. As reported by *Chen et al.*, vanillin induced neuroprotective ability diminishing apoptosis and down-regulating the HIF-α action in spinal tissue, in spinal cord injured rats [73]. It was reported by *Salau et al.*, that vanillin, along with vanillic acid can alter antioxidant mechanism through the improvement of metabolic issues related to brain tissue damage caused by Fe^{2+} [74].

ANTIFUNGAL ACTIVITY

Many researchers reported the impediment of fungal infections that deteriorate human health, food quality, plant and animal health on treatment with vanillin. Along with its 33 different variants, vanillin was considered for the antifungal activity study using *Cryptococcus neoformans, by Kim et al.,* and RNA-sequence analyses of ortho-vanillin and ortho-ethyl vanillin introduced *Cryptococcus neoformans* indicated mitochondrial dysfunction and oxidative stress which appreciably reduce the development *Cryptococcus neoformans* and thereby they depicted preventive action in case of cryoptococcal meningitis. [75] Again, in the work reported by *Romero-Cortes et al.*, vanillin (250 mg/L), signifying its antifungal potential, inhibited the growth of *Alternaria* strains, in which the fungal life cycle was delayed from 50h to 112h and in addition, up to 37.5% decrease of mycelial development was reported [76].

ANTIBACTERIAL AND ANTI-QUORUM SENSING AND ANTIBIOTIC POTENTIATION ABILITY

Vanillin has been reported to successfully inhibit the bacterial growth, in case of various bacteria like *Pseudomonas aeroginosa*, *Enterobacter aerogenes*, *Pantoea agglomerans*, *Escherichia coli*, *Aeromonas enteropelogenes*, *Lactobacillus casei*, *Sphingobacterium spiritovorun*, *Micrococcus lyla*, *Salmonella enterica subspecies Enterica serovar*, etc., [77-79]. It was observed by *Fitzgerald et al*., that introduction of vanillin (10–40 mM) prevented the respiration processes in *Listeria innocua* and *E. coli* and vanillin caused proton gradient dissipation with DNA damage leading to pH homeostasis loss in *Lactobacillus plantarum,* when used in concentrations around 50–100 mM [80]. The proteomic analysis of vanillin treated *E.coli,* as reported by *Pattrick et al.,* indicated noteworthy alteration of almost 147 proteins in response to vanillin [81]. On the other hand, molecules with anti-quorum sensing ability can avert the biofilm production that usually known to greatly reduce the action of antibacterial agents or antibiotics. Research by *Ponnusamy et al.,* suggested that vanillin can hinder homoserine and acyl-homoserine lactones in case of *Aeromonas hydrophila* [82]. In vitro experiments of the bacteria, *Pseudomonas aeruginosa* and in silico docking experiments by *Mok et al.,* indicated the inhibition of PQS-binding response regulator expression through the binding of vanillin to its active site, which is linked with quorum sensor agent, pyocyanin [83]. Again, *Bezerra et al.*, *Arya et al.*, and *Brochado et al.*, reported that vanillin controls and augments and the power of a broad spectrum of antibiotic medicines like meropenem, norfloxacin, ciprofloxacin, imipenem, tigecycline, chloramphenicol, gentamycin, and spectinomycin, trimethoprim, levofloxacin and fosfomycin etc., [10,84- 86].

ANTIVIRAL ACTIVITY

Hariono et al., reported the anti-neuraminidase activity of a vanillin derivative that contains a guanidino group, which might occur because of its interaction with preserved and vital residues of neuraminidase [87].

ANTI-SICKLE CELL ANAEMIA ACTIVITY

Vanillin inhibits the sickling of cells by forming a covalent bond with the sickle hemoglobin and therefore vanillin pro-drug was designed and effectively utilized for the treatment of sickle cell anemia of rats [88]. According to the reported work of *Abraham et al.,* vanillin exhibited inhibition of cell sickling caused by deoxygenation and haemoglobin polymer production without imparting any undesirable impact on cellular water. It was observed via X-ray crystallography that vanillin binding is next to Cys 104α, His 103α and Gln 131β in the cavity of central water molecule, along with additional binding site next to His 117β and His 116β [89]. As reported by *Hannemann et al.*, the membrane permeability of red blood cells was affected by ortho-vanillin, exciting the K^+ ion efflux, which additionally prevents sickle cell diseases [90]. In addition, in vitro studies revealed that plentiful of vanillin derived compounds demonstrated superior allosteric prevention and anti-sickling activity than vanillin [91].

COSMECEUTICAL PROPERTY

Attributable to the antioxidant properties and fragrance, vanillin has been extensively used in scores of cosmeceuticals. With its existence in non-toxic concentration, the transcription factors, that manage human adult stem cell specific signatures, were observed to be up-regulated. Besides, it was reported to augment epithelial adhesive protein activity [92], reduced cytokines growth having pro-inflmmation property, UV-B induced ataxia telangiectasia mutated phosphorylation, protein-p53 that have tumour suppressive power, serine/threonine kinase Chk2, S6 ribosomal protein, p38 mitogen-activated protein kinase, histone 2A family member X and stress activated c-Jun N-terminal kinase [93]. These significant factors are very much important for in skin repair and renewal and consequently, vanillin can be said to have cosmeceutical property. So use of vanillin and its derived compounds as cosmeceutical compounds may possibly endow other therapeutic benefits along with the antioxidant benefits and pleasant fragrance.

WOUND HEALING PROPERTIES

Xu et al., developed a chitosan-vanillin derived Schiff base hydrogel [94] that can be used in the treatment to cure wounds. On introduction of Schiff base hydrogel to rat skin, collagen deposition, angiogenic response, re-surfacing of wound via epithelialization, and enhancement of the gene expression of transforming growth factor-β, vascular endothelial growth factor and interleukin-10, reduction in interleukin-1β levels and tumour necrosis factor-α levels, along with wound healing were observed [95]. Different concentrations of vanillin/chitosan derivatives were employed for the treatment to cure wounds in various tissues like osteochondral tissues and promising outcomes were observed [96].

CONCLUSIONS

Till date, vanillin has been known to be mostly utilized as a flavouring material and fragrance ingredient. However vanillin has grabbed the interest of the recent research society, attributable to its versatility and effectiveness. To summarise, vanillin is omnipresent, starting from our kitchen to our medicine or perfume cabinet, from our anti-hypertension prescriptions to the sweet dish, favourite chocolate or ice-cream. The analyses presented in this review reveal that it exhibits diverse range of bioactive properties which makes it a potential therapeutic agent for prevention of various diseases and health problems. Attributable to its non-toxicity in rats, it can be concluded that vanillin can be effectively incorporated and removed from the rat bodies. Additionally, the use of vanillin containing vegetables and fruits might also be helpful in preventing problems like oxidative stress, tumour and cancer development. More insight to its bioactive applicability and in depth research may facilitate the further assessment of its possible utilization as an potential bioactive molecule with an assortment of therapeutic benefits to tackle vital health problems like neurodegenerative diseases, tumour, cancer, viral infections, fungus and bacterial infections, sickle cell anaemia etc., and if properly analysed and utilized, it might provide us the next generation – super molecule or the next generation wonder drug from various vanillin derived compounds.

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