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Vanillin: Chemical Synthesis, Biosynthesis, Metabolism, Behaviour in Food Processing and Antibacterial Properties

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Abstract. Vanillin is produced via various chemical and biosynthetic processes, including enzymatic conversions, lignin, and guaiacol. Vanillin metabolises in the living body primarily from the pathways of vanillic acid and vanillyl alcohol. Vanillin's contribution to flavour and colour in food processing can be analysed in the context of its reaction with secondary amines. Finally, vanillin's significant antibacterial properties not only enhance the shelf life of food products but also suggest potential applications in medicinal chemistry as a reactant or intermediate in synthesising antimicrobial agents.

Keywords: Vanillin, vanillin biosynthesis, vanillin chemical synthesis, metabolism of vanillin, vanillin in food processing, antibacterial properties of vanillin

1. Introduction

Vanillin, known as 4-hydroxy-3-methoxybenzaldehyde, is universally acknowledged today for its distinctive fragrance and taste. Nevertheless, its use has captivated humans for centuries. The first major historical appearance of vanilla is generally agreed to be its domestication in Mesoamerica [1]. The isolation of vanillin was achieved in 1858 by Nicolas-Theodore Gobley through evaporation and crystallisation from vanilla extract [2]. Vanillin was first chemically synthesised in 1876 from guaiacol [3], and by the late 19th century, semisynthetic vanillin derived from eugenol began to be commercialised. Following this, guaiacol and lignin-derived vanillin gained popularity due to their burgeoning availability. The marketing of biosynthetic vanillin started after the 2000s when biosynthetic routes based on ferulic acid (extracted from rice bran) began to be researched more extensively.

Considering the compound's great annual market demand of 12,000 tons to a natural availability of only 1,800 tons, refining its industrial production is of great importance [4]: it is critical to understand the compound's synthesis and behaviours. Specifically, the recent rise in demand for sustainability and "natural" products in industry calls for a deeper understanding of the compound's biosynthesis. Research on vanillin metabolism and its interactions with food systems remains under-refined. Moreover, understanding its antibacterial properties can better its use in food preparation and drive the development of food preservation.

This paper aims to examine the syntheses of vanillin, both biological and synthetic, followed by an exploration of vanillin's metabolic pathways. Finally, this paper will analyse the behaviour of vanillin during food processing and preservation and investigate its antibacterial properties.

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2. Chemical synthesis

The first chemical synthesis of vanillin was executed in 1874 by German scientists Ferdinand Tiemann and Wilhelm Haarmann from coniferin, a glucoside of isoeugenol and a component of pine bark [5].

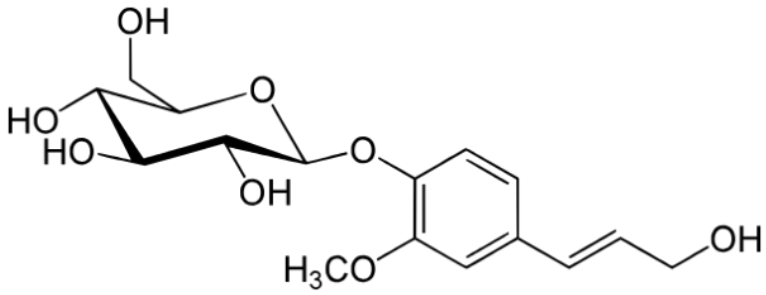


Figure 1. β-D-glucoside of vanillin

After the 1920s, chemical synthesis by lignin underwent development. In the synthesis, lignin is hydrolysed off in an alkaline oxidative depolymerisation process [6], where the section of lignin is substituted by a hydroxyl group. After oxidisation, the structure is hydrolysed in an alkaline aqueous solution and distilled to produce vanillin, as illustrated in Fig 2. Although this method is inexpensive, uses abundant raw materials, and has a simple process, its popularity has declined due to environmental concerns and high energy requirements.

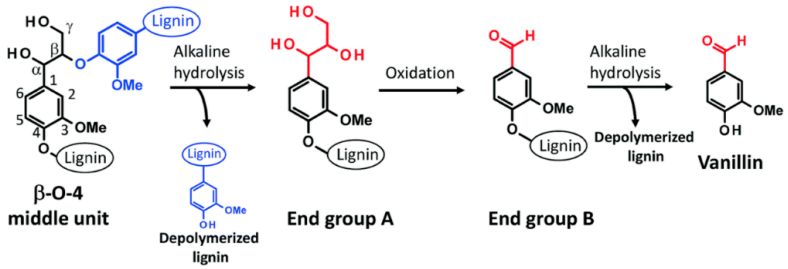


Figure 2. The chemical synthesis of vanillin from lignin

Source: Hirano, Yuki, et al. "Degradation Mechanism of a Lignin Model Compound during Alkaline Aerobic Oxidation: Formation of the Vanillin Precursor from the β-O-4 Middle Unit of Softwood Lignin." Reaction Chemistry & Engineering, vol. 7, no. 7, Royal Society of Chemistry, Jan. 2022, pp. 1603–16, https://doi.org/10.1039/d2re00036a.

In today's market, 85% of vanillin is chemically synthesised from guaiacol [7]. Guaiacol first undergoes electrophilic aromatic substitution by glyoxylic acid under basic conditions [8] to give vanillylmandelic acid. Fig. 3 shows the result of the oxidation of vanillylmandelic acid to the corresponding phenylglyoxylic acid, followed by its decarboxylation to vanillin. This oxidative decarboxylation is catalysed by copper(II) [6], and the vanillin is ultimately purified via vacuum distillation and recrystallization.

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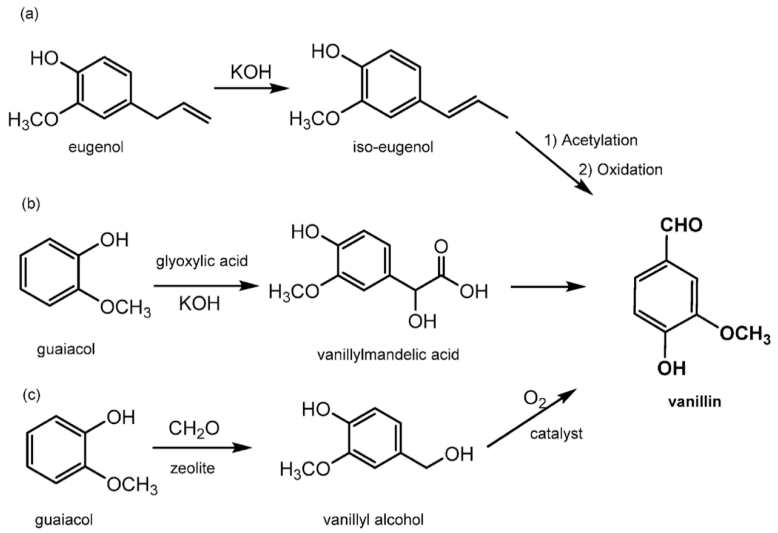


Figure 3. The chemical synthesis of vanillin from guaiacol

Source: D'Arrigo, Paola, et al. "From Waste to Value: Recent Insights into Producing Vanillin from Lignin." Molecules, vol. 29, no. 2, Multidisciplinary Digital Publishing Institute, Jan. 2024, pp. 442–42, https://doi.org/10.3390/molecules29020442.

3. Biosynthesis

While the chemical synthesis of vanillin is quite well-researched and is industrially universalised, it has several disadvantages, such as being highly energy-consumptive and pollutive. Until recently, it has not been economical or labour-efficient to produce vanillin from vanilla orchids, as vanilla makes up only 1/500th of one vanilla pod extraction [9]. Thus, it is reasonable that vanilla orchids are only used to produce 1% of vanillin globally [10]. However, rapidly growing demands for sustainability and natural vanillin have induced interest in industrial applications of the biological syntheses of vanillin. The major metabolic pathways leading to the formation of vanillin are illustrated in Fig. 4.

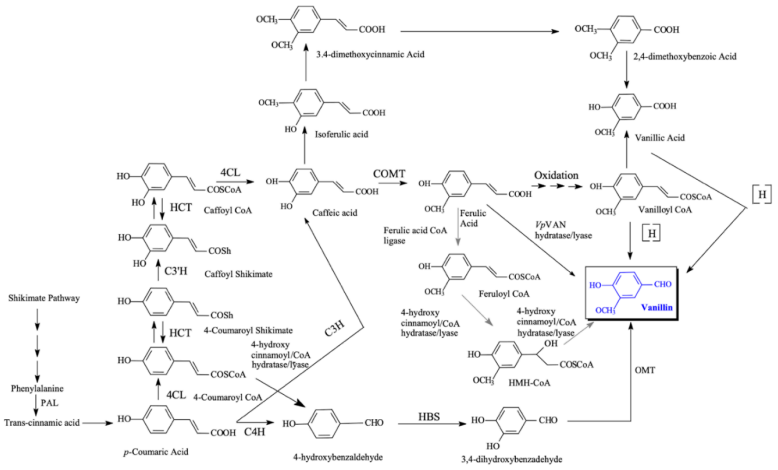


Figure 4. The major proposed biosynthetic pathways to vanillin

Source: Kundu, Anish. "Vanillin biosynthetic pathways in plants." Planta, vol. 245, no. 6, Mar. 2017, pp. 1069–78. https://doi.org/10.1007/s00425-017-2684-x.

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Table 1. The key enzymes involved in vanillin biosynthesis, their functions, and their molecular characteristics

Enzyme	Function
4-Hydroxycinnamoyl-CoA hydratase/lyase (HCHL)	Converts feruloyl-CoA to vanilloyl-CoA
Hydroxybenzaldehyde synthase (HBS)	Converts 4-courmaric acid to 4-hydroxybenzaldehyde [11]
Vanillin synthase (VpVAN)	Converts ferulic acid to vanillin [9]
O-methyl transferase (OMT)	Converts 3,4-dihydroxybenzaldehyde to vanillin [12]

Source: Kundu, Anish. "Vanillin biosynthetic pathways in plants." Planta, vol. 245, no. 6, Mar. 2017, pp. 1069–78. https://doi.org/10.1007/s00425-017-2684-x.

4-hydroxybenzaldehyde synthase (4-HBS) has been suggested to convert 4-coumaric acid to 4-hydroxybenzaldehyde. From this, vanillin or vanillin glucoside biosynthesis can occur by an enzymatic side-chain shortening reaction [13-16]. Hydroxylation can also produce 3,4-dihydroxybenzaldehyde from 4-hydroxybenzaldehyde. Tab. 1 exhibits how O-methyltransferase (OMT) methylates 3,4-dihydroxybenzaldehyde to yield vanillin [17].

Coming from a variety of naturally occurring plants (most notably clove buds), eugenol is used to produce ferulic acid (by an olefin shift and the conversion of the methylene group to a hydroxymethyl by hydroxylation). A catechol-O-methyl-transferase (COMT) can also convert caffeic acid into ferulic acid [18]. From ferulic acid, vanillin is formed directly by a side-chain shortening process involving the enzyme VpVAN, also known as vanillin synthase [9].

Additionally, it was proposed that caffeic acid, or 3,4-dihydroxycinnamic acid. Methylation produces isoferulic acid, or 3-hydroxy-4-methoxycinnamic acid, and further methylation gives 3,4-dimethoxycinnamic acid. As demonstrated in Fig. 4, shortening of the side chain and demethylation first produces vanillic acid and ultimately vanillin by reduction.

4. Metabolism

The metabolism of vanillin in rats has been observed mostly through the mechanisms of oxidation and reduction. The main metabolites of vanillin are vanillic acid and vanillyl alcohol; most of the metabolites in Tab. 2 were seen to be excreted within 24 hours [19].

Table 2. Urinary metabolites of vanillin after oral administration to rats

Compound	Metabolites detected	Free fraction	Conjugated fraction
Vanillin	Vanillin	0/6	6/6
	Vanillyl alcohol	6/6	6/6
	Vanillic acid	6/6	6/6
	Protocatechuic acid	0/6	4/6
	Vanilloylglycine	6/6	6/6 (trace)
	Catechol	3/6	6/6
	4-Methylcatechol	0/6	6/6
	Guaiacol	0/6	5/6
	4-Methylguaiacol	0/6	5/6

Source: Strand, Linda P., and Ronald R. Scheline. "The Metabolism of Vanillin and Isovanillin in the Rat." Xenobiotica, vol. 5, no. 1, Taylor & Francis, Jan. 1975, pp. 54, https://doi.org/10.3109/00498257509056093.

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Of the 83% ingested, 69% was oxidised to vanillic acid, and 8% was excreted in the form of an ethereal sulphate. The other 14% of ingested vanillin was excreted conjugated and not oxidised. In total, the conjugated vanillin and vanillic acid excreted was 39%. Glucurovanillin and glucurovanillic acid were the two conjugated glucuronides excreted [20].

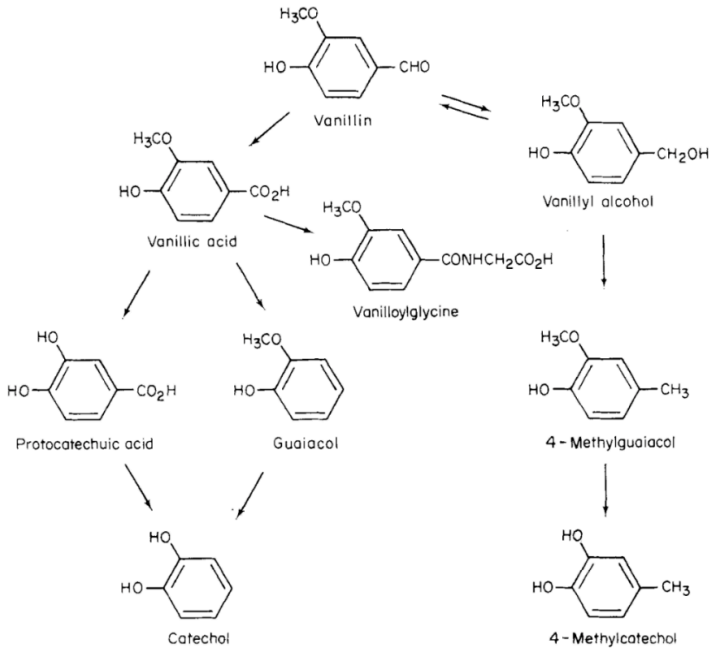


Figure 5. The proposed metabolic pathways of vanillin in the rat

Source: Strand, Linda P., and Ronald R. Scheline. "The Metabolism of Vanillin and Isovanillin in the Rat." Xenobiotica, vol. 5, no. 1, Taylor & Francis, Jan. 1975, pp. 58, https://doi.org/10.3109/00498257509056093.

5. Food processing

To externally aromatise baked goods and lessen aroma loss, vanillin is applied to meals before baking, or sprayed on surfaces after cooking. In food products, Maillard reactions between amino acids and carbonyl moieties are the main contributors to flavour and colour formation [21,22]. Secondary amines are produced as the Maillard reaction progresses; Barbero et al. noted that vanillin formed 2,5-dimorpholino-1,4-benzoquinone almost exclusively when reacted with secondary amines.

Barbero et al. proposed the mechanism illustrated in Fig. 6 for the transformation of vanillin to 2,5-diamino-1,4-benzoquinone. After condensation and deprotonation, (6a), a quinomethide, is produced. Dioxetane (7a) is formed through aerobic oxidation [23]. Following ring fragmentation [24] and instances of oxidation, 2,5-dimorpholino-1,4-benzoquinone (3a) is produced.

The colouring properties of the 2,5-diaminoquinones spark great interest regarding the shades of certain baked goods. The Maillard reaction aids in the formation of the brown colour in foods, and the 2,5-diaminoquinones' broad colour spectrum - ranging from brilliant orange to brilliant dark red – may likely impact the overall colour in baked products. The colouring qualities of such compounds may be further assessed to identify new possible colourants in the food industry.

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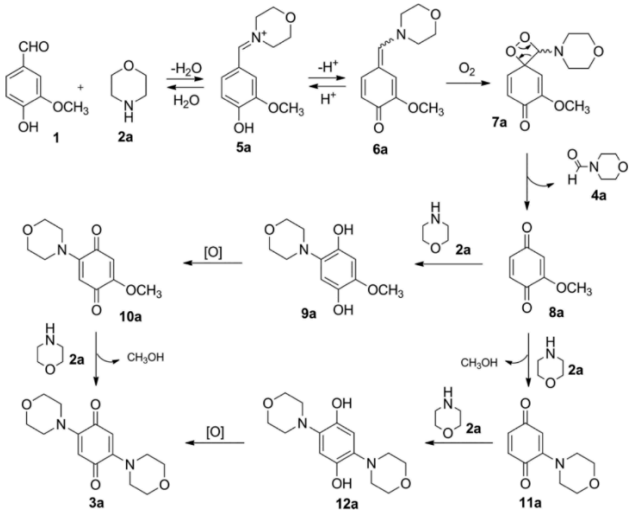


Figure 6. The proposed mechanism for the conversion of vanillin to 2,5-diamino-1,4-benzoquinone

Source: M. Barbero, et al. “Unprecedented Formation of 2,5-Diaminoquinones from the Reaction of Vanillin with Secondary Amines in Aerobic Conditions.” ResearchGate, ResearchGate, 2019, pp. 138, https://doi.org/10.1002//ejoc.201901553.

6. Antimicrobial behaviours

Vanillin's antibacterial qualities make it useful not only in the culinary and fragrance industries but also in the food preservation sector. It has been demonstrated that vanillin inhibits the growth of a variety of moulds, yeasts, and bacteria that cause food degradation. Hence, vanillin is frequently used to extend the shelf life of sweetened food products.

Retnosari et al. have proposed a synthetic pathway from vanillin to compounds 1a and 1b (shown in Fig. 7) and demonstrated their potent antibacterial abilities. Dimedone (3) attacks vanillin after protonation by sulfuric acid. Product (4) is produced following dehydration, which is then attacked by dimedone (3), hydrogenated, and cyclised to give products 1a and 1b. Additionally, to improve the compounds' antibacterial action, the methoxy group can be substituted by an ethoxy group.

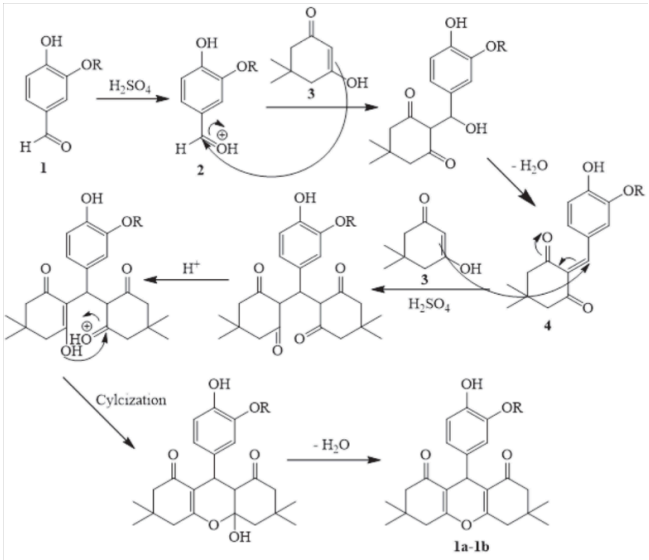


Figure 7. The proposed mechanism for the formation of products 1a and 1b

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Source: Rini Retnosari, et al. “The Antibacterial Activity of Vanillin Derivative Compounds.” AIP Conference Proceedings, American Institute of Physics, Jan. 2021, https://doi.org/10.1063/5.0051523.

7. Conclusion

This paper explores the chemical and biosynthetic methods of vanillin production, from electrophilic aromatic substitution of guaiacol and alkaline oxidative depolymerization of lignin to multiple enzymatic conversions. This paper also illuminates the metabolic transformations of vanillin within the living body, which are driven by oxidation and reduction reactions, leading to several metabolites, most importantly, vanillic acid and vanillyl alcohol. In food processing, vanillin's behaviour during the Maillard reaction, its interactions with secondary amines, and its ability to form coloured quinones offer valuable insights into its role in flavour and colour development in food products. Vanillin's antibacterial properties demonstrate its potential in antimicrobial agent production, highlighting its versatility and broad uses in food preservation and medicinal chemistry.

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