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Review

How Effective Is *Vanilla planifolia* Beyond Flavor in Protecting Against Oxidative Stress?

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Abstract

Emerging evidence indicates that low-grade chronic systemic inflammation is a key contributor to the onset and progression of numerous chronic diseases. *Vanilla planifolia*, a globally valued spice recognized for its characteristic sweet aroma and flavor, is primarily derived from its beans and widely utilized in culinary, therapeutic, and medicinal contexts. Beyond its traditional use, vanilla provides essential nutrients and bioactive compounds, including B vitamins such as vitamin B6, niacin, and riboflavin, which are integral to metabolic regulation. In addition to its applications in food and pharmaceuticals, vanilla exhibits complementary medicinal properties. Vanillin, the principal bioactive constituent of vanilla, imparts its distinctive flavor and aroma and is accompanied by other phenolic compounds with notable antioxidant activity. This review highlights the potential of vanillin as a therapeutic agent, shifting its perception from a conventional flavoring compound to a promising bioactive molecule with relevance in chronic disease prevention. Furthermore, the applications of vanillin within the food industry are discussed.

Keywords: antioxidant; cancer; inflammation; oxidative stress; *Vanilla planifolia*; vanillin

1. Introduction

Emerging research evidence has suggested that low-grade chronic systemic inflammation plays a vitally important role in modulating several chronic diseases such as cancer, cardiovascular disease (CVD), metabolic syndrome, and type 2 diabetes [1,2], which is known as "inflammatory diseases" [3]. Although the underlying molecular inflammatory process involved in each disease may vary from other diseases, the basic mode of action of the inflammatory mediators and proinflammatory cytokines is similar.

Oxidative stress is closely linked to chronic inflammation [4], and additional factors may further exacerbate the accumulation of proinflammatory cytokines, perpetuating a "vicious cycle" [5]. In cultured adipocytes, reactive oxygen species (ROS) enhance the production of monocyte chemotactic protein-1 (MCP-1) and upregulate interleukin-6 (IL-6) expression [1]. Within adipose tissue, ROS facilitate macrophage infiltration, thereby fostering a proinflammatory microenvironment [6]. ROS also activate intracellular signaling cascades, predominantly via NF-κB, which in turn stimulate the expression of IL-6 and tumor necrosis factor-α (TNF-α). Furthermore, oxidative stress can induce cellular senescence, particularly in adipocytes, through oxidative damage. Senescent adipocytes may subsequently recruit macrophages and amplify proinflammatory cytokine production [3].

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Substantial evidence indicates that excessive macronutrient intake promotes oxidative stress, thereby driving inflammation through NF-κB-mediated signaling pathways [7].

Vanilla planifolia is a perennial, climbing tropical plant of the *Orchidaceae* family [8]. The term "Vanilla" derives from the Spanish word Vainilla, a diminutive of Vaina meaning "sheath" or "pod," which aptly reflects the morphology of the vanilla bean [9]. Native to Central and South America and the Caribbean, vanilla was first cultivated by the Totonacs along Mexico's eastern coast [9]. Vanilla contains essential nutrients and bioactive compounds that underpin its culinary, therapeutic, and medicinal applications, including B vitamins that support metabolic functions and alleviate pain in conditions such as arthritis [9]. Vanillin, the primary bioactive compound, imparts its characteristic flavor and aroma, while phenolic compounds provide antioxidant activity that mitigates oxidative stress and cellular damage [10]. Beyond antioxidant effects, vanilla demonstrates anti-inflammatory, antimicrobial, and anti-carcinogenic properties, and in Ayurvedic medicine it is traditionally used to relieve stress and promote well-being [9,11].

The rising prevalence of chronic diseases such as diabetes, cancer, and obesity underscores the need for alternative bioactive compounds. *Vanilla planifolia* emerges as a promising source of plant-derived molecules with potential roles in disease prevention and management, warranting exploration beyond its traditional use as a flavoring agent. This review highlights its bioactive properties, therapeutic applications in chronic disease prevention, and potential utilization in functional foods and nutraceuticals.

2. Method

A comprehensive literature search was conducted using electronic databases including PubMed, Scopus, Web of Science, and Google Scholar. The search covered studies published from January 1998 to December 2025. The following keywords and their combinations were used: "vanillin", "oxidative stress", "antioxidant activity", "genotoxicity", "DNA damage", "anticancer", "antidiabetic", "anti-inflammatory", "neuroprotective", "antimicrobial", "apoptosis", "flavoring agent", "safety", "toxicity", "mitochondrial dysfunction", and "cell cycle arrest". Boolean operators (AND, OR) were applied to refine the search strategy. Additional relevant studies were identified by manually screening the reference lists of selected articles.

3. Oxidative Stress and Chronic Diseases

This review focuses on oxidative-stress-related diseases with well-established mechanistic links to redox imbalance, including cardiovascular diseases, type 2 diabetes mellitus, and cancer. These conditions were selected because oxidative stress plays a central role in the pathogenesis via mechanisms, including mitochondrial dysfunction, chronic inflammation, DNA damage, and impaired cellular signalling. In addition, these diseases represent major contributors to global morbidity and mortality, making them highly relevant from both mechanistic and public health perspectives. By concentrating on these representative conditions, this review aims to provide a comprehensive overview of the pathological consequences of oxidative stress and therapeutic implications.

3.1. Cardiovascular Disease

Cardiovascular disease (CVD) encompasses a range of disorders affecting the heart and blood vessels, and it is a leading cause of morbidity and mortality worldwide. The term cardiovascular disease broadly refers to conditions such as coronary heart disease (CHD), stroke, peripheral artery disease (PAD), and aortic disease [12]. CHD, characterized by the build-up of plaque in the coronary arteries, often leads to angina or myocardial infarction (heart attack). Stroke occurs when blood flow to the brain is obstructed or reduced, leading

to brain cell damage. PAD involves narrowing or blockage of the peripheral arteries, typically in the legs, while aortic diseases affect the body's largest blood vessel, the aorta. A common condition is an aortic aneurysm, where the aorta weakens and bulges, which can further cause life-threatening bleeding if it ruptures [12].

The prevalence of CVD is alarmingly high, making it a global health crisis. According to the World Health Organization [12], CVD represents the leading cause of mortality worldwide, accounting for an estimated 17.9 million deaths annually. This statistic underscores the significant impact of CVD on public health and highlights the urgent need for effective prevention and treatment strategies. CVD affects individuals across all demographics, though risk factors such as age, sex, lifestyle, and genetics contribute to its development and progression.

The underlying mechanisms of CVD are complex and multifaceted, involving a combination of genetic predispositions, environmental, and lifestyle factors. A primary mechanism in the development of CVD is the process of atherosclerosis, where fatty deposits (atheromas) build up on the arterial walls, leading to reduced blood flow and increased risk of clot formation [13]. This process is often exacerbated by factors such as high cholesterol levels, hypertension, smoking, and diabetes. Oxidative stress plays a critical role in the pathogenesis of CVD. It arises from an imbalance between the production of ROS and the body's ability to neutralise them with antioxidants, causing cellular and molecular disruptions that can lead to cardiac dysfunction [14]. ROS can damage endothelial cells lining the blood vessels, leading to inflammation and endothelial dysfunction. This damage promotes the progression of atherosclerosis and contributes to the development of other cardiovascular conditions. Oxidative stress not only affects the endothelial cells but also impacts various lipoproteins and cellular components, further aggravating cardiovascular damage [15]. Elevated levels of oxidised low-density lipoprotein (LDL) cholesterol, often referred to as "bad cholesterol," for instance, are a significant risk factor for atherosclerosis. Chronic oxidative stress can lead to persistent inflammation, which compounds endothelial injury and accelerates the development of cardiovascular diseases [1]. Thus, understanding the mechanisms of oxidative stress and its impact on cardiovascular health is crucial for developing targeted interventions to reduce the burden of CVD.

3.2. Type 2 Diabetes Mellitus

The chronic metabolic disease known as type 2 diabetes mellitus (T2DM) is characterised by decreased insulin production and insulin resistance. Type 2 diabetes is characterised by increased blood glucose levels due to the body's inability to utilise insulin efficiently, in contrast to type 1 diabetes, which is caused by the body's inability to make insulin. This disease usually manifests at maturity, while it is increasingly being identified in younger populations. It is linked to obesity, sedentary lifestyles, and genetic predispositions [16]. Targeting oxidative stress in treatment techniques is crucial because of its involvement in developing insulin resistance and causing problems related to diabetes.

There are 422 million people worldwide who have diabetes; most of them live in low- and middle-income countries. Every year, the illness is directly to blame for 1.5 million deaths. Both the incidence and the number of cases of diabetes have steadily increased during the last few decades. Given that this incidence is significantly higher than in previous years, it suggests a growing public health risk. Among the causes of this trend are fast urbanisation, dietary modifications that lead to a rise in the consumption of high-calorie foods, and a decline in physical activity. As evidenced by the disease's increasing prevalence, comprehensive public health programmes are badly needed to control and alleviate Malaysians' burden from type 2 diabetes [17].

Oxidative stress is one of the primary causes and developments of type 2 diabetes. It is distinguished by an imbalance between the body's antioxidant defences and the generation of ROS [18]. Chronic hyperglycemia in type 2 diabetes is a factor in the overproduction of ROS. These very reactive compounds have the potential to seriously harm DNA, proteins, and lipids in cells. Insulin signalling pathway degradation is a major mechanism via which oxidative stress contributes to type 2 diabetes. Oxidative stress contributes to insulin resistance predominantly via degradation and disruption of the insulin signalling cascade. Under physiological conditions, insulin binds to the insulin receptor (IR), leading to tyrosine phosphorylation of insulin receptor substrate (IRS-1 and IRS-2), activation of phosphatidylinositol 3-kinase (PI3K), and thereby stimulates the Akt. Akt activation promotes glucose uptake through translocation of GLUT4 to the plasma membrane. Nonetheless, excessive production of ROS activates stress-sensitive serine/threonine kinases, for instance, c-Jun N-terminal kinase (JNK), inhibitor of κB kinase β (IKKβ), and p38 MAPK. These kinases trigger serine phosphorylation of IRS proteins, which inhibits normal tyrosine phosphorylation and promotes their dissociation from the insulin receptor. Serine-phosphorylated IRS becomes a target for ubiquitination and subsequent proteasomal degradation, and subsequently decreasing IRS protein availability. Moreover, oxidative stress can impair Akt activation and enhance activity of phosphatases including PTEN, further attenuating downstream signalling. Taken together, these alterations disrupt GLUT4 translocation, reduce glucose uptake in adipose tissue and skeletal muscle, and contribute to the development of type 2 diabetes and insulin resistance [19]. ROS have the ability to alter important signalling molecules, which can interfere with cells' normal reactions to insulin and exacerbate insulin resistance [20]. Furthermore, pancreatic beta-cell activity may be impaired by oxidative stress, which would decrease insulin output and worsen hyperglycemia. Increased oxidative stress from elevated blood sugar levels exacerbates insulin resistance and beta-cell malfunction, creating an endless cycle [21].

Moreover, oxidative stress has been connected to the development of problems associated with diabetes, including retinopathy, neuropathy, nephropathy, and cardiovascular illnesses [18]. ROS can increase the risk of cardiovascular events by damaging endothelial cells, causing inflammation, and hastening the production of atherosclerotic plaques in the vascular system. Oxidative stress in peripheral tissues can harm the kidneys and nerves, causing neuropathy and kidney damage [22]. Due to a combination of hereditary and lifestyle factors, type 2 diabetes is becoming common worldwide. Targeting oxidative stress in treatment techniques is crucial because of its involvement in developing insulin resistance and causing problems related to diabetes. Reducing oxidative stress through glycemic control enhancements, antioxidant therapy, and lifestyle modifications may lessen the consequences of type 2 diabetes and enhance the quality of life for those who have this long-term illness.

3.3. Cancer

Research has demonstrated that elevated oxidative stress contributes to cancer development, including colorectal cancer [23]. Oxidative stress is hypothesized to be closely associated with both obesity and cancer. Evidence from an obese animal model of non-alcoholic steatohepatitis supports this hypothesis, showing that adiponectin deficiency promotes hepatic tumor formation and enhances oxidative stress [24]. ROS play a pivotal role in carcinogenesis [25]. Increased ROS levels elevate mutation rates and susceptibility to mutagenic agents, thereby contributing to DNA damage during the early stages of tumorigenesis [26]. ROS also drive tumor proliferation through ligand-independent transactivation of receptor tyrosine kinases [27], facilitating metastasis and cancer cell invasion [28]. Furthermore, Semenza [29] reported that ROS stabilize hypoxia-inducible

factor 1, a transcriptional regulator of vascular endothelial growth factor, thereby promoting tumor angiogenesis.

Interestingly, insulin has been identified as a proliferative factor in prostate cancer, suggesting that carbohydrate restriction may reduce serum insulin levels and slow prostate cancer progression [30]. Epidemiological studies further indicate that patients with type 2 diabetes and obesity exhibit an increased risk of liver, colorectal, breast, and pancreatic cancers [31]. These associations implicate leptin, insulin/insulin-like growth factor-1, adiponectin, and chronic inflammation as additive mediators linking type 2 diabetes and obesity to cancer. Fat accumulation is frequently associated with systemic oxidative stress via ROS elevation [32]. Elevated oxidative stress can induce chronic inflammation, which in turn contributes to the pathogenesis of cancer [33]. Mechanistically, oxidative stress activates transcription factors such as Wnt/β-catenin, NF-κB, and nuclear factor E2-related factor 2 (Nrf2), thereby stimulating inflammatory signaling pathways [25]. Collectively, these findings suggest that increased circulating or local ROS derived from adipose tissue expansion within the tumor microenvironment exacerbate oxidative stress in tumor cells, ultimately enhancing cancer progression in patients with type 2 diabetes or obesity.

The underlying mechanism of cancer involves genetic and epigenetic changes that lead to the uncontrolled proliferation of cells. These changes can be caused by various factors, including exposure to carcinogens, inherited genetic mutations, and errors during cell division [1]. One important factor in the development of cancer is oxidative stress, which can lead to DNA damage and genomic instability. ROS generation and the body's capacity to neutralise them are out of balance, which leads to oxidative stress [34].

Numerous studies have demonstrated that natural plant-derived compounds, particularly polyphenols, flavonoids, and phenolic acids, exhibit strong antioxidant properties that can neutralize ROS [35,36]. *Vanilla planifolia* represents a promising candidate due to its rich profile of phenolic constituents, including vanillin and related derivatives, which may contribute to oxidative stress mitigation. This rationale provides the foundation for our subsequent investigation into the bioactivity of *Vanilla planifolia* extracts.

4. *Vanilla planifolia*

Vanilla planifolia is a perennial, climbing tropical plant belonging to the *Orchidaceae* family [8]. The term "vanilla" derives from the Spanish word vainilla, a diminutive of vaina meaning "sheath" or "pod," aptly describing the morphology of the vanilla bean [9]. Indigenous to Central and South America and the Caribbean, vanilla was first cultivated by the Totonacs of Mexico's eastern coast [9]. Following the Aztec conquest of the Totonacs in the fifteenth century, vanilla became integrated into Aztec culture [9]. Natural vanilla thrives within a 20-degree latitudinal band on either side of the Equator, with major production occurring in Indonesia and Madagascar, although the species is native to Mexico. The plant requires approximately three years to reach maturity and produce flowers, while the fruit (vanilla beans) must remain on the vine for nine months before harvest. At this stage, the beans are devoid of flavor and require post-harvest curing to develop their characteristic aroma and taste [37].

The vanillin molecule (Figure 1) comprises a benzene ring attached to a hydroxyl group, an aldehyde group, and an ether group. This chemical structure is responsible for its characteristic bioactive properties and enables modification or combination with other compounds to synthesize various derivatives [38].

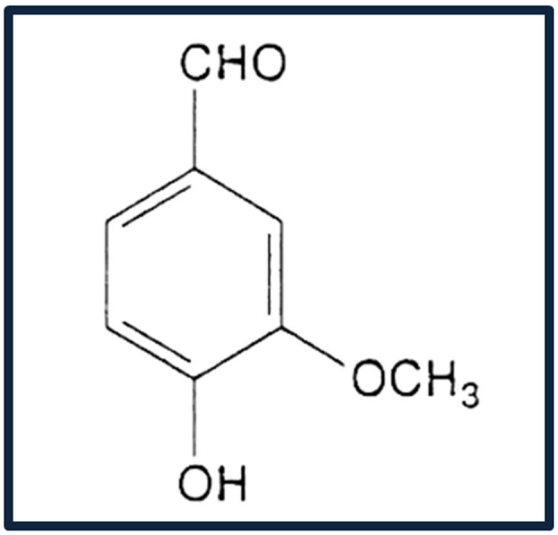


Figure 1. Molecular structure of vanillin.

Vanillin can be obtained from three primary sources including biotechnological, chemical/synthetic, and natural. Its classification as either an artificial or natural flavor depends on the method of synthesis and origin. Biotechnologically produced vanillin, as well as natural vanillin synthesized using ferulic acid as a substrate, have been recognized as food-grade additives by several international food regulatory authorities [39]. In contrast, chemically synthesized vanillin is typically derived from cost-effective precursors such as lignin, eugenol, or guaiacol, and may be supplemented with ethyl vanillin. Compared to natural vanillin, artificial vanillin generally exhibits a simpler and less complex flavor profile [40,41].

5. Bioactive Compounds of Vanilla

Limited information is available regarding the chemical composition of mature green vanilla beans. Fiber components, including cellulose, lignin, and hemicellulose, contain approximately 8% of the fresh weight, which is significantly higher than the typical 1–4% found in most fruits and vegetables [42]. Sucrose is the predominant carbohydrate, although the total carbohydrate content is lower than that of most fruits [43]. Similarly, protein content is less than 1%, comparable to that of most fruits and vegetables. The high glucosidase activity in vanilla suggests the presence of elevated levels of aromatic compounds [44].

Vanilla beans contain remarkably high lipid content, approximately 12% of fresh weight, which is substantially greater than the 0.2–0.4% typically found in fruits and vegetables. The predominant organic acids are citrate and malate, accounting for approximately 80% of total organic acids. Additionally, vanilla beans contain 470 mg of potassium and 170 mg of calcium, both of which are present in significantly higher concentrations than in most vegetables and fruits [45].

Vanilla planifolia Jacks. ex Andrews contains a notably high concentration of glucovanillin, accounting for approximately 1.7% of its fresh weight. Vanillin (4-hydroxy-3-methoxybenzaldehyde) is the principal volatile compound, comprising 80–90% of the total volatiles. The characteristic flavor and aroma of vanilla develop through a series of enzymatic reactions during the curing process. Other reported compounds include benzyl ethers, lactones, carbonyl compounds, eugenol, phenols, phenol ethers, caproic acid, vitispiranes, anisyl alcohol, anisaldehyde, anisic acid, and vanillic acid [46]. In addition, vanilla contains B-complex vitamins, 25% carbohydrates, 15% fats, and approximately 6% mineral salts, including potassium, manganese, iron, calcium, magnesium, and zinc.

The water content of vanilla beans ranges from 35–40% [47]. The bioactive constituents of *Vanilla planifolia*, particularly vanillin, demonstrate rapid gastrointestinal absorption but undergo extensive hepatic metabolism, predominantly via glucuronidation and sulfation, resulting in limited systemic bioavailability. Pharmacokinetic investigations report rapid clearance and urinary excretion of conjugated metabolites. These pharmacokinetic characteristics constrain therapeutic applicability, and thus more research is required to elucidate the formulation strategies and delivery systems such as encapsulation or nanoparticle carriers to improve the bioavailability [48].

6. Pharmaceutical Roles of Vanillin

6.1. Anti-Inflammatory Properties

Vanillin, a bioactive compound found in *Vanilla planifolia*, exhibits strong antioxidant properties [9]. Studies have shown that vanillin and vanillic acid can protect brain cells from oxidative stress [9]. A study conducted on aging rats found that vanillin may help reduce inflammation and enhance antioxidant defences [8]. Due to its antioxidant properties, vanillin can prevent oxidative damage to membranes in mammalian tissues [8]. Recent experiments also suggest that vanillin can alleviate inflammation, reduce anxiety, and enhance appetite [49]. In addition, vanilla extract also recognized in Ayurveda as a stress-relieving and calming agent, possesses the ability to neutralize free radicals and oxidants [9]. This natural remedy has been employed for centuries in various cultures as a means of promoting overall well-being. According to Ayurvedic practices, the consumption of water infused with vanilla flavor is a traditional method known to mitigate inflammation. This ancient wisdom aligns with contemporary scientific understanding, as vanilla's anti-inflammatory properties have been increasingly acknowledged [9].

6.2. Anticancer Effects

Vanillin has demonstrated antimutagenic and anticancer activities by reducing chemically induced genotoxicity in experimental models such as mouse bone marrow cells and *Drosophila melanogaster*, protecting against mutagens including methylmethane, mitomycin C, N-ethyl-N-nitrosourea, and bleomycin, and inhibiting proliferation of colorectal cancer cells (HT-29) through cell cycle arrest at the G2/M and G0/G1 phases and induction of apoptosis [50–52]. Similarly, studies on hamster lung cells indicated that vanillin reduced UV-induced DNA mutations and chromosomal damage, while enhancing DNA repair mechanisms [53]. In human cancer cell lines like lung cancer (NCI-H460), vanillin suppressed metastasis and reduced gene expression related to tumor growth [54]. Apart from that, as a potent antioxidant, vanillin neutralizes free radicals that can damage cells and DNA. Vanillin protected DNA from radiation-induced damage in both laboratory and animal models [55]. The free radical scavenging ability underscores its importance in preventing oxidative stress, a precursor to various diseases, including cancer.

A recent study showed that *Vanilla planifolia* extracts significantly decreased cell viability in HepG2 cells at a dosage of 5000 µg/mL for 72 h, 48 h, and 24 h. A similar effect was observed in mouse liver fibroblast (FC3H) cells [50]. In addition, ethanolic *Vanilla planifolia* leaf extract has also demonstrated antiproliferative activity against squamous carcinoma and breast cancer cells [56,57]. A study by Chang et al. [58] evaluated the antitumor effect of *Vanilla planifolia* on glioblastoma multiforme cells. The study found that the ethanol extract of *Vanilla planifolia* stem significantly reduced the viability and colony-forming ability of glioblastoma multiforme cells via downregulation of 14 hub DEGs and upregulation of 9 hub DEGs. Table 1 summarizes the pharmacological effects of *Vanilla planifolia*, vanillin, and its derivatives.

Table 1. Pharmacological effects of *Vanilla planifolia* extract, vanillin, and its derivatives.

Plant/Bioactive Compounds	Diseases	Findings	Reference
Vanillin	Melanoma	Decreased cell viability and melanoma tumor size	[59]
Vanilla planifolia stems (Ethanol extract)	Glioblastoma multiforme	Decreased cell proliferation, inhibited colony formation, and triggered autophagy	[58]
Vanillin	Breast cancer	Inhibits colony formation and decreases cell survival in human cancer cell lines, including MCF-7 and A549	[60]
VALD-3, a Schiff base ligand produced from derivatives of o-vanillin	Breast cancer	VALD-3 induced cell cycle arrest and apoptosis by modulating key apoptotic regulators. It upregulated anti-apoptotic proteins (Bcl-2, Bcl-xl, survivin, and XIAP) while downregulating pro-apoptotic proteins (Bad and Bax)	[61]
Vanillin derivatives	Breast cancer	Induced apoptotic cell death in breast cancer cell lines by activating the caspase-8-mediated pathway	[62]
Vanillin derivative, [5-((1E,15E)-16-(3-methoxy-4-hydroxyphenyl)hexadeca-1,15-diimine)-2-methoxyphenol]	Gram-positive bacteria *Staphylococcus aureus* ATCC 29213, *Bacillus subtilis* ATCC 6633, and *Bacillus cereus* ATCC 11778 and the Gram-negative bacteria *Escherichia coli* ATCC 25922, *Klebsiella pneumonia* ATCC 43816, and *Pseudomonas aeruginosa* ATCC 27853	The compound demonstrated the lowest antibacterial activity against *Escherichia coli* and the highest activity against *Staphylococcus aureus*	[63]
Vanillin-crosslinked chitosan nanocomposites with different concentrations of ZnO nanoparticles	Gram-positive (*Staphylococcus aureus*) and Gram-negative (*Escherichia coli* and *Pseudomonas aeruginosa*) bacteria	The antibacterial activity of chitosan was enhanced in the presence of vanillin	[64]
Vanillin	Primary dermal fibroblast cells and human keratinocytes (HaCaT)	Vanillin prevents ROS-induced cellular death and may also promote wound healing in vitro	[65]

Vanillin is a natural compound with anti-neoplastic properties with minimal adverse effects [66]. Vanillin (5, 4, 3, 2, 1 μg/mL) significantly reduced B16F10 cell viability following 24 h of incubation. Melanoma tumor size was decreased after treatment at both 100 and 50 mg/kg/day of vanillin for 10 days. NF-κB is a pivotal transcription factor that regulates the expression of genes involved in immune responses and cell proliferation [2]. The previous study showed that NF-κB protein expression was downregulated in the C57BL/6 mice treated with 100 mg/kg/day vanillin for 10 days compared to the control group [59].

Of particular interest are novel metal-based complexes incorporating vanillin or its derivatives, which have demonstrated anti-inflammatory properties with potential anti-cancer benefits [67]. For instance, ruthenium (III), iron (III), and chromium (III) complexes

incorporating ortho-vanillin derivatives exhibited significant inhibition of carrageenan-induced (1% *w*/*v*) tumor edema in the legs of Wistar rats. These effects were evaluated in comparison to the established anti-inflammatory drugs DMSO and sodium diclofenac, both administered at the same concentration [68]. Moreover, vanillin and its novel derivatives are being evaluated for their potential efficacy against breast cancer through in vitro and in vivo studies. Apoptosis induced by vanillin is a key anticancer mechanism, not only for vanillin itself but also for its derivatives. 4-hydroxy-3-methoxy benzaldehyde (vanillin) derivatives have been shown to inhibit the survival and proliferation of MCF-7 cells in a time- and dose-dependent manner (1, 2, 4, 8, 12, 16, 32, 64, 128, 256, 512 µg/mL for 72 h) by inducing apoptotic cell death through the activation of a caspase-8-mediated pathway [62]. Additionally, the vanillin-derived compound VALD-3 induces apoptosis and cell cycle arrest in human breast cancer cells by inhibiting Wnt/β-catenin signaling, highlighting its potential as a therapeutic agent for breast cancer treatment [61]. Evidence indicates that VALD-3, a Schiff base ligand synthesized from o-vanillin derivatives (10 and 20 mg/L for 48 h), promotes apoptosis by activating caspase-3 and caspase-8 and modulating the balance of Bcl-2 family proteins, thereby shifting cells toward programmed death [61]. It also interferes with cell cycle progression, inducing arrest at the S and G2/M phases in MCF-7 cells (40 mg/L for 48 h) through regulation of cyclins and cyclin-dependent kinases, which suppresses uncontrolled proliferation [61]. In addition, vanillin (5 mM for 24 h) reduces metastatic potential by inhibiting matrix metalloproteinase-9 (MMP-9) expression via inhibition of NF-κB in human hepatocellular carcinoma cells (HepG2) [69]. The anti-inflammatory effects are mediated through suppression of NF-κB signaling, leading to decreased expression of pro-inflammatory cytokines that otherwise support tumor growth and survival. Furthermore, vanillin (90 µg/mL for 24 h) decreased mitochondrial membrane potential fluorescence in MCF-7 cells, indicating that vanillin induced mitochondrial dysfunction or early apoptosis in the treated cells [70]. Collectively, these mechanisms highlight vanillin's multifaceted role in targeting cancer cell viability, proliferation, and metastasis, providing a mechanistic foundation for its potential therapeutic application.

6.3. Antidiabetic Properties

The therapeutic efficacy of vanillin in ameliorating muscle dysmetabolism associated with T2DM was investigated in male Sprague–Dawley rats. Experimental induction of T2DM elicited a pronounced redox imbalance, characterized by reduced glutathione content, diminished activities of key antioxidant enzymes such as catalase and superoxide dismutase, and elevated levels of nitric oxide and malondialdehyde. Notably, oral administration of vanillin at low (150 mg/kg) and high (300 mg/kg) doses over a five-week period significantly attenuated metabolic and biochemical perturbations, restoring antioxidant defenses, and enhancing glycogen reserves [71]. Moreover, oral administration of vanillin at doses of 150 mg/kg and 300 mg/kg for five weeks significantly reduced blood glucose levels in diabetic rats. Beyond glycemic control, vanillin treatment enhanced pancreatic tissue and serum glutathione (GSH) concentrations, increased superoxide dismutase and catalase activities, and elevated hepatic glycogen content [72]. Collectively, these findings highlight vanillin's capacity to reinforce antioxidant defenses and modulate metabolic regulation in the context of diabetes. A similar observation was reported by Salau et al. [73], where oral administration of ferulic acid at doses of 150 or 300 mg/kg for five weeks significantly lowered blood glucose levels and increased serum insulin levels in male Sprague–Dawley rats using the fructose–streptozotocin model. The concomitant reduction in hyperglycemia, elevation of circulating insulin, and reduction of insulin resistance in ferulic acid–treated diabetic rats collectively demonstrate the potential of this phenolic compound to enhance glucose homeostasis in T2DM.

Diabetic nephropathy represents a major microvascular complication of diabetes mellitus. Oral administration of ferulic acid (200 mg/kg for eight weeks) showed nephroprotective effects in mice with high-fat diet/streptozotocin-induced diabetic nephropathy. Treatment with ferulic acid improved lipid metabolism, as evidenced by reducing low-density lipoprotein cholesterol (LDL-C), total cholesterol, and triglycerides, along with modulating high-density lipoprotein cholesterol (HDL-C). Ferulic acid also enhanced autophagic activity via increased light chain 3 (LC3) expression, while suppressing p62 accumulation and downregulating inflammatory mediators, including NOD-like receptor family pyrin domain containing 3 (NLRP3) and interleukin-1β (IL-1β), within renal tissues [61].

6.4. Cardiovascular Health

Myocardial infarction (MI) represents a leading global health burden, contributing substantially to morbidity and mortality worldwide. Oral administration of vanillin (150 $mg \cdot kg^{-1} \cdot day^{-1}$) mitigated isoproterenol-induced pathological alterations while concomitantly enhancing Akt/HIF-1α/VEGF signaling, suggesting potential modulation of oxidative stress, inflammation, and apoptosis [74]. The study evaluated the antihypercholesterolemic potential of ethanol fruit extract of vanilla (*Vanilla planifolia* Andrews) in mice fed a high-fat quail egg suspension. Administration of vanilla extract (200 $mg \cdot kg^{-1}$ for 30 days) significantly reduced blood cholesterol levels compared with the negative control [75]. The current evidence evaluating the role of *Vanilla planifolia* in cardiovascular health remains limited, suggesting the need for further studies to elucidate its mechanisms.

6.5. Neuroprotective Effects

The progressive degeneration of neurons in the central nervous system (CNS), accompanied by their functional impairment, underlies the pathogenesis of various neurodegenerative diseases, including several neuropsychiatric disorders, multiple sclerosis, stroke, spinal cord injuries and traumatic brain, Parkinson's disease, and Alzheimer's disease [76]. Although the neuroprotective mechanisms of vanillin are not yet fully elucidated, they are thought to be mediated through its combined anti-inflammatory and antioxidant properties [77,78]. Oxidative stress is known to amplify the chronic secretion of pro-inflammatory cytokines, playing a pivotal role in the pathogenesis of neurodegenerative diseases [1,78]. Vanillin (100 nM for 24 h) exerts protective effects against rotenone-induced injury by inhibiting intracellular ROS formation in SH-SY5Y neuroblastoma cells [79]. In addition, vanillin exerts anti-inflammatory and neuroprotective effects by regulating the expression of genes involved in pro-inflammatory and anti-inflammatory cytokine production. Specifically, vanillin reduces the secretion of pro-inflammatory cytokines by activated microglial cells, including interleukin-1β, interleukin-6, interferon-β, and tumor necrosis factor-α, while simultaneously promoting the production of anti-inflammatory cytokines such as interleukin-4, interleukin-10, and TGF-β in tissues. Moreover, it has been shown to reduce apoptosis rates in cases of spinal cord injury [78–80]. Lan et al. [81] investigated the neuroprotective effects of vanillin in a hypoxic–ischemic brain damage (HIBD) model using 7-day-old Sprague–Dawley rats. Vanillin was administered at doses of 40 or 80 mg/kg every 12 h for two consecutive days. The results demonstrated that vanillin significantly promoted early neurofunctional recovery, ameliorated histomorphological injury, particularly by preserving blood–brain barrier ultrastructure and reduced neuronal damage in the cortex and hippocampal CA1 and CA3 regions.

Vanillin has been shown to provide a calming effect [37]. A study has shown that the scent of vanillin helped soothe infants who undergo blood sampling, as it reduced their stress responses and discomfort. The aroma of vanilla has been shown to reduce

crying in newborns [37]. The aroma of vanilla has calming effects in adults, reducing startle reflexes and alleviating symptoms of sleep apnea, a sleep disorder characterized by repeated interruptions in breathing during sleep. Vanilla also gives mental health benefits. Animal studies have shown that vanillin can reduce anxiety and depression [37]. The study showed that smelling vanillin reduced signs of depression in rats. Intraperitoneal administration of vanillin (100 mg/kg) markedly attenuated $KBrO_3$-induced oxidative stress, as evidenced by the preservation of brain fatty acid composition, suppression of lipid peroxidation, and restoration of antioxidant enzyme activities [82].

6.6. Antimicrobial Properties

Vanillin has demonstrated significant antimicrobial properties, making it valuable in both health and food applications [49]. Its antimicrobial activity enables it to inhibit or kill harmful microorganisms, including bacteria, fungi, and yeasts. Vanillin disrupts ion gradients like potassium ion flow, impairing respiration and energy production against bacteria such as *E. coli*, *Lactobacillus plantarum*, and *Listeria innocua*. Vanillin's antifungal properties are particularly strong against various fungi, making it effective in food systems like soft drinks, fruit purées, and agar-based mediums. It also inhibits food spoilage in fungi such as *Alternaria alternata*. Moreover, vanillin exhibits activity against medically significant fungi, including *Cryptococcus neoformans* and *Candida* albicans, attributed to its aldehyde group, which disrupts fungal growth mechanisms. These properties make vanillin useful in preventing food spoilage and extending the shelf life of products like muffins, cookies, and soft drinks, while maintaining taste and appearance [49].

The antimicrobial mode of action primarily involves (a) interaction with the cell membrane, (b) inactivation or destruction of genetic material, or (c) inactivation of essential enzymes. Owing to their hydrophobic nature, phenolic compounds such as vanillin interact with membrane proteins and bilayer lipids, leading to the destabilization of the plasma membrane [83]. Vanillin (0.5, 1.0, 1.5, 2.0 mg/mL for 1 day) has demonstrated antimicrobial activity in vitro against *E. coli* O157:H7 [84]. Treatment with 80 mM vanillin for 1 min delayed the total aerobic bacteria and mold and yeast populations in fresh-cut mango [85]. Furthermore, the combination of vanillin with natural polymers such as chitosan is being explored as a non-toxic and effective method for food preservation and inhibiting the growth of harmful bacteria [86]. Vanillin derivatives exhibit antibacterial properties with potential applications in biocompatible implants, particularly in the development of antimicrobial scaffolds in reducing the risk of implant rejection and infections [87].

6.7. Other Potential Health Benefits

Traditionally, vanilla has been used in many cultures therapeutically, including as an aphrodisiac and to aid with gas relief [37]. Studies have shown that the spice's aroma and flavor can provide certain health benefits. Interestingly, vanilla can curb sugar intake [37]. Vanilla contains fewer calories and carbohydrates than sugar, but provides natural sweetness. Vanilla serves as an excellent substitute for reducing sugar consumption in daily diets. Additionally, vanilla has practical applications in pain relief. The alcohol content in vanilla extract may provide a numbing effect for toothache pain, while its antioxidant compounds have the potential to support the healing process. A few drops of vanilla extract in the affected area can provide temporary relief [37]. Research also indicates that vanillin, a primary compound in vanilla, demonstrates promising biological activities [49]. Animal studies suggest that orally administered vanillin can alleviate certain types of pain, such as those caused by nerve damage or inflammation [37]. Exposure to vanillin has been shown to prevent bradycardia and decrease the incidence of breathing pauses, possibly through

activation of the olfactory nerve and increased orbitofrontal blood flow in both adults and newborns [88].

Hydrogels are moist, flexible materials composed of 3D cross-linked macromolecular polymer chains that incorporate a significant amount of water within their network. Due to their ability to mimic human tissues, biocompatible hydrogels can be developed for wound dressings and tissue engineering scaffolds by combining polymers with natural crosslinkers [89]. Chitosan-based hydrogels crosslinked with vanillin have demonstrated efficacy in promoting wound healing [90]. When combined with polyvinyl alcohol (PVA), these hydrogels exhibit potent scavenging effects on PTIO free radicals, $ABTS^{+}$, and DPPH [91]. Additionally, hydrogels made from PVA, vanillin, and carboxymethyl chitosan effectively inhibit the growth of *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* (*S. aureus*) [92]. A novel hydrogel synthesized by crosslinking chitosan with the vanillin isomer 5-methoxysalicylaldehyde displayed promising physicochemical properties and effectively suppressed the fungus *Candida albicans*, demonstrating potential for treating various skin lesions [93]. Vanillin also exhibited cytoprotective and cytocompatibility properties, mitigating cellular damage caused by ROS. Human fibroblast and keratinocyte cells exposed to vanillin (10–500 μM) showed >80% survival. Furthermore, vanillin promoted cell migration and inhibited ROS-induced cell death, thus contributing to enhanced wound healing [65]. Ethyl vanillin is another promising candidate for hydrogel production, which facilitates the formation of hydrogels and its ability to couple with gelatin via a Schiff base reaction. The antibacterial properties of the resulting complex, which inhibits *S. aureus* and *E. coli*, alongside its non-toxic nature, suggest that new polymeric wound dressings composed of ethyl vanillin, polyvinyl alcohol, and gelatin could be effective for wound healing applications [89]. In a study on diabetic rats, a novel vanillin-derived zinc complex [Zn(phen)(van)2] (ZPV) demonstrated significant improvements in wound healing, including reduced levels of IL-1β and TNF-α, upregulated transcriptional activity of TGF-β and VEGF, reduced size of wound, and enhanced re-epithelialization, angiogenesis, and collagen deposition, indicating its potential to improve healing in diabetic conditions [94].

7. Application in Food Industry

Flavoring Agent

Vanilla, a spice renowned for its distinctive flavor and aroma, holds substantial economic significance worldwide. Its production primarily relies on extracting compounds from specific *Vanilla* species, which share key molecules, such as vanillin, that contribute to its characteristic flavor [95]. The main commercially cultivated species include *Vanilla pompona* Schiede, *Vanilla* × *tahitensis* J. W. Moore, and *Vanilla planifolia* Jacks. ex Andrews, with the majority of cultivation focused in Madagascar and smaller-scale production elsewhere [96]. This highlights the economic significance of vanilla and the necessity of preserving and optimizing this valuable resource.

Vanilla is a chemical extract derived from the beans of orchid species such as *Vanilla planifolia* Jacks. ex Andrews [45]. The flavor profile of vanilla extracts exhibits significant variations, and even within the same species, aroma and flavor can differ depending on the region of cultivation due to climatic conditions and agronomic practices. Despite being a labor-intensive product, vanilla is one of the most expensive condiments, ranking after saffron and cardamom [45].

Pure organic vanilla contains a richer and more diverse composition of fragrance and flavor compounds compared to synthetic vanilla [97]. Authentic vanilla extract, derived from vanilla beans, is highly pure and possesses an elegant flavor, attributed to the presence of over 250 organic compounds that contribute to its complex taste. Notably, natural vanilla extract has a characteristic dark brown hue and a sweet, fruity aroma. Due to the global

shortage of organic vanilla, synthetic vanilla has gained popularity in the market as an alternative. However, efforts are being made to enhance the production of organic vanilla to meet international demand [98].

Vanilla is one of the most popular and expensive spices globally, serving as a premium flavoring agent and a key ingredient in the perfume industry, with high international demand [99]. Naturally, a vanilla bean contains approximately 2% vanillin, along with other compounds that enhance its overall quality [45]. Madagascar is the world's leading producer of orchid-derived vanillin, followed by China, Indonesia, and Mexico, which are also the largest exporters of vanilla seed pods [100]. The United States is the largest importer of both vanilla seed pods and vanillin extract [97]. The demand for vanillin derived from *Vanilla* orchids is expected to increase in the future.

Extracts from the dried vanilla bean are widely utilized in a diverse range of food products. Industrially produced vanillin is in high demand and is used extensively in food, beverages, and confectionery [101]. The food industry is the largest consumer of vanilla, with ice cream being the primary application. Vanilla is also widely used in yogurt, cookies, brownies, and cakes.

Natural extracts from *Vanilla planifolia* may be utilized for specific culinary applications. In most food applications, cost-effective imitation vanilla extract is utilized to replicate the desired flavor profile. In numerous baked products, particularly those in which vanilla does not serve as the primary flavor, imitation and natural vanilla extracts are frequently indistinguishable. As a noncaloric sweet flavoring agent, vanilla may contribute to dietary strategies designed to reduce consumer sugar intake. Moreover, the utilization of vanillin extends beyond food applications, with notable use in products such as cigarettes [101].

The distinctive flavor of vanilla results from the integrated orosensory contributions of numerous aromatic volatiles formed during bean processing. Although hundreds of chemical constituents collectively shape this complex flavor profile, vanillin (4-hydroxy-3-methoxybenzaldehyde) is the predominant compound, typically present at concentrations of 1–2% (wt./wt.) in cured pods. Other key flavor compounds include vanillyl alcohol, anise alcohol, p-hydroxybenzyl alcohol, vanillic acid (4-hydroxy-3-methylbenzoic acid), p-hydroxybenzaldehyde, and p-hydroxybenzoic, along with other nonvolatile compounds, free amino acids, resins, and tannins. Both vanillic acid and vanillin are approved as food-flavoring agents [102].

8. Safety and Toxicity

The global vanilla market generates millions in annual revenue and depends primarily on *Vanilla planifolia*, a species with limited genetic diversity and susceptibility to pathogens. Increasing consumer demand for natural vanilla, valued for its authentic flavor profile, highlights the urgent need for sustainable production methods. Wild relatives of vanilla represent a promising resource for expanding and stabilizing supply, but their safety must be carefully evaluated to identify potential toxicity risks. Vanilla extract, oil, seed powder, and vanillin are classified as Generally Recognized as Safe (GRAS) by the U.S. Food and Drug Administration (FDA) for use as spices, natural seasonings, and flavoring agents in food (section 409 of the Federal Food, Drug, and Cosmetic Act [21 CFR 182.10; 21 CFR 182.60; CFR582.10]). Vanillic acid is also approved as a food flavoring agent by the Joint FAO/WHO Expert Committee on Food Additives under designation number 959 [103]. Long-term animal studies have shown no adverse effects of vanillin at dietary concentrations of 50 and 20 g/kg [104], and additional work confirmed its safety at 300 and 150 mg/kg administered orally and intragastrically for fourteen weeks [105].

De Oliveira et al. [106] investigated ethanolic extracts of *Vanilla planifolia*, *Vanilla cribbiana*, *Vanilla chamissonis*, and *Vanilla bahiana*. The study found mutagenic effects in *Vanilla*

cribbiana at high doses (5000 µg/plate) in the TA98 strain without metabolic activation, but extracts were safe at lower concentrations. Araujo et al. [50] reported that *Vanilla planifolia* induced mutations at the highest tested concentrations (4000 and 5000 µg/plate) in the TA98 strain. These mutagenic effects may be linked to phenolic compounds and other organic molecules with antioxidant potential. At elevated concentrations, antioxidants can exhibit pro-oxidant behavior, as observed in other plant extracts with high antioxidant content [107,108]. The complex mixture of bioactive compounds in plant extracts may also interact with multiple cellular targets, leading to adverse biological effects [109]. Importantly, the doses tested in these studies are far higher than typical human exposure, reinforcing the safety of vanilla under normal dietary conditions. El-Wahab and Moram [110] reported reduced growth and decreased liver and blood antioxidant enzyme activity in rats fed vanillin at 1.25 g/kg diet for forty-two days, although the reasons for these differing responses remain unclear.

Vanillin, the major bioactive metabolite of *Vanilla planifolia*, has been associated with anticarcinogenic, antimutagenic, and antioxidant properties [111,112]. At relatively high concentrations, vanillin has not been linked to significant side effects [113]. Mirza and Panchal [114] demonstrated that oral administration of vanillic acid at doses 1000 mg/kg/day for fourteen days did not induce toxicity in rats. Synthetic vanillin is widely used in the food industry, but studies have reported genotoxic effects in mice [115], emphasizing the importance of distinguishing between natural and synthetic sources in safety evaluations.

Vanillin and related aromatic compounds such as vanillic acid and p-hydroxybenzaldehyde contribute to the distinctive flavor and fragrance of vanilla, which underpins its economic importance. Species with higher concentrations of these compounds have supported the long-standing popularity and global consumption of vanilla, maintaining its critical role in the food and perfumery industries [116]. Extracts of Vanilla planifolia are recognized as safe by the U.S. FDA [117]. Human exposure is typically low because vanilla is primarily used as a flavoring agent and spice. For example, most baking recipes incorporate approximately one teaspoon of vanilla extract, equivalent to about 4 g [37].

9. Limitations of the Study

This study has several limitations. Most findings are derived from animal models or cell culture experiments, and no large-scale randomized controlled trials have yet confirmed efficacy in human studies. The potential synergistic effects among bioactive compounds remain poorly understood. Moreover, the concentration of phytochemicals in *Vanilla planifolia* varies with geographic origin, cultivation practices, and extraction methods, which may potentially confound results. The dose–response relationship in diabetes has not been systematically evaluated. Future studies should compare moderate and high concentrations of vanillin, vanillic acid, and other phenolic compounds within the same experimental framework. Future clinical trials should evaluate vanillin, vanillic acid, and other phenolic compounds at varying concentrations to clarify their individual and combined effects.

10. Conclusions and Future Perspectives

The available research evidence showed the diverse bioactivities and potential applications of vanillin in human health. The preclinical studies have indicated its non-toxic effects, suggesting efficient assimilation and elimination. Vanillin has also predominantly been used as a flavoring and fragrance compound. Although preclinical studies have demonstrated the potential beneficial effects of vanillin, certain effects of vanillin remain controversial and require further elucidation through long-term clinical trials involving large cohorts from the general population. Additionally, further research is needed to

elucidate their precise mechanisms of action under both pathological and healthy conditions, facilitating their potential integration into clinical practice. Future research on nanocarrier-based delivery systems may also enhance vanillin's stability, bioavailability, and bioactivity. While vanillin derivatives show promise, their safety and efficacy must be validated through rigorous human clinical trials. Overall, more randomized clinical trials are needed to comprehensively assess the sustained impacts of dietary interventions.

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Abbreviations

The following abbreviations are used in this manuscript:

CHD	Coronary heart disease
CNS	Central nervous system
CVD	Cardiovascular disease
FC3H	Mouse liver fibroblast cells
HepG2	Liver cancer cell
HT-29	Colorectal cancer cells
IL-6	Interleukin-6
LDL	Low-density lipoprotein
MCP-1	Monocyte chemotactic protein-1
NCI-H460	Lung cancer cell
PAD	Peripheral artery disease
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor-α

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