

VANILLIN: IS IT JUST AN AROMATIC OR A CURE FOR CANCER?

Arda Ulaş Mutlu¹, Martin Kanev², Büşra Diler Zenginer³, İlker Dıbırdık³

¹Trakya University School of Medicine, Edirne, TURKEY

²Department of Biotechnology and Genetics, Trakya University Institute of Science, Edirne, TURKEY

³Department of Medical Biochemistry, Trakya University School of Medicine, Edirne, TURKEY

ABSTRACT

Abstract: Cancer is one of the most challenging diseases mankind has confronted, and it is listed as the second most common reason of death according to the World Health Organization. Its damage to global economy is valued trillions of dollars and it is increasing day by day. This literature review is aiming to reflect on vanillin's anticancer potential, a natural chemical being used in different industrial areas. Beside flavour, it is a powerful antioxidant and a strong antimutagenic. Oxidative stress and mutations are two major reasons for carcinogenesis. Therefore, the cancer prevention and/or therapeutic potential of vanillin is being investigated. Many studies using different cell lines have noted that vanillin had positive effects on cancer. **Keywords:** Cancer, reactive oxygen species, oxidative stress, vanillin

INTRODUCTION

Heretofore, a wide range of organic and inorganic chemicals have been searched to observe their antioxidant effects for cells and antimutagenic potential against the cancer tissue. Among these chemicals, vanillin is an outstanding one that has been researched since the late '80s. Vanillin, 4-hydroxy-3-methoxybenzaldehyde, has always been an economically important flavor of daily lives (Figure 1). It is being used in a wide scale of products, from drinks to perfumes; with different aims to heal wounds, or to increase physical performance since the 14th century. Until the late '80s, vanillin was not a center of focus as a chemical of modern medicine and oncological pharmacology. A study by Ohta et al. (1) changed the perspective to vanillin rapidly. In this study, vanillin's antioxidant effects, as well as antimicrobial and anti-inflammatory potential, were mentioned and lead up to new clinical usages of vanillin (2-4). Since the publication of the forenamed article, vanillin has influenced cancer research and treatment modalities.

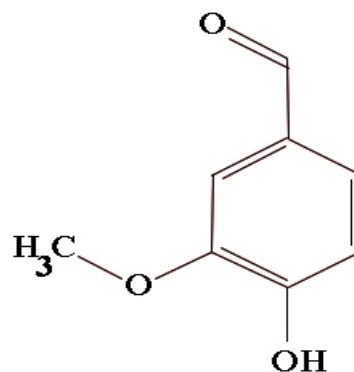


Figure 1: Chemical structure of 4-hydroxy-3-methoxybenzaldehyde.

According to the World Health Organization (WHO) data, in 2018 alone, 18.1 million people were diagnosed with cancer and 9.9 million people died of this disease. While the global cancer bill was estimated to rise to \$1.5 trillion in 2018, the United States made the most cancer related spendings with \$90 billion (5).

Address for Correspondence: Arda Ulaş Mutlu, Trakya University School of Medicine, Edirne, TURKEY

e-mail: ardamutlu.1999@gmail.com ORCID: orcid.org/0000-0001-7499-7155

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The formation of normal cells into tumor cells in multiple steps causes cancer. Various genetic and epigenetic related factors such as mutation, chromosome aberration, nuclear exchange, and exogenic stress factors like tobacco and/or alcohol use, radiation can start this formation (5, 6). Most of the stages causing this formation are still unknown, but studies have shown that reactive oxygen species (ROS), namely hydrogen peroxide (H₂O₂), hydroxyl radical (HO•) and superoxide anion (O₂⁻) have a major role in cancer's exhibition, also known as malignancy (7). ROS are produced as endogens in every cell as the result of mitochondrial oxidative metabolism and each cell has its compensation limit called "ROS scavenging capacity". In the case of exceeding this limit, the cellular antioxidant defense system remains incapable and that leads to cellular oxidative stress. As a result, chemical stress factors can damage mitochondrial deoxyribonucleic acid (mtDNA) and nuclear deoxyribonucleic acid (nuclear DNA). It can also cause lipid peroxidation, and reversible or irreversible modifications of cellular proteins. It is well known that mtDNA is more sensitive than nuclear DNA to oxidative conditions (8). However, the effect of mtDNA mutation on the development of pseudo-hypoxic conditions and creation of metastatic potential have not been explained thoroughly yet (9). The latest studies demonstrated that abnormality in citric acid (Krebs) cycle, which creates more ROS than the ROS-suppressing machinery can compensate, is originated from nuclear DNA mutation, not mtDNA mutation. This mutation pushes the cell to work like, there is a hypoxic environment even in normal conditions, and this process controls the tumor's aggressiveness (10).

REACTIVE OXYGEN SPECIES AND THEIR ROLES IN CANCER DEVELOPMENT

Reactive oxygen species are highly reactive molecules, usually produced by the aerobic respiratory system in all aerobic organisms. Molecular oxygen (O₂), the terminal receiver of electron transport chain (ETC), is an unreactive molecule compared to ROS. ROS definition includes different kinds of radicals, also known as free radicals, and described as molecules which have unpaired electrons (11). Hydrogen peroxide (H₂O₂), hydroxyl radical (HO•) and superoxide anion (O₂⁻) are the examples of ROS molecules produced by aerobic respiratory mechanisms (12). Aerobic organisms use mitochondria, ETC to produce enough adenosine triphosphate (ATP) to maintain vital activities. In this aerobic process, electrons pass through different comp-

lexes until they reach O₂, but electron leakage results in excessive O₂⁻ production (13). In addition to the aerobic mechanism and nicotinamide adenine dinucleotide phosphate oxidases (NOX), which are the two major endogenous ROS sources, different ROS sources can also cause ROS activities in organism (14). Exergonic sources such as ionizing radiation, drugs, lipoxygenases, cytochrome p450, peroxisome, and inflammatory cells are the additional ROS sources to the aerobic respiratory system (15).

It is well known that ROS and cellular redox changes have major roles in the development of carcinogenesis and various diseases since they have been held responsible for having a significant impact on hemostatic cellular signaling pathways (16). H₂O₂, one of the major ROS molecules, is a fundamental component of epidermal growth factor, angiotensin II and platelet-derived growth factor as intracellular messengers. Messenger effects of H₂O₂ were noticed with specific inhibition of it in A431 human epidermoid carcinoma cells (17). ROS molecules' production in high levels and oxidative stress in the cells are defined as characteristic features of the carcinoma with in vivo and in vitro studies (12, 15, 16). Hypoxia starts the butterfly effect. Butterfly effect defines major changes caused by very small changes at the beginning of the situation. This butterfly effect continues with macrophage infiltration into the tumor and followed by an oxidative upsurge in the damaged vascular tissue at the reperfusion phase (18).

In 1970, Cameron et al. (19, 20) have published two studies about antioxidants' effects on cancer. He substantiated this relation with applying intravenous ascorbic acid, an important antioxidant, in patients with terminal period cancer, and noted clinical improvement. Sabharwal et al. (21) also pointed out that, ROS promote cancer cells' proliferation and survival in rat models and cell lines. Therefore, if ROS are causing carcinogenesis, it should be prevented by antioxidants. However, some studies have turned the tables. In these studies, dietary supplemented antioxidant, N-acetylcysteine (NAC), has accelerated the tumorigenesis and mortality in v-raf murine sarcoma viral oncogene homolog BV600E or Kirsten rat sarcoma viral oncogene G12D induced lung cancer model in mice (22). NAC has also accelerated tumorigenesis in melanoma human xenografts (23). Different antioxidants have been tried in different cancer types such as colorectal, prostate, lung, head and neck, but it was noted that applied antioxidants like β-carotene, NAC, vitamin A or ascorbic acid have not caused progress in treatment of these cancer types, on the contrary accelerated the mortality in used cancer models (24).

VANILLIN

Vanillin (4-hydroxy-3-methoxybenzaldehyde) is a natural aromatic used in various industrial areas like food, perfumes, and medicines. It grows in the pods of *Vanilla planifolia* (25, 26). Vanillin is one of the most studied antimutagenic and antioxidant chemicals over the past three decades, thanks to the study of Ohta et al. (1). Vanillin has also shown antimutagenic effects on X-ray, ultraviolet light, methylmethane sulphonate and mitomycin C induced mutations in mammalian cells (27). Although antimutagenic effects have been shown in studies, this effect does not always occur. On N-methyl-N'-nitro-N-nitrosoguanidine induced mutations, vanillin has shown no significant antimutagenic effects (28). This contradiction is based on different repair pathways to overcome different mutagenic effects. For example, ROS scavenging and non-homologous end joining, and recA-dependent recombination repair enhancement is shown as one of them (29).

Besides vanillin's effective antimutagenic ability, its antioxidant abilities are not outstanding. It has weak O₂- scavenging activity, and also its effect on lipid peroxidation has been undefined (30). In different studies, different assays were used to control the antioxidant effects of vanillin but some specific assays showed negative results whilst some showed positive. It has shown negative results in 1,1-diphenyl-2-picrylhydrazyl radical scavenging, carotene decolorization, and cholesterol oxidation and linoleic acid assays (31). However, its lipid peroxidation and protein oxidation inhibiting activities against the HO• in rat liver were positive (32). It also showed strong antioxidant activity against peroxynitrite-mediated reactions, and inhibited DNA-dependent protein kinase of cancer cells (33).

VANILLIN AND CANCER

Reactive oxygen species' effects on cancer formation was discussed in detail before. It is known that ROS and genetic mutations are the main reasons for cancer formation. Since vanillin has the antioxidant ability in suitable conditions and an efficient antimutagenic ability, its anticarcinogenic and anti-metastatic abilities were an area of interest. Different cell lines have been used and different parameters have been researched.

Many organisms have developed different mechanisms to survive from hypoxia and the hypoxia-inducible factor 1 (HIF-1) gene is one of these mechanisms. This gene can interact with transcription factors and enzymes to control tissue development and vascularity (34). This adaptation to hypoxia is also used by the

tumor microenvironment and accelerates the tumor's development. Park et al. (35) used A2058 and A375 malignant melanoma cells and investigated the effects of vanillin. They have noted that vanillin has no significant effects on cell viability under hypoxic conditions. However, vanillin has had a major effect on HIF-1 α metabolism. It has suppressed HIF-1 α accumulation due to hypoxia. Whilst inhibiting the HIF-1 α , no A2058 and A375 cytotoxic effects have noted. It suppresses the HIF-1 α accumulation pathway in the nucleus and also decreases HIF-1 α protein levels, not only transcriptional factors (35).

Lirdrapamongkol et al. (36) have noted the positive effects of vanillin on tumor growth and metastasis suppression by tamoxifen comparison. Tamoxifen is a highly effective chemotherapeutic used to prevent or treat breast cancer. It binds to the estrogen receptor and prevents mammalian cell's proliferation by a complicated mechanism (37). At 4T1 cell line used in vivo studies, vanillin has decreased the number of tumor colonies in the lungs whilst tamoxifen has shown no effect (36). Despite vanillin's positive result at fighting with metastasis, vanillin and tamoxifen have not shown any significant effect on primer tumor growth (37).

A colon cancer cell line, HCT-116 carries a mutation in KRAS proto-oncogene. King et al. (38) have reported the positive effect of vanillin at repairing various mutations in the HCT-116 cell line. Furthermore, study of the Ho et al. (2) confirmed this profound anti-mutagenic effect of vanillin on human colon cancer. HT-29 is also a human colon adenocarcinoma cell line (39). Ho et al. (2) noted that vanillin against HT-29 cells showed cytolytic and cytostatic effects. Vanillin's half-maximal inhibitory concentration (IC₅₀) was 400 μ g/ml against HT-29 cells (2).

DISCUSSION

Many different therapies have been tried to cure cancer. The combined procedure of surgery, chemotherapy, and radiotherapy is the standard procedure of cancer treatment, but 5-year and 10-year mortality rates are showing us that this standard procedure and different drug therapies are not enough to fight against cancer. To increase the success rate, different therapy methods have been developed. For this aim, multiple plants and their products have been tried with different chemotherapeutics. The potential synergistic effects and decreasing toxicity against the healthy cells of these molecules with drugs are the most important parameters in these researches. Vanillin, the focal point of

this literature review, is not a major molecule in cancer research area but previous studies, which have a small part in cancer studies, have promising results. Its anti-oxidant and antimutagenic effects were studied and exemplified with different studies from the literature. Even the lack of up-to-date studies was a major problem while writing this review, cited articles were briefly showing the aforementioned positive effects against carcinogenesis.

CONCLUSION

Vanillin is a promising molecule with its antioxidant and antimutagenic abilities. In the rapidly developing cancer research area, vanillin's effects with other drugs or alone should be researched and new studies should be made to expose the vanillin's potential against carcinogenesis.

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