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REVIEW

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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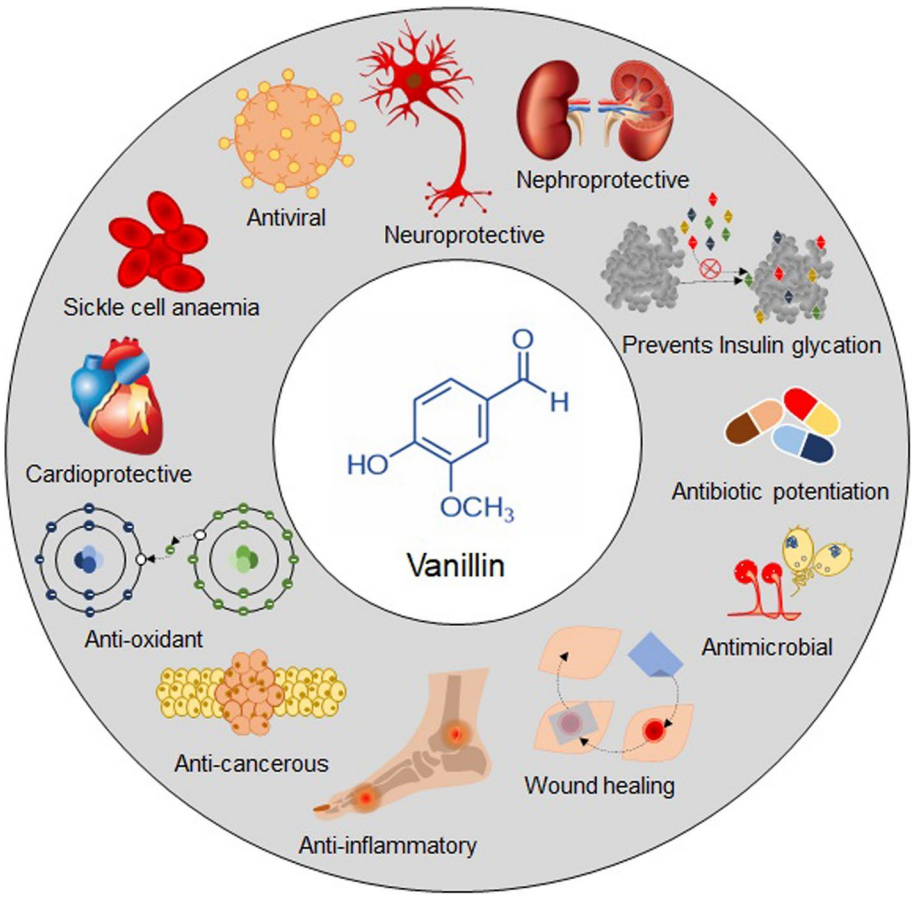
Graphic abstract



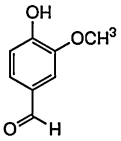
Keywords Vanillin · Anticancer · Neuroprotective · Antibiotic potentiation · Antimicrobial · Cosmeceutical

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.

Table 1 Physicochemicalcharacteristics of vanillin

Chemical name	4-hydroxy-3-methoxybenzaldehyde
C.A.S number	121-33-5
Molecular formula	$C_8H_8O_3$
Molecular weight	152.15 g/mol
Chemical structure	
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 °C
Melting point	81.5 °C
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 °C
Dissociation constant	pKa = 17.40, pKa = 211.4 (25 °C)
Food additive status	FDA approved

Therefore, due to the potential emerging reports of usage of vanillin as a therapeutic molecule and its inclusion in the food additive on generally regarded as safe (GRAS) list, it is an ideal candidate for health care applications (Tai et al. 2011b). Our focus here is to provide an in-depth look at the bioactive properties of vanillin (Table 2) as an attempt to identify it as a mainstream bioactive small molecule like curcumin. Readers are also directed to the reviews by Singletary (2020), Sharma et al. (2020), Anand et al. (2019) and Bezerra-Filho et al. (2019) that highlighted the therapeutic use of vanilla, vanillin, and vanillic acid.

The literature for this review was extracted from the last three decades published in various research and review articles, book chapters, and conference proceedings. The search engines used to search this information includes PubMed, Google Scholar, Science direct and ScopeMed. The keywords or search terms, "vanillin", "vanillin derivatives, bioactivities, anticancer, antioxidant, anti-inflammatory, neuroprotective, anti-sickling, anti-amyloid aggregation and inhibition of non-enzymatic glycation, antibacterial, anti-fungal, anti-quorum sensing, antibiotic potentiation, wound healing/tissue engineering, antiviral", "toxicity", "nanoparticles", "nanocarriers" and their combination were used (Fig. 1).

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

Table 2 Summary of literature into the effects of vanillin and vanillin derivatives on potential cellular targets and associated molecular mechanisms

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)

Table 2 (continued)

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, neurofunctional 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 (iNOS), 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), Hannemann 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)

Table 2 (continued)

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-Cortes 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 subtitles, 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 C_6-HSL and C_8-HSL, downregulation of transcriptional regulator (*halR*) and acyl-homoserine-lactone synthase (*halI*), may act as inhibitor of HalR protein	Vanillin	Li et al. (2019)

Table 2 (continued)

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	H9c2cardiomyocytes	Decreased sub-G1 appearance, activation of caspase-3 and PARP1, reduction in doxo-related 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)

Table 2 (continued)

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

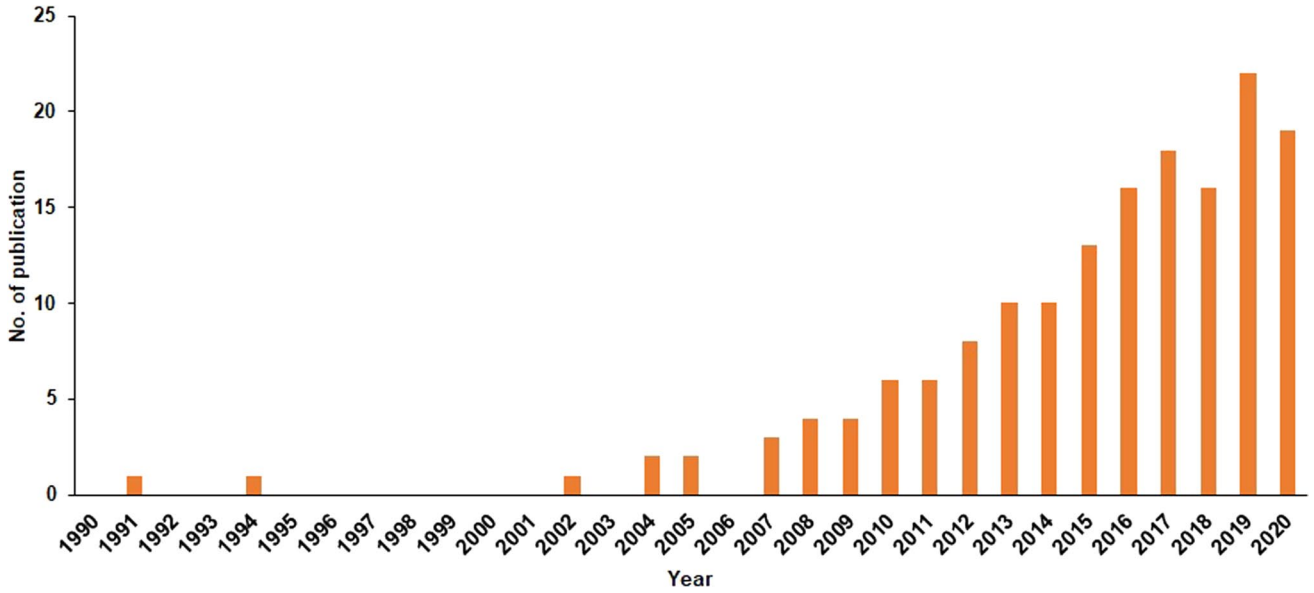


Fig. 1 Number of published articles on bioactivities of vanillin (Accessed on 07th September, 2020)

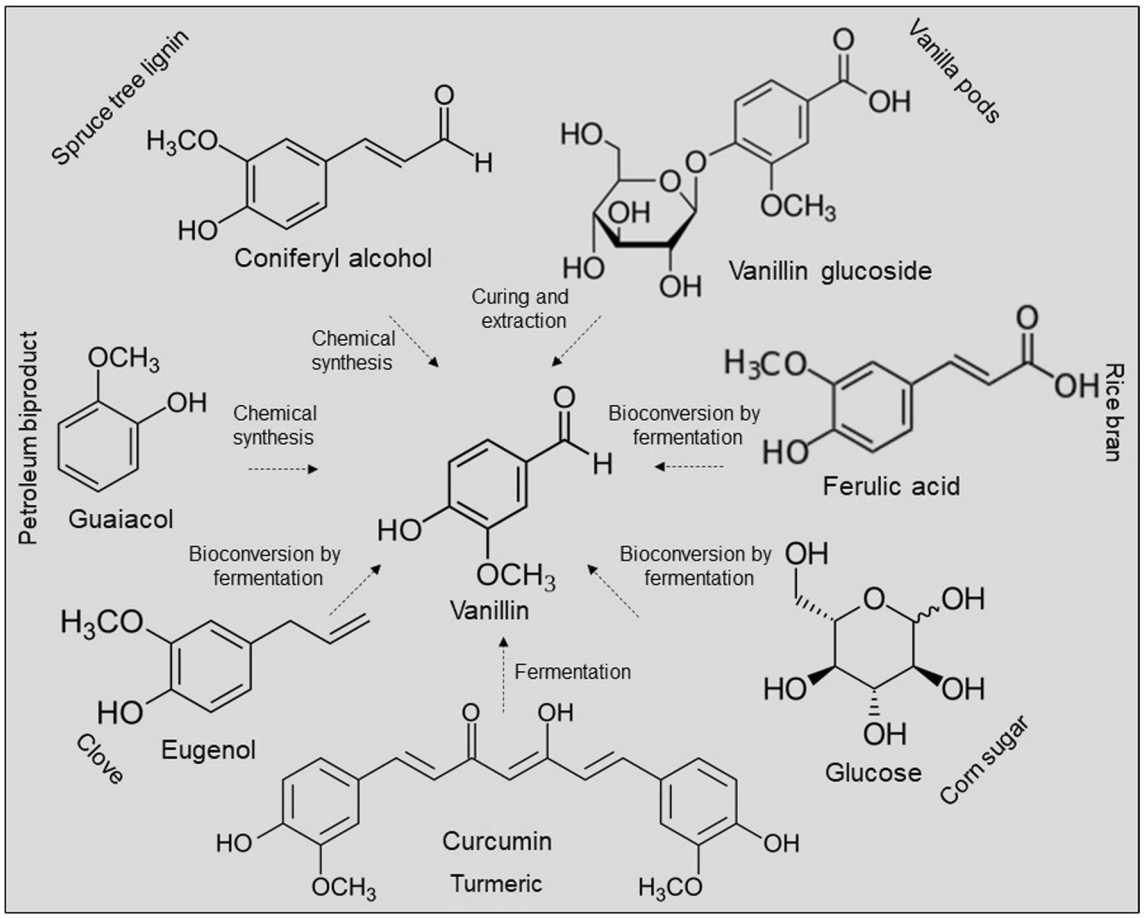


Fig. 2 Different sources and routes of vanillin synthesis

(Hardcastle et al. 2001; Kun 2002; Sharma et al. 2006; Sostaric et al. 2000; Voisine et al. 1995; Waliszewski et al. 2007). 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 it 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- hydroxybenzaldeyde, 3-bromo-4-hydroxybenzaldeyde, 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 *Nocardia* 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 antimutagenic 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]-phenanthrolin-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′-azinobis(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 Fe^{2+}-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 sever 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 cryoptococcal 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 spiritovorun* 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* (Bezerra 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 its 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 ΔG_{bind} (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

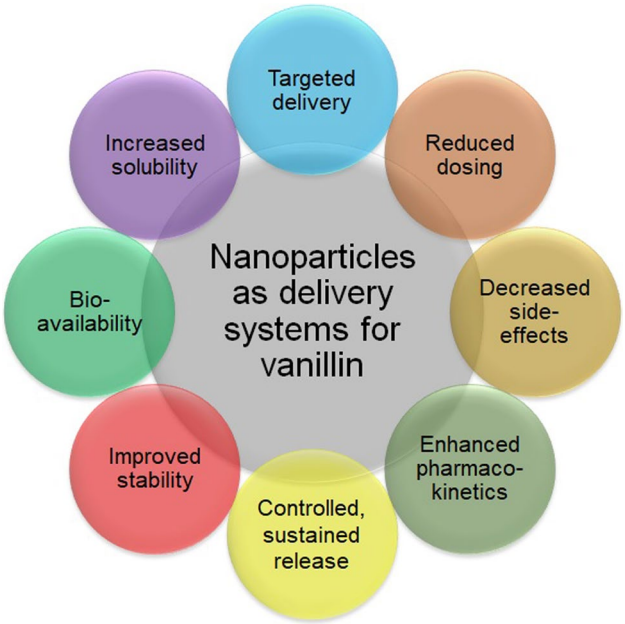


Fig. 3 Specific features of nanoparticles as delivery systems

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 without mother's breast milk feeding	Recruiting	Preterm infant	None	France	NCT03626974
Effects of vanilla on hypoxic intermittent events in premature infants	Recruiting	Premature birth and neonatal hypoxia	Hypoxia	Canada	NCT02630147
Isoflavone in prostate-specific antigen recurrent prostate cancer	Phase II completed	Biochemical recurrent prostate cancer	Prostate cancer	United states	NCT00596895

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.

Conflict of Interest Sagar S. Arya has no conflict of interest. James Rookes has no conflict of interest. David Cahill has no conflict of interest. Sangram K. Lenka has no conflict of interest.

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