Vanillin: a review on the therapeutic prospects of a popular flavouring molecule

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Abstract
Vanilla is the world’s most popular flavour extracted from the pods of Vanilla planifolia orchid. It is a mixture of ~ 200 compounds but its characteristic flavour and fragrance primarily come from vanillin. While the importance of its wide usage in flavour and fragrance is well established, there have been limited investigations to evaluate its bioactive potential. However, a few studies have reported a promising array of bioactivities that could be exploited for multiple therapeutic applications. Recently, bioactive properties of vanillin, such as neuroprotection, anticarcinogenic, and antioxidant are gaining attention. Besides this, vanillin and its synthetic analogues are found to regulate gene expression and exhibit biological activities. Therefore, here we summarize the potential bioactivates of vanillin and its derivative with an aim to change the perspective from being a popular flavour to a new age therapeutics molecule.

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Introduction

Vanilla is arguably the world’s most popular flavour and is derived from mature pods of the orchid Vanilla planifolia. It constitutes one of the most preferred flavours and fragrance ingredients in ice-creams, confectioneries, milk products, perfumes, pharmaceuticals, liqueur and other cordial industries, thereby forming a whopping multimillion-dollar market (Gallage and Møller 2018). For centuries vanilla flavour remained classified for the rest of the world since it was ascribed as a flavour of nobility by Aztecs and pre-Columbian Mayas. It was in 1519 that vanilla was exposed to the world with the Spanish invasion of the Aztecs. It was transported to Europe and subsequent development of hand pollination techniques led to its expansion to other parts of the world (Teoh 2019). Today, Madagascar is the largest producer of natural vanilla with 75% of world production followed by Indonesia, China, Mexico, and Papua New Guinea. Vanilla is a mixture of ~200 compounds; however, it’s characteristic flavour and fragrance comes mainly from the molecule vanillin (Gallage and Møller 2018).

Vanillin is a specialized metabolite and the main ingredient of vanilla extract that occurs in concertation of 1.0–2.0% w/w in cured vanilla beans (Zhang and Mueller 2012). Vanillin has different functional groups, like aldehyde, hydroxyl and ether attached to an aromatic ring. The physicochemical properties of vanillin are described in Table 1. Vanillin is either isolated from vanilla extract or is chemically synthesized from guaiacol. Besides being known for flavour and fragrance, it has diverse bioactive properties, namely anticancer, neuroprotective, antibiotic potentiation, and anti-quorum sensing (Arya et al. 2019; Bezerra et al. 2016; Li et al. 2018). Moreover, the bioactivities of curcumin are now attributed to the constituent and stable degradation products, i.e. vanillin and ferulic acid (Iannuzzi et al. 2017). Though recent studies on vanillin have eluded to its bioactive potential, in comparison to curcumin the level of research activity is very limited.
sible on exposure to light and moist air

| Physical state | Solid |
|----------------|-------|
| Colour         | White or off-white |
| Form           | Non-hygroscopic crystalline needles |
| Odour          | Sweetish smell, Pleasant aromatic vanilla odour |
| Taste          | Pleasant vanilla taste |
| Boiling point  | 285 ºC |
| Melting point  | 81.5 ºC |
| Solubility     | Slightly soluble in ethanol and water (1 g/100 mL), soluble in chloroform, ether, in solutions of fixed alkali hydroxides; solutions in glycerine and hot water |
| Light sensitivity | Slowly oxidizes on exposure to light and moist air |
| Density        | 1.056 g/ml |
| Vapour pressure| 2.103 mmHg at 25 ºC |
| Dissociation constant | pKa = 17.40, pKa = 211.4 (25 ºC) |
| Food additive status | FDA approved |

Sources of vanillin

Typically, there are three sources of vanillin, i.e. natural, chemical/synthetic and biotechnological (Fig. 2). Depending on the source and the synthesis procedure, the vanillin is categorized as either natural or artificial flavour. Of these, the natural and biotechnologically produced vanillin (from ferulic acid as a substrate) is considered as food-grade additives by most food control authorities across the world.

Major sources

Natural

Vanillin is naturally extracted from vanilla pod extract of *Vanilla planifolia*, *Vanilla tahitensis*, and *Vanilla pompona* which are by far the main sources of vanillin (Bezerra et al. 2016). Commercial extraction methods for vanillin include Soxhlet, supercritical fluid extraction (SCEF), microwave and ultrasound-assisted extraction, enzymatic extraction, solid-phase extraction and biphasic sonoelectroanalysis.
| Properties     | Study          | Subjects                                      | Cellular and molecular targets                                                                 | Vanillin/derivative                  | References                          |
|----------------|----------------|-----------------------------------------------|-------------------------------------------------------------------------------------------------|--------------------------------------|--------------------------------------|
| Anticancer     | In vitro       | HCT116 and SW480                             | Inhibit cell proliferation, migration and induce the apoptosis by affecting PI3K-related protein expression | Vanillin derivative                  | Ma et al. (2020)                     |
|                | In vitro and in vivo | HT-29, HCT116 cells, mice                  | Wnt/β-catenin receptor, proteasome genes, MAPK, nuclear factor-κB, promotes intestinal repair following radiation injury by enhancing the expression of DNA-dependent protein kinases | Vanillin and its derivative          | Li et al. (2018, 2020), Ma et al. (2019) |
|                | In vitro and in silico | HepG2, SH-SY5Y and HEK293 cells   | Induces apoptosis cancer cells, molecular docking reveals binding of vanillin to CAMKIV enzyme associated with cancer and neurodegenerative diseases, decrease the metastatic potential of HepG2 cells by inhibiting FAK/PI3K/Akt signalling pathway | Vanillin, divanillin                | Jantaree et al. (2017), Naz et al. (2018) |
| Anti-oxidant   | In vivo        | Mice                                         | Increases antioxidation in plasma                                                                | Vanillin                             | Tai et al. (2011a)                   |
| Anti-inflammatory | In vivo   | Mice                                         | Protects blood-milk barrier and inhibits the inflammatory response in lipopolysaccharide induced mastitis, inhibits myeloperoxidase activity, decreases production of pro-inflammatory mediators such as TNF-α, IL-6, IL-1β, inducible nitric oxide synthase and cyclooxygenase-2, and repairs the blood-milk barrier by increasing the protein levels of the tight junction proteins such as zona occludens 1, claudin-3, and occludin | Vanillin                             | Guo et al. (2019)                   |
|                | In vitro       | RAW264.7 Macrophages                         | Nitric oxide (NO) synthase mRNA in macrophages                                                   | Vanillin                             | Lim et al. (2008)                   |
| Neuroprotective | In vitro      | HT22 cell lines                              | Inhibition of acetylcholinesterase and butyrylcholinesterase activities, and restoration of oxidative imbalance in Fe^{2+}-induced brain cell damage | Vanillin and vanillic acid           | Salau et al. (2020)                 |
| Properties                    | Study                        | Subjects                  | Cellular and molecular targets                                                                                           | Vanillin/derivative | References                                      |
|-------------------------------|------------------------------|---------------------------|--------------------------------------------------------------------------------------------------------------------------|---------------------|-------------------------------------------------|
| In vitro and in silico        | N/D                          | Acetylcholinesterase inhibition and bettered butyrylcholinesterase selectivity                                              | Vanillin derivatives | Blaikie et al. (2020)                          |
| In vivo                      | Mature and neonatal rats     | Neuroprotection in ischemic neuronal cell death, neuro-functional development, ameliorates brain infarct volume, brain edema, reduce apoptosis and downregulates HIF-α in spinal tissues | Vanillin            | Chen et al. (2019), Lan et al. (2019)          |
| In vitro                     | Microglial cells             | Inhibited the production of nitric oxide, pro-inflammatory cytokines, IL-1β, TNF-α, and IL-6, nitric oxide synthase, MAPKs, NF-κB, cyclooxygenase-2, and reduces mRNA expression levels of IL-1β, TNF-α, and IL-6  | Vanillin            | Kim et al. (2019)                             |
| In vitro                     | Microglial BV-2 cells        | Protect dopaminergic neurons by reducing LPS-induced expression of inducible nitric oxide (nNOS), cyclooxygenase-2, IL-1β, and IL-6 through regulating ERK1/2, p38 and NF-κB signaling | Vanillin            | Yan et al. (2017)                             |
| In vivo                      | Mice                         | Mitigation of KBrO3-induced depression by reducing IL-1β, IL-6 and cyclooxygenase-2                                        | Vanillin            | Ben Saad et al. (2017)                        |
| Anti-sickling (sickle cell anaemia) | In vitro                    | Blood cells               | Binds near central water cavity of haemoglobin, affects membrane permeability stimulating the efflux of K⁺ ions             | Vanillin and its derivative | Abraham et al. (1991), Hanne mann et al. (2014) |
| Anti-Amyloid aggregation and inhibition of non-enzymatic glycation | In vitro                     | SH-SY5Y cells             | Affects non-enzymatic glycation and amyloid aggregation in human insulin                                                | Vanillin            | Iannuzzi et al. (2017)                         |
| Anti-fungal                  | In vitro                     | Candida albicans          | Inhibition of glyoxylate pathway, morphogenesis, virulence and biofilm formation, induces mitochondrial dysfunctioning via impaired retrograde signaling leading to abrogated iron homeostasis and DNA damage | Vanillin            | Saibabu et al. (2020), Venkata et al. (2020) }
| Properties               | Study                      | Subjects                                                                 | Cellular and molecular targets                                                                 | Vanillin/derivative                      | References               |
|-------------------------|----------------------------|--------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------|--------------------------|
|                         | In vitro                   | *Alternaria* strains, *Cryptococcus neoformans*                          | Fungistatic, mitochondrial dysfunction and triggers reactive oxygen species (ROS)               | Vanillin and its derivative             | Kim et al. (2014), Romero-Cor-tes et al. (2019) |
| Anti-bacterial          | In vitro and in vivo       | *Xanthomonas oryzae pv. oryzae* (*Xoo*) and *Xanthomonas oryzae pv. oryzicola* | Reduced bacterial exopolysaccharide production, damage the cell membrane and increase permeability | Vanillin derivatives                    | Wu et al. (2020)         |
|                         | In vitro                   | *E. coli*                                                                | RpoS/DksA-based gene expression, MarA, OxyR, and SoxS regulatory network, AcrD and AaeAB as potential vanillin efflux systems | Vanillin                                | Pattrick et al. (2019)   |
|                         | In silico and in vitro     | *Bacillus subtilis, Methicillin-resistant Staphylococcus aureus, Staphylococcus epidermidis, Staphylococcus saprophyticus and Vancomycin-resistant Enterococcus* | Inhibition of bacterial DNA synthesis                                                           | Vanillin derivatives                    | Hussain et al. (2019)    |
| Antibiotic potentiation | In vitro                   | *Pseudomonas aeruginosa*                                                 | Potentiates the activity of antibiotics and reduces the activity of MexAB-OprM efflux pumps   | Vanillin                                | Arya et al. (2019)       |
|                         | In vitro                   | *E. coli*                                                                | Potentiated the activity of spectinomycin                                                        | Vanillin                                | Brochado et al. (2018)   |
|                         | In vitro                   | *E. coli, P. aeruginosa, Staphylococcus aureus*                          | Modulates the activities of antibiotics                                                          | Vanillin                                | Bezerra et al. (2017)    |
| Anti-quorum sensing     | In vitro and in silico     | *P. aeruginosa*                                                          | Vanillin binds to the active site of PqsR (PQS-binding response regulator) and inhibits pqs expression associated with pyocyanin (quorum sensing molecule) and the virulence | Vanillin                                | Mok et al. (2020)        |
|                         | In vitro and in silico     | *Hafnia alvei*                                                           | Inhibition of C6-HSL and C8-HSL, downregulation of transcriptional regulator (halR) and acyl-homoserine-lactone synthase (halR), may act as inhibitor of HalR protein | Vanillin                                | Li et al. (2019)         |
| Properties               | Study     | Subjects               | Cellular and molecular targets                                                                                       | Vanillin/derivative | References                        |
|--------------------------|-----------|------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------|-----------------------------------|
|                         | In vitro  | *Chromobacterium violaceum* | Inhibit the production of anti-quorum sensing molecule violacein                                                   | Vanillin            | Tomadoni et al. (2016)            |
|                         | In vitro  | *Aeromonas hydrophila*  | Inhibit short-chain homoserine lactones (HSL) and long-chain acyl-homoserine lactones (ASL)                        | Vanillin            | Ponnusamy et al. (2009)          |
| Nephroprotective         | In vivo   | Rats                   | Inhibition of NOX-4 and stimulation of Nrf2/HO-1 signalling pathway reduced the inflammation and apoptosis in nephrotoxic rats | Vanillin            | Younis et al. (2020)             |
|                         | In vivo   | Rats                   | Decreases advanced glycation end products, MDA and SOD activity in renal tissues, reduces renal expression of NF-κB and renal concentration of IL-6, TGF-β1 and collagen, attenuates histological abnormalities in kidney | Vanillin            | Zabad et al. (2019)              |
| Cardioprotective         | In vitro  | H9c2 cardiomyocytes    | Decreased sub-G1 appearance, activation of caspase-3 and PARP1, reduction in doxorrelated apoptosis induction, also hindered doxo-induced ROS accumulation and impaired the ERK phosphorylation | Vanillin            | Sirangelo et al. (2020)          |
| Hepatoprotective         | In vivo   | Wistar rats            | Vanillin alone or in combination with chitosan nanoparticles reduced the ROS, hepatotoxicity and genotoxicity in aging male rats | Vanillin and vanillic acid | Al-Baqami et al. (2020), Sindhu et al. (2015) |
| Pancreatoprotective      | In vivo   | Rats                   | Vanillin alone or in combination with naringenin mitigated cadmium-induced pancreatic injury by inhibiting JNK and p38 MAPK pathways | Vanillin            | Fouad et al. (2020)              |
| Wound healing/tissue engineering | In vivo | Rats                   | Re-epithelialization, reduced levels of IL-1β and TNF-α as well as increased IL-10 and expression of TGF-β and VEGF | Vanillin            | de Aragão Tavares et al. (2018), Hunger et al. (2019) |
| Properties               | Study                                | Subjects                     | Cellular and molecular targets                                                                 | Vanillin/derivative | References                                                                                     |
|-------------------------|--------------------------------------|------------------------------|------------------------------------------------------------------------------------------------|---------------------|-----------------------------------------------------------------------------------------------|
| Antiviral               | In vitro and in silico               | H1N1 virus                   | Interacts with conserved residues in neuraminidase                                               | Vanillin derivative | Hariono et al. (2016)                                                                            |
|                         | In silico                            | SARS-CoV-2                   | Moderate specificity towards SARS-CoV-2 spike protein, RNA-dependent RNA polymerase and main protease | Vanillin            | Pendyala and Patras (2020), Rout et al. (2020)                                                   |
| Cytoprotective          | In vitro                             | *Lactuca sativa*             | Chelating and cytoprotective activity were observed against the toxic action of iron III ions and mercuric acid respectively | Vanillin            | da Silva et al. (2020)                                                                            |
|                         | In vitro and in vivo                 | Wistar rats                  | Reduces the radiation induced pneumonitis and fibrosis (i.e. EMT - epithelial to mesenchymal transition leading to fibrosis) | Vanillin            | Sunnaghatta Nagarajs et al. (2020)                                                              |
| Increase bioavailability of drugs | In vitro, in vivo and in silico       | Caco-2 cells                 | Increases the bioavailability of drug by enhancing in the fluidity of the lipid bilayer and reducing the energy barrier of drugs passing through the cell membrane | Vanillin            | Yang et al. (2020)                                                                               |
| DNA binding             | In vitro and in silico               | N/A                          | Vanillin binds DNA in minor groove                                                               | Vanillin            | Qais et al. (2019)                                                                               |
| Antitremor              | In vivo                              | Rats                         | Amelioration of harmaline induced tremor                                                         | Vanillin            | Asmari et al. (2016)                                                                            |
| Cosmeceutical           | In vitro                             | Human HaCaT keratinocytes    | Up-regulate Oct-4, pOct-4 and Nanog, E-cadherin and down-regulates phosphorylation of ATM, Chk2, p53, p38, JNK, S6RP, and H2A.X | Vanillin            | Lee et al. (2014), Taboonpong et al. (2017)                                                      |

*N/A: not applicable*
Fig. 1  Number of published articles on bioactivities of vanillin (Accessed on 07th September, 2020)

Fig. 2  Different sources and routes of vanillin synthesis
Natural vanillin is the most expensive form at a cost of nearly US$ 1200/kg to more than US$ 4000/kg (Gallage and Møller 2018).

Chemical synthesis

Compared to the natural source, chemically synthesized vanillin is considerably cheaper ($15/kg), however, is labeled as artificial vanillin which attracts negative consumer sentiments. Various substrates have been tried for the synthesis of synthetic vanillin, like lignin, guaiacol, 4- hydroxybenzaldehyde, 3-bromo-4-hydroxybenzaldehyde, 3-methoxy-4-hydroxybenzyl alcohol, cow dung and lignin-rich crop residual waste materials with varying success (Banerjee and Chattopadhyay 2019; Ciriminna et al. 2019).

Minor source

Biotechnological

Bioengineering is a modern route for the production of vanillin. Various proprietary bacterial and fungal strains are genetically engineered that use a spectrum of starting materials like ferulic acid, eugenol, iso-eugenol and glucose. Also, enzymatic synthesis of vanillin using proteins from Nocardiia sp. and white-rot basidiomycetes have been reported (Banerjee and Chattopadhyay 2019). Furthermore, genetically engineered plants or plant cell cultures producing vanillin are proposed as a future alternative to produce vanillin and increase its commercial and medical applicability (Chee et al. 2017).

Bioactivities

As a popular flavour and fragrance compound, vanillin has received less attention for the bioactive properties it possesses. However, to be used as a pharmaceutical ingredient, it must have the desired bioactivity and should be bioavailable in humans and/or animals. In this regard, bioavailability studies have identified the rate and concentration at which vanillin is absorbed in the blood, plasma and also its target site (Beaudry et al. 2010). It is shown that vanillin has an LD50 (lethal dose to kill half of a tested population) of 4333 mg/kg for mice and 4730 mg/kg for rats (Makaruk 1980). Furthermore, toxicology studies on rats via oral and intraperitoneal administration of vanillin confirms that it is safe even at a high concentration of 300 mg/kg and did not exhibit any toxic effect on kidney, liver, blood cells, and also showed blood and neuroprotective properties (Ho et al. 2011). Owing to its non-toxicity in rats, it is worthwhile to consider vanillin as a candidate bioactive molecule and highlight its potential pharmacological applicability.

Anticancer activity

Reports that implicate vanillin in mediation of DNA damage and antimitogenic potential have encouraged researchers to evaluate the anticancer effects at cellular and molecular levels (Bezerra et al. 2016). Vanillin (1000 µg/mL) inhibited the proliferation of HT-29 cells (Colon cancer cells) where significant cell arrest occurred during the G0/G1 phase and an increase in apoptotic cells in sub-G0 phase was observed (Ramadoss and Sivalingam 2019). Further, a derivative of vanillin, 4-(1H-imidazo [4,5-f] [1,10]-phenanthroline-2-yl)-2-methoxyphenol (IPM711) showed growth inhibition, invasion and migration of HT-29 and HCT116 cells by binding to a Wnt/β-catenin signalling receptor (Ma et al. 2019). In this study, vanillin down-regulated proteasome genes in colon tissues and significantly suppressed proteasome activity. Furthermore, at 10 mM it hindered the mitogen-activated protein kinase (MAPK) phosphorylation, reducing the number of granulocytes in colon tissue, proliferating cells and p65-positive cells. Amelioration of cancerous activity by vanillin might be associated with downregulation of the proteasome genes, MAPK pathway and nuclear factor-κB (Li et al. 2018). A vanillin derivative VND3207 has shown a strong radio-protective effect in radiation-induced intestinal injury in mice (Li et al. 2020). VND3207 was found to alleviate the radiation injury in human lymphoblastoid cells by enhancing the expression of the catalytic subunit of the DNA-dependent protein kinase (DNA-PKcs) which is an essential part of DNA double-strand break repair mechanism. Another in vitro study suggested that vanillin induces apoptosis in human hepatic carcinoma and neuroblastoma cells (Naz et al. 2018). Further molecular docking reveals binding of vanillin to CAMKIV enzyme associated with cancer and neurodegenerative diseases. Also, monodimer of vanillin was found to decrease the metastatic potential of HepG2 cells by inhibiting FAK/PI3K/Akt signalling pathway (Jantaree et al. 2017). With these leads, we can use a multi-omics and modelling approach to more precisely identify the potential molecular targets of vanillin.

Antioxidant and anti-inflammatory activity

Vanillin is reported to be a potent scavenger of ROS as observed in multiple antioxidant assays like ORAC (oxygen radical absorbance capacity), ABTS* (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid), and oxidative haemolysis inhibition where it operates by self-dimerization
contributing to high reaction stoichiometry (Tai et al. 2011b). Also, it is found to have anti-inflammatory activity, for instance, vanillin was found to inhibit nitric oxide in the lipopolysaccharide activated (LPA) RAW264.7 macrophages (Lim et al. 2008). Moreover, suppression of inducible nitric oxide synthase (iNOS) is closely related to anti-inflammatory activity. RT-PCR studies revealed that vanillin concentration-dependently reduced the induction of iNOS mRNA in LPA macrophages.

**Neuroprotective activity**

Experimental evidence in animals has shown that vanillin acts as a neuroprotective agent in Huntington’s disease (HD) and global ischemia (Gupta and Sharma 2014; Kim et al. 2007). Vanillin significantly affected the 3-nitropropionic acid (3-NPA) induced HD in rats by attenuating motor coordination, learning-memory, locomotory and biochemical impairments (Gupta and Sharma 2014). Moreover, vanillin (40 mg/kg) exhibited neuroprotection against neuronal cell damage in the hippocampal CA1 region (Kim et al. 2007). Vanillin is further reported to promote early neurofunctional development, ameliorates histomorphological damage, brain infarct volume and brain edema after hypoxic-ischemic damage in neonatal rats (Lan et al. 2019). In spinal cord injury rat model, vanillin exerted neuroprotective effect reducing apoptosis and downregulating the expression of HIF-α in spinal tissues (Chen et al. 2019). This neuroprotective effect of vanillin is proposed to be mediated by ROS scavenging, attenuating mitochondrial dysfunction, decreasing lipid peroxidation, and apoptosis (Dhanalakshmi et al. 2015). Recently, it was reported that vanillin and vanillic acid modulate antioxidant system via alleviation of metabolic complications linked to Fe²⁺-induced brain tissue damage (Salau et al. 2020). Thus, vanillin and its analogues can be further evaluated as a potential therapeutic agent for neuroprotection and stroke therapy.

**Sickle cell anaemia**

Vanillin was evaluated as an agent to treat sickle cell disease (SCD) by Abraham et al. in 1991. It showed dose-dependent inhibitory effect on deoxygenation (HbA) induced sickling and sickle haemoglobin (HbS) polymer formation with no adverse effect on cellular water or ionic content. Through X-ray crystallography, it is realized that binding of vanillin is near His 103α, Cys 104α and Gln 131β in central water cavity, with a secondary binding site at His 116β and His 117β (Abraham et al. 1991). o-vanillin also affects the membrane permeability of red blood cells stimulating the efflux of K⁺ ions which further ameliorated the complication of SCD (Hannemann et al. 2014). Moreover, numerous vanillin derivatives have been developed which exhibit enhanced in vitro allosteric inhibition and anti-sickling as compared to vanillin (Pagare et al. 2018). Thus, vanillin or its derivatives can be designed and tested for allosteric modulation in stereospecific inhibition of HbS polymerization and high-affinity HbS.

**Amyloid aggregation and non-enzymatic glycation (NEG) of insulin**

Advanced glycation end products (AGE) are formed as end products of glycation reaction and are associated with developing severe diabetic complications that include neuropathy, nephropathy, retinopathy, and further progress in amyloid based neurodegenerative diseases. Vanillin was found to restrain NEG and AGE of albumin by functioning like a chemical chaperone (Awasthi and Saraswathi 2016). This in vitro study provided preliminary evidence for vanillin mediated insulin glycation and amyloid aggregation and AGE formation by methyl-glyoxal was strongly reduced in the presence of vanillin. It is presumed that vanillin binds non-covalently to positively charged Arg22 of insulin B chain and hinder the glycation reaction (Iannuzzi et al. 2017). Furthermore, vanillin also showed cytoprotective and anti-oxidant effect against AGE induced ROS products. These studies open new avenues for vanillin in the treatment of NEG and AGE induced diabetes.

**Antifungal activity**

Fungal pathogens are well known to affect food, human health and agriculture. It is found that vanillin can impede the growth of such fungal pathogens. For instance, vanillin (250 mg/L) decreased the growth of Alternaria strains, suggesting its fungistatic behaviour where the lag time of fungal life cycle was increased from initial 50 h to 112 h and also inhibition of mycelial growth of up to 37.5% was observed (Romero-Cortes et al. 2019). Antifungal activity of vanillin and its 33 variants were tested against Cryptococcus neoformans which is the causative agent of cryptococcal meningitis (Kim et al. 2014). RNA-seq of o-vanillin and o-ethyl vanillin treated C. neoformans showed that they caused mitochondrial dysfunction and triggered oxidative stress, significantly reducing their growth. Omics based analysis of vanillin treated fungus may further reveal the molecular targets of vanillin and pave a way for its use as an antifungal molecule in food, agriculture and the pharmaceutical industry.
**Antibacterial activity**

Vanillin was found to affect the growth of spoilage bacteria like Pantoea agglomerans, Aeromonas enteropelogenes, Micrococcus lylae and Sphingobacterium spiritivorum with the minimum inhibitory concentration (MIC) ranging from 10 to 13.3 mM (Ngarmsak et al. 2006). It was found that exposure to 10–40 mM vanillin inhibited respiration of E. coli and Listeria innocua and treatment with 50–100 mM resulted in complete dissipation of proton ion gradient with loss of pH homeostasis in Lactobacillus plantarum (Fitzgerald et al. 2004). In order to gain detailed insight into the cellular response to vanillin, the proteomics of vanillin treated E. coli showed that around 147 proteins exhibited a significant change in abundance in response to vanillin (Pattrick et al. 2019). The treatment caused accumulation of ROS invoking adaptations mediated by a MarA, OxyR, and SoxS regulatory network and increased in RpoS/DksA-dependent gene expression. Also, AcrD and AaeAB were identified as potential vanillin efflux systems (Pattrick et al. 2019). Further omics-based studies are required for other pathogenic bacteria specially listed as critical threats by world health organization in order to identify novel gene/protein targets of vanillin in bacteria.

**Antibiotic potentiation activity**

Vanillin at sub-inhibitory concentrations was found to modulate the activities of antibiotics. It was reported to regulate the activities of gentamycin, imipenem, norfloxacin and spectinomycin used against Pseudomonas aeruginosa, Staphylococcus aureus and Escherichia coli (Benezza et al. 2017; Brochado et al. 2018). It also potentiated the activities of some commonly used and last line antibiotics like chloramphenicol, ciprofloxacin, levofloxacin, tigecycline, meropenem, trimethoprim and fosfomycin against extremely drug-resistant P. aeruginosa clinical isolates (Arya et al. 2019, 2020). These studies suggest that vanillin has the potential to be used as an antibiotic adjuvant in future.

**Anti-quorum sensing activity**

Bacteria either grow as planktonic cells or in films known as biofilms. These biofilms are highly resistant towards antibacterial agents and can be inhibited by anti-quorum sensing molecules that affect bacterial signalling. Reports on vanillin suggest that it can inhibit short-chain homoserine lactones and long-chain acyl-homoserine lactones in Aeromonas hydrophila (Ponnusamy et al. 2009). Recently, the in vitro analysis in P. aeruginosa and in silico docking studies revealed that vanillin binds to the active site of PqsR (PQS-binding response regulator) and inhibits pqs expression which is associated with pyocyanin (quorum sensing molecule) and the virulence thereafter (Mok et al. 2020). Vanillin can, therefore, be explored to evaluate its antibiofilm properties against other biofilm-forming bacteria which are usually found resistant to antibacterial agents.

**Application in wound healing and tissue engineering**

Vanillin is used as a natural crosslinker to fabricate chitosan hydrogel for wound healing. Self-healing chitosan-vanillin hydrogel is developed based on Schiff base and hydrogen bond hybrid linkages between chitosan and vanillin (Xu et al. 2018). At the atomic level, aldehyde moiety of vanillin reacts with amino group of one chitosan molecule through Schiff-base reaction and it’s hydroxyl moiety forms hydrogen bond with the hydroxyl or the amino groups in another chitosan molecule. The self-healing effect is generated by reconstruction of Schiff-base bond. Along with wound healing, rat skin samples treated with chitosan-vanillin membrane showed angiogenic stimulus, collagen deposition, re-epithelialization, and reduced levels of IL-1β and TNF-α as well as increased IL-10 and gene expression of TGF-β and VEGF (de Aragão Tavares et al. 2018). Various concentrations of vanillin/chitosan along with other metallic and organic components are used for wound healing and tissue engineering such as osteochondral tissues (Hunger et al. 2019). Although chitosan-vanillin hydrogels have promising outcomes for wound healing and tissue engineering, these studies are yet to be replicated in human and therefore clinical trials are needed to determine their applicability.

**Antiviral activity**

A novel vanillin derivative MY21 was designed, synthesized and evaluated for its anti-neuraminidase (NA) activity (Hariono et al. 2016). Vanillin with guanidino group (MY21) at the C3 position played a vital role in NA inhibition. Modelling studies suggested that these predicted activities might be due to the interaction with conserved and essential residues of NA with ΔGbind (binding affinity of the ligand to the active site of the receptor) values comparable to those of oseltamivir and zanamivir, two commercially available NA inhibitors. Recently reports on SARS-CoV-2 suggests that vanillin has moderate affinity towards spike protein and main protease. Thus, further studies should be undertaken to enhance the inhibitory potential of vanillin and its derivative on SARS-CoV-2. Altogether, such findings suggest that vanillin and its derivatives can become suitable starting compounds for further lead optimization as NA inhibitors.
**Vanillin as a cosmeceutical ingredient**

Vanillin is used in many cosmeceuticals owing to its fragrance and antioxidant properties. At non-toxic concentrations, vanillin was found to up-regulate the stemness mediators Oct-4, pOct-4 and Nanog (transcription factors that control the stem cell signatures in humans) and it also increased the expression of epithelial adhesive protein (E-cadherin) (Taboonpong et al. 2017). Vanillin decreased the production of pro-inflammatory cytokines and reduced UV-B induced phosphorylation of ataxia telangiectasia mutated (ATM), serine-threonine kinase checkpoint kinase 2 (Chk2), tumor suppressor protein 53 (p53), p38/mitogen-activated protein kinase (p38), c-Jun N-terminal kinase/stress-activated protein kinase (JNK), S6 ribosomal protein (S6RP), and histone 2A family member X (H2A.X) (Lee et al. 2014). All these factors play a central role in skin renewal and repair; therefore, using vanillin or its derivatives as cosmeceutical ingredients could also provide therapeutic benefit in addition to providing fragrant and antioxidant effects.

**Clinical studies**

So far, only a few clinical trials with vanilla or vanillin have been undertaken or completed. The details of these studies are summarized in Table 3. However, only one out of these clinical trials was directed to assess the therapeutic potential of vanilla, while others were aimed to study the calming effect of vanilla/vanillin fragrance on the distressed infants with neonatal hypoxia and temporary Apnoea. Although few in numbers, these trails suggest that it is time to work towards and realize the therapeutic potential of vanilla/vanillin. The increase in the number of reports on the cyto-, neuro, nephron-, cardio-, and hepatoprotective potential of vanillin may therefore enhance the chances of vanillin to be considered for clinical trials in the future.

**Nanoparticles to deliver vanillin**

The bioavailability and hydrophobicity limit the bioactive efficiency and pharmacokinetics of vanillin. Nanocarriers or nanoparticles (NPs) can potentiate the bioactive profile of vanillin (Fig. 3). Various reports are available were vanillin is either capped /functionalized onto the NPs

![Fig. 3 Specific features of nanoparticles as delivery systems](image)

**Table 3 Clinical studies involving vanillin/vanilla**

| Official title                                           | Status       | Requirements/criteria                                      | Condition/disease target                  | Country  | Reference/ ClinicalTrail.gov identifier |
|----------------------------------------------------------|--------------|------------------------------------------------------------|------------------------------------------|----------|----------------------------------------|
| Odors to insufflate life                                 | Recruiting   | Premature new-borns with gestational age 28 to 33 weeks    | Temporary Apnoea                          | France   | NCT02851979                            |
| The calming effect of vanilla odor on preterm infant     | Recruiting   | Preterm infant                                             | None                                     | France   | NCT03626974                            |
| without mother’s breast milk feeding                     |              |                                                            |                                          |          |                                        |
| Effects of vanilla on hypoxic intermittent events in pre- | Recruiting   | Premature birth and neonatal hypoxia                       | Hypoxia                                  | Canada   | NCT02630147                            |
| mature infants                                           |              |                                                            |                                          |          |                                        |
| Isoflavone in prostate-specific antigen recurrent prostate | Phase II completed | Biochemical recurrent prostate cancer                        | Prostate cancer                          | United states | NCT00596895                            |

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or encapsulated into the NPs (Table 4). These NPs also allow controlled/sustained release to prolong the effect of vanillin. Apart from delivering vanillin using NPs, vanillin itself can be used to synthesize NPs for the delivery of other drug molecules (Table 4). It is an interesting development that a popular and one of the oldest flavoring molecule vanillin has found applications in the latest nanotechnology discipline as well. Due to these developments, it is essential to realize the potential of vanillin and consider it for therapeutic purposes.

Table 4  Summary of nanoparticles with vanillin as cargo/component of nanoparticles

| Vanillin as cargo/component of nanoparticles (NPs) | Carrier/material | Study | Subjects | Application | References |
|-------------------------------------------------|-----------------|-------|----------|-------------|------------|
| Vanillin as cargo | Ortho-vanillin NPs doped with glucan | In vivo | Rats | Anti-arthritic effects, reduction in TNF-α and IL-6 | Nasr et al. (2020) |
| | Gold NPs | In vitro | P. aeruginosa | Antibiotic potentiation and efflux pump inhibition | Arya et al. (2019) |
| | Graphene oxide | In vitro | THP-1 cells | Immunomodulation in human acute monocytic leukemia | Gurunathan et al. (2019) |
| | Chitosan-coated silica nanocapsules | In vitro | N/A | Controlled release of small volatile molecules for industrial application | Fan et al. (2018) |
| | Starch NPs | N/A | N/A | Enhance the bioavailability and flavour sensory quality of vanillin | Ege et al. (2017) |
| | Poly(lactic-acid) NPs | In vitro | N/A | Controlled release of vanillin with antioxidant potential | Dalmolin et al. (2016) |
| | Almond gum/PVA nanofibers | In vitro | N/A | Thermostable delivery system for vanillin | Rezaei et al. (2016) |
| | Poly(vanillin oxalate) | In vitro and in vivo | RAW 264.7 cells and mice | ROS-associated inflammation, reduce the expression of pro-inflammatory cytokines | Kwon et al. (2013) |
| | Ethylcellulose-steric acid core-shell NPs | In vitro | N/A | Nanocarrier for vanillin | Eltayeb et al. (2013) |
| | Polyvinyl alcohol nanowebs | In vitro | N/A | Prolonged self-life and temperature stability of vanillin | Kayaci and Uyar (2012) |
| Vanillin as a component of NPs | Rifampicin loaded chitosan-vanillin NPs | N/A | N/A | Increase the bioavailability of rifampicin | Dhamane and Jagdale (2020) |
| | Chitosan-vanillin-calcium ferrite | In vitro | L929 fibroblast and MCF-7 cells | Biocompatible and anti-cancer | Kamaraj et al. (2018) |
| | Chitosan-vanillin NPs | In vitro | HT-29 cells | Inhibition of human colon cancer cells | Li et al. (2016a) |
| | Bovine serum albumin-vanillin NPs | In vitro | BGC-823 cells | Inhibition of human gastric cancer cells | Li et al. (2016b) |
| | Folate conjugated chitosan-crosslinked vanillin NPs | N/A | N/A | Use for targeted delivery | Zhou et al. (2012) |

N/A not applicable
Conclusions

To date, vanillin has been utilized primarily as a flavour and fragrance ingredient. As discussed in this review, vanillin has shown diverse bioactivities that can be harnessed for human, animal and agricultural benefits. As it exhibited non-toxic effects in rat models, it is likely that vanillin is efficiently assimilated and eliminated from their bodies. Future studies in nanocarrier systems for vanillin may increase its stability, bioavailability and bioactivity. Hence with some promising inroads in this area, it would be interesting to systematically investigate the possible effects of vanillin with the multi-omics approach at cellular and molecular levels. This will enable us to further assess its applicability as an active biopharmaceutical ingredient to tackle important issues like neurodegeneration, antibiotic resistance, sickle-cell anaemia, tissue engineering, viral infections and industrial applications such as food preservation.

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Compliance with ethical standards

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

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References

Abraham D, Mehanna A, Wireko F, Whitney J, Thomas R, Orringer E (1991) Vanillin, a potential agent for the treatment of sickle cell anemia. Blood 77:1334–1341
Al-Baqami NM, Hamza RZ (2020) Synergistic antioxidant capacities of vanillin and chitosan nanoparticles against reactive oxygen species, hepatotoxicity, and genotoxicity induced by aging in male Wistar rats. Hum Exp Toxicol. https://doi.org/10.1177/0960327120943267
Anand A, Khurana R, Wahal N, Mahajan S, Mehta M, Satija S, Sharma N, Vyas M, Khurana N (2019) Vanillin: a comprehensive review of pharmacological activities. Plant Arch 19:1000–1004
Arya SS, Sharma MM, Das RK, Rookes J, Cahill D, Lenka SK (2019) Vanillin mediated green synthesis and application of gold nanoparticles for reversal of antimicrobial resistance in Pseudomonas aeruginosa &nbsp;clinical isolates. Heliyon 5:e02021
Arya SS, Sharma MM, Rookes J, Cahill D, Lenka SK (2020) Vanilla modulates the activity of antibiotics and inhibits efflux pumps in drug-resistant Pseudomonas aeruginosa. Biologia. https://doi.org/10.2478/s11756-020-00617-5
Asmari AA, Otaibi LA, Kunnathodi F, Ghulaydhawi FA, Arshaduddin M (2016) Vanillin a food additive ameliorates harmaline induced tremor in rats. J Neurol Exp Neurosci 2(1):2–8
Awasthi S, Saraswathi N (2016) Vanillin restrains enzymatic glycation and aggregation of albumin by chemical chaperone like function. Int J Biol Macromol 87:1–6
Banerjee G, Chattopadhyay P (2019) Vanillin biotechnology: the perspectives and future. J Sci Food Agric 99:499–506
Beaudry F, Ross A, Lema PP, Vachon P (2010) Pharmacokinetics of vanillin and its effects on mechanical hypersensitivity in a rat model of neuropathic pain. Phytother Res 24:525–530
Ben Saad H, Kherrat N, Driss D, Gargouri M, Marrakchi R, Jammoussi K, Magné C, Boudawara T, Ellouz Chaabouni S, Zeghal KM, Hakim A (2017) Effects of vanillin on potassium bromide-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Bezerra CF, Camilo CJ, do Nascimento Silva MK, de Freitas TS, Ribeiro-Filho J, Coutinho HDM (2017) Vanillin selectively modulates the action of antibiotics against resistant bacteria. Microb Pathog 113:265–268
Bezerra DP, Soares AKN, de Sousa DP (2016) Overview of the role of vanillin on redox status and cancer development. Oxid Med Cell Longev 2016
Bezerra-Filho CS, Barboza JN, Souza MT, Sabry P, Ismail NS, de Sousa DP (2019) Therapeutic potential of vanillin and its main metabolites to regulate the inflammatory response and oxidative stress. Mini Rev Med Chem 19(20):1681–1693
Blakie L, Kay G, Lin PK (2020) Synthesis and in vitro evaluation of vanillin derivatives as multi-target therapeutics for the treatment of Alzheimer’s disease. Bioorganic Med Chem Lett: 127505
Brochado AR et al (2018) Species-specific activity of antibiotic drug combinations Nature 559:259
Chee MJY, Lycett GW, Khow T-J, Chin CF (2017) Bioengineering of the plant culture of Capsicum frutescens with vanillin synthesize gene for the production of vanillin. Mol Biotechnol 59:1–8
Chen H, Zheng J, Ma J (2019) Vanillin ameliorates changes in HIF-1 α expression and neuronal apoptosis in a rat model of spinal cord injury. Restor Neurol Neurosci: 1–9
Cirimmina R, Fidalgo A, Meneguzzo F, Farrino P, Ibarco LM, Pagliaro M (2019) Vanillin: the case for greener production &nbsp;droven by sustainability megatrend. ChemistryOpen 8:660–667
Dalmolin LF, Khalil NM, Mainardes RM (2016) Delivery of vanillin by poly (lactic-acid) nanoparticles: development, characterization and in vitro evaluation of antioxidant activity. Mater Sci Eng C 62:1–8
da Silva JP, Costa MD, Campina CF, Bezerra CF, de Freitas TS, Sousa AK, Souza CE, de Matos YM, Pereira-Junior FN, Menezes IR, Coutinho HD (2020) Evaluation of chelating and cytoprotective activity of vanillin against the toxic action of mercuric chloride as an alternative for photoremediation. Environ Geochem Hlth 4:1–8
de Aragão Tavares E et al (2018) Chitosan membrane modified with a new zinc (II)-vanillin complex improves skin wound healing in diabetic rats. Front Pharmacol 9
Dhamane SP, Jagdale SC (2020) Development of Rifampicin loaded Chitosan nanoparticles by 32 full Factorial design . Res J Pharm Technol 13(6):2545–2550
Dhanalakshmi C, Manivasagam T, Nataraj J, Justin Thenmozhi A, Essa AK, Souza CE, de Matos YM, Pereira-Junior FN, Menezes IR, Coutinho HD (2020) Evaluation of chelating and cytoprotective activity of vanillin against the toxic action of mercuric chloride as an alternative for photoremediation. Environ Geochem Hlth 4:1–8
Ege ZR, Akan A, Oktar FN, Kalkandelen C, Gündüz O (2017) Probiotic effects of vanillin on Pseudomonas aeruginosa BL21 (DE3) growth. J Appl Microbiol 123:1234–1243
Fidalgo A, Meneguzzo F, Farrino P, Ibarco LM, Pagliaro M (2019) Vanillin: the case for greener production &nbsp;droven by sustainability megatrend. ChemistryOpen 8:660–667
Gargouri M, Marrakchi R, Jammoussi K, Magné C, Boudawara T, Ellouz Chaabouni S, Zeghal KM, Hakim A (2017) Effects of vanillin on potassium bromide-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
Hakim A (2017) Effects of vanillin on potassium bromate-induced neurotoxicity in adult mice: impact on behavior, oxidative stress, genes expression, inflammation and fatty acid composition. Arch Physiol Biochem 123(3):165–174
El Tayeb M, Stride E, Edrissingehe M (2013) Electrospayed core–shell polymer–ligand nanoparticles for active

component delivery. Nanotechnology 24(46):465604

Fan Q, Ma J, Xu Q, Wang J, Ma Y (2018) Facile synthesis of chi
tosan-coated silica nanocapsules via interfacial condensation
approach for sustained release of vanillin. Ind. Eng Chem Res
57(18):6171–6179

Fitzgerald D, Stratford M, Gasson M, Uckert J, Bos A, Narbad A (2004) Mode of antimicrobial action of vanillin against Escheri
cchia coli, Lactobacillus plantarum and Listeria innocua. J Appl
Microbiol 97:104–113

Fouda AA, Amin EF, Ahmed AF (2020) Naringenin and vanillin
mitigate cadmium-induced pancreatic injury in rats via inhibi
tion of JNK and p38 MAPK. Pathways Pharmacogn J 12(4)

Gallage NJ, Møller BL (2018) Vanilla: the most popular flavour. In:
Biotechnology of natural products. Springer, pp 3–24

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

Guo W, Liu B, Hu G, Kan X, Li Y, Gong Q, Xu D, Ma H, Cao Y, Hu G, Kan X, Li Y, Gong Q, Xu D, Ma H, Cao Y, Huang B, Fu S (2019) Vanillin protects the blood-milk barrier and inhibits the inflammatory response in LPS-induced mastitis in mice. Toxicol Appl Pharmacol 365:9–18

Gurunathan S, Kang MH, Jeyaraj M, Kim JH (2019) Differential
immunomodulatory effect of graphene oxide and vanillin-
functionalized graphene oxide nanoparticles in human acute
monocytic leukemia cell line (THP-1). Int J Mol Sci 20(2):247

Hannemann A, Cytlak U, Gbotosho O, Rees D, Tewari S, Gibson J (2014) Effects of o-vanillin on K+ transport of red blood
cells from patients with sickle cell disease. Blood Cells Mol
Dis 53:21–26

Hardcastle JL, Paterson CJ, Compton RG (2001) Biphasic sonoelec
troanalysis: simultaneous extraction from, and determination of
vanillin in food flavoring. Electroanal Int J Devot Fundam Pract
Aspects Electroanalnbsp;: 13;899–905

Hariono M et al (2016) Potential new H1N1 neuraminidase inhibitors from ferulic acid and vanillin: molecular modelling, synthesis and in vitro &nbsp; assay . Sci Rep 6:38692

Ho K, Yazan LS, Ismail N, Ismail M (2011) Toxicology study of vani
llin on rats via oral and intra-peritoneal administration. Food
Chem Toxicol 49:25–30

Hunger M, Domalik ‑Pyzik P, Chłopek J (2019) Double crosslinking
Hussain M, Qadri T, Hussain Z, Saeed A, Channar PA, Shehzadi

Kim HJ, Hwang IK, Won MH (2007) Vanillin, 4-hydroxybenzyl alde
hyde and 4-hydroxybenzyl alcohol prevent hippocampal CA1
cell death following global ischemia. Brain Res 1181:130–141

Kim JH et al (2014) A vanillin derivative causes mitochondrial dys
function and triggers oxidative stress in Cryptococcus neofo
r mans. PLoS ONE 9:e89122

Kim ME, Na JY, Park Y-D, Lee JS (2019) Anti-neuroinflammatory
effects of vanillin through the regulation of inflammatory factors
and NF-kB signaling in LPS-stimulated microglia. Appl Biochem
Biotechnol 187:884–893

Kun FYiZZZ (2002) Study on the extraction of vanillin from vanilla
planifolia Andr. with supercritical CO_2 Fluid. Flavour Fragr
Cosmet: 6

Kwon J, Kim J, Park S, Khang G, Kang PM, Lee D (2013) Inflamma
tion-responsive antioxidant nanoparticles based on a polymeric
prodrug of vanillin. Biomacromolecules 14(5):1618–1626

Lan X-B et al (2019) Neuroprotective effect of Vanillin on hypoxic-
 ischemic brain damage in neonatal rats. Biomed Pharmacother
118:109196

Lee J, Cho JY, Lee SY, Lee K-W, Lee J, Song J-Y (2014) Vanillin
protects human keratinocyte stem cells against ultraviolet B irra
diation. Food Chem Toxicol 63:30–37

Li PW, Wang G, Yang ZM, Duan W, Peng Z, Kong LX, Wang QH (2016a) Development of drug-loaded chitosan-vanillin nanoparticles
and its cytotoxicity against HT-29 cells. Drug Deliv 23(1):30–35

Li F, Zheng C, Xin J, Chen F, Ling H, Sun L, Webster TJ, Ming X, Liu J (2016) Enhanced tumor delivery and antitumor response of
doxorubicin-loaded albumin nanoparticles formulated based on a
Schiff base. Int J Nanomedicine &nbsp; 11:3875

Li J-M et al (2018) Vanillin-ameliorated development of azoxymeth
ane/dextran sodium sulfate-induced murine colorectal cancer: the
involvement of proteasome/nuclear factor-κB/mitogen-activated
protein kinase pathways. J Agric Food Chem 66:5563–5573

Li et al (2020) Vanillin derivative VND3207 activates DNA-PKCs
confering protection against radiation-induced intestinal epili
thelial cells injury in vitro and in vivo. Toxicol Appl Pharmacol
387:114855

Li T, He B, Mei Y, Wang D, Sun X, Li J (2019) Inhibitory effect of
vanillin on the virulence factors and biofilm formation of Hafnia alvei. LWT 102:223–229

Lim E-J, Kang H-J, Jung H-J, Song Y-S, Lim C-J, Park E-H (2008)
Anti-angiogenic, anti-inflammatory and anti-nociceptive activities
of vanillin in ICR&nbnbsp; mice. Biomol Ther 16:132–136

Ma W et al (2019) A vanillin derivative suppresses the growth of HT29
cells through the Wnt/β-catenin signaling pathway. Eur J Phar
macol 849:43–49

Ma W, Zhang Q, Li X, Ma Y, Liu Y, Hu S, Zhou Z, Zhang R, Du K, Syed A, Yao X (2020) PIM712, a vanillin derivative as potential
antitumor agents, displays better antitumor activity in colorectal
cancers cell lines. Eur J Cancer Sci 1(152):105464

Makaruk M (1980) Toxicity of vanillin. Gigiena i Sanitariya: 78–80

Mok N, Chan SY, Liu SY, Chua SL (2020) Vanillin inhibits PgsR-
mediated virulence in Pseudomonas aeruginosa. Food Funct
11(7):6496–6508

Nasr S, Varshosaz J, Hajhashemi V (2020) Ortho-vanillin nanoparticle-
doped glucan microspheres exacerbate the anti-arthritic effects of
methotrexate in adjuvant-induced arthritis in rats. Pharmacol
Rep 72(3):680–691

Naz H et al (2018) Evidence of vanillin binding to CAMKIV explains
the anti-cancer mechanism in human hepatic carcinoma and neu
roblastoma cells. Mol Cell Biochem 438:35–45

Ngarmasak M, Delaquis P, Toivonen P, Ngarmasak T, Ooraikul B, Mazza
G (2006) Antimicrobial activity of vanillin against spoilage micro-
organisms in stored fresh-cut mangoes. J Food Prot 69:1724–1727
Vanillin: a review on the therapeutic prospects of a popular flavouring molecule

Pagare PP et al (2018) Rational design of pyridyl derivatives of vanillin for the treatment of sickle cell disease. Bioorg Med Chem 26:2530–2538

Pattrick CA, Webb JP, Green J, Chaudhuri RR, Collins MO, Kelly DJ (2019) Proteomic profiling, transcription factor modeling, and genomics of evolved tolerant strains elucidate mechanisms of vanillin toxicity in Escherichia coli. mSystems 4:e00163–e00119

Pendyala B, Patras A (2020) In silico screening of food bioactive compounds to predict potential inhibitors of COVID-19 main protease (Mpro) and RNA-dependent RNA polymerase (RdRp). Chemrxiv. https://doi.org/10.26434/chemrxiv.12051927.v1

Ponnusamy K, Paul D, Kweon JH, Ponnusamy K, Paul D, Kweon JH (2009) Inhibition of quorum sensing mechanism and Aeromonas hydrophila biofilm formation by vanillin. Environ Eng Sci 26:1359–1363

Qais FA, Husain FM, Khan MS (2019) Deciphering the interaction of food additive, vanillin with DNA: A biophysical and computational study. J Biomol Struct Dyn 21:1–9

Ramadoss DP, Sivilingam N (2019) Vanillin extracted from Proso and Barnyard millets induce apoptotic cell death in HT-29 human colon cancer cell line Nutr Cancer: 1–16

Rezaei A, Tavanai H, Nasirpour A (2016) Fabrication of electrospun almond gum/PVA nanofibers as a thermostable delivery system for vanillin toxicity in Escherichia coli. mSystems 4:e00163–e00119

Salau VF, Erukainure OL, Ibeh CJ, Olaesheinde TA, Koornanally NA, Sunnaghatta Nagaraja S, Raviraj R, Selvakumar I, Dharmalingam D, Ramadas N, Chellappan DR, Prabhuc PC, Nagarajan D (2020) Radiation-induced H3K9 tri-methylation in E-cadherin promoter during lung EMT: in vitro and in vivo approaches using Vanillin. Free Radic Res: 1–40

Taboonpong S, Kiratipairoon C, Phiboonchayianan PP, Junthongpin P, Trithosudach P, Chanvorachote P (2017) Vanillin increases stem cell signal and cell adhesion in keratinocytes. Thai J Pharm Sci 41

Teoh ES (2019) The story of vanilla. In: Orchids as aphrodisiac, medicine or food. Springer, pp 109–130

Tomadoni B, Moreira MR, Ponce A (2016) Anti-quorum sensing activity of natural compounds against Chromobacterium violaceum. Annu Rev Food Sci Technol 11(1):43–48

Venkata S, Zeeshan F, Kamal A, Luqman AK, Saif H (2020) Efficiency of vanillin in impeding metabolic adaptability and virulence of Candida albicans by inhibiting glyoxylate cycle, morphogenesis, and biofilm formation. Curr Med Mycol 6(1):1

Voisine R, Carmichael L, Chaleri P, Cormier F, Morin A (1995) Determination of glucovanillin and vanillin in cured vanilla pods. J Agric Food Chem 43:2658–2661

Waliszewski KN, Ovando SL, Pardo VT (2007) Effect of hydration and enzymatic pretreatment of vanilla beans on the kinetics of vanillin extraction. J Food Eng 78:1267–1273

Wu Q, Cai H, Yuan T, Li S, Gao X, Song B (2020) Novel vanillin derivatives containing a 1, 3, 4-thiadiazole moiety as potential antibacterial agents. Bioorganic Med Chem Lett 16:127113

Xu C, Zhan W, Tang X, Mo F, Fu L, Lin B (2018) Self-healing chitosan/vanillin hydrogels based on Schiff-base/hydrogen bond hybrid&nb isspace;linkages. Polym Test 66:155–163

Yan X, Liu DF, Zhang XY, Liu D, Xu SY, Chen GX, Huang BX, Ren WZ, Wang W, Fu SP, Liu JX (2017) Vanillin protects dopaminergic neurons against inflammation-mediated cell death by inhibiting ERK1/2, p38 and the NF-kB signaling pathway. Int J Mol Sci 18(2):389

Yang Y, Wen W, Luo Y, Wu J, Xiang L, Hu Y, Xu S, Chen S, Wang P (2020) Vanillin enhances the passive transport rate and absorption of drugs with moderate oral bioavailability in vitro and in vivo by affecting the membrane structure. Food Funct 11(1):700–10

Younis NN, Elsherbiny NM, Shaheen MA, Elseweidy MM (2020) Modulation of NAPDH oxidase and Nrf2/HO-1 pathway by vanillin in cisplatin-induced nephrotoxicity in rats. J Pharm Pharmacol. https://doi.org/10.1111/jphp.13340

Zabad IE, Amin MN, El-Shishtawy MM (2019) Protective effect of vanillin on diabetic nephropathy by decreasing advanced glycation end products in rats. Life Sci 239:117088

Zhang S, Mueller C (2012) Comparative analysis of volatiles in traditionally cured Bourbon and Ugandan vanilla bean (Vanilla planifolia) extracts. J Agric Food Chem 60:10433–10444

Zhou M, Li PW, Wang G, Yang ZM, Peng Z, Kong LX (2012) Preparation of nanoparticles by crosslinking folate conjugated chitosan with vanillin and its characterization. Adv Mater Res 466:454–457

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