

# Anti-Cancer Potential of Cinnamaldehyde

Subjects: **Oncology**

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Cinnamaldehyde has anti-cancer effects through a number of different mechanisms that are interconnected with one another. These effects reduce some of the most severe symptoms of abnormally rapid cell growth. Some of the mechanistic approaches include the induction of apoptosis, cell cycle arrest, interruption in angiogenesis, free radical scavenging, inhibition of inflammation, and interference with cellular invasion and metastasis. According to the types, doses and duration of treatment of cancer, the mechanisms involved could change.

cancer prevention

cinnamaldehyde and its congeners

cinnamon plant

## 1. Cinnamaldehyde on Bladder Cancer

Researchers are becoming increasingly concerned about the rising global incidence of bladder cancer, and the adverse effects of chemotherapy medications have long been recognized as a primary barrier to developing effective cancer treatments. Bladder cancer, the most common among other forms of cancer, initiates with the lining cells of the bladder (urothelial cells). It is important to note that urothelial cells are not limited to the urinary tract. This can also be found in the kidneys and ureters <sup>[1]</sup>. Cinnamaldehyde, the active component in cinnamon, has been thought to possess anti-inflammatory and antioxidant properties for a considerable amount of time. In the present study, cinnamaldehyde was taken into account to evaluate its anticancer activity against bladder cancer 5637 cell lines. It has been observed that the exposure of bladder cancer 5637 cells with cinnamaldehyde for 24, 48, and 72 h at concentrations 0.02, 0.04, and 0.08 mg/mL induced apoptosis (confirmed using Annexin V-FITC/PI and Hoechst 33258 staining) in a dose-dependent way. In addition to this, when the scratch test was performed, it had shown to have a significant inhibitory effect on cell migration. Apart from that, cinnamaldehyde also exhibited inhibitory activity on glucose uptake and lactate production ( $p < 0.05$ ), as well as on Heat Shock Protein Transcription Factor-1 (HSF-1), epidermal growth factor receptor 2 (ErbB2), and lactate dehydrogenase A (LDHA) gene expressions, and finally, HSF1 and LDHA protein levels. Therefore, it concludes that cinnamaldehyde induces apoptosis by suppressing ErbB2-HSF1-LDHA pathway to inhibit 5637 cell lines <sup>[2]</sup>.

## 2. Cinnamaldehyde on Blood Cancer

Blood cancer is a kind of cancer that affects the blood cells. Myeloma, leukaemia, and lymphoma are the three most common types of cancer that originate in the bone marrow or blood and may spread throughout the body <sup>[3]</sup>. Leukaemia is a kind of cancer that affects both the blood cells and the bone marrow. It manifests itself when the body produces an abnormally high number of white blood cells, which subsequently inhibit the bone marrow's ability to make healthy red blood cells and platelets <sup>[4]</sup>. Whereas, lymphoma is of 2 types, viz. Non-Hodgkin

lymphoma originates in lymphocytes, a kind of white blood cell that assists the body in its battle against infections and Hodgkin lymphoma is a kind of cancer that affects the blood and originates in lymphocytes, which are the cells that make up the lymphatic system [5]. Hodgkin lymphoma may be diagnosed when an aberrant form of lymphocyte known as a Reed-Sternberg cell is present in the patient's body. Finally, multiple myeloma may be traced back to a cancer that begins in the plasma cells, a subtype of white blood cell that is produced in the bone marrow [6].

To examine the effects of trans-cinnamaldehyde on the human leukaemia K562 cell line and the cytotoxicity of cytokine-induced killer (CIK) cells against K562 cells. In order to investigate apoptosis, Fas expression, and mitochondrial transmembrane potential in the K562 cells, flow cytometry was used. Apoptosis seemed to be induced in 8.9% of K562 cells when they were treated with trans-cinnamaldehyde at a concentration of 180  $\mu\text{mol}$  per litre for nine hours. After 24 h of treatment with 120 or 180  $\mu\text{mol}$  per litre trans-cinnamaldehyde, the percentage of apoptotic cells increased to 18.63% and 38.98%, respectively. In K562 cells, trans-cinnamaldehyde has a considerable inducing effect on the expression of Fas and has a suppressive effect on the mitochondrial transmembrane potential. Trans-cinnamaldehyde treatment at 120 and 180  $\mu\text{mol}$  per L for 9 h increased the percentage of K562 cells that were lysed by expanded CIK cells from 34.84% to 48.21% and 64.81% at an E:F ratio of 25:1 and from 49.26% to 57.81% and 73.36% at an E:F ratio of 50:1. Therefore, it was noticed that trans-cinnamaldehyde induces apoptosis in human leukaemia K562 cells, which contributes to the cytotoxic effects that it has on these cells, and it also enhances the cytotoxicity of CIK cells against K562. These advantages of trans-cinnamaldehyde may become particularly helpful for those who have leukaemia and have already had a hematopoietic stem cell transplant (HSCT) [7].

When cinnamaldehyde, a major component of cinnamon bark extract, was taken to investigate its possible antiproliferative effects on myeloma cells by studying its anti-angiogenic and anti-inflammatory effects on the cells. The researchers discovered that cinnamaldehyde suppressed the proliferation of myeloma cells when tested on the human myeloma cell line RPMI 8226. After 24 h of treatment, the  $\text{IC}_{50}$  value was discovered to be 72 mg per mL, which resulted in a 50% decrease in cell growth in comparison to untreated controls. The administration of cinnamaldehyde over a prolonged period of time resulted in a significant reduction in the expression of angiogenic factors and cyclooxygenase at the mRNA and protein levels, respectively. The cell cycle of the exposed cells became stopped time dependently at the  $\text{G}_0/\text{G}_1$  phase. Cinnamaldehyde has been shown to inhibit cell growth in addition to causing DNA to fragment in a time-dependent way, which ultimately results in cell death. In conclusion, it would seem that there are a few different approaches that may be used in order to eradicate myeloma cells, some of which include inhibiting the proliferation of the cells, lowering inflammatory responses, and triggering cell death. As a result, cinnamaldehyde has the potential to open the door to research that might lead to the development of an effective chemotherapeutic agent or herbal medicine for the treatment of multiple myeloma [8].

In order to find out the mechanistic pathway to suppress canonical  $\text{IL-1}\beta$  secretion, Ho et al., in the year 2018 discovered that cinnamaldehyde and 2-methoxy cinnamaldehyde at concentrations 25 to 100  $\mu\text{M}$  exhibited to inhibit  $\text{IL-1}\beta$  secretion dose dependently in human monocytic THP-1 cell lines. The tested compounds resulted in the expressions of pro- $\text{IL-1}\beta$  (Interleukin- $1\beta$ ) and NLRP3 (NLR Family Pyrin Domain Containing 3) to bring down to

a lower level. Both the cinnamaldehyde and 2-methoxy cinnamaldehyde were found to be able to inhibit the ATP (adenosine triphosphate)-induced, decrease the cytosolic pro-caspase-1, and increase the secreted caspase-1 [9].

Due to the potential to suppress the antitumor immune response by restricting T cell proliferation, cytokine production, and tumour cell death, myeloid-derived suppressor cells have emerged as new therapeutic targets in cancer treatment. Hence, the aim of the authors of this research was to screen the antimyeloid-derived suppressor cell activity of cinnamaldehyde. Therefore, researchers used myeloid-derived suppressor cells isolated from the spleens of TLR4<sup>-/-</sup> mice that had colon cancer (MC38 tumour) and had exposure to cinnamaldehyde (4 µg/mL) for a certain period of time. They have the increased capacity to inhibit cell proliferations via the TLR (Toll-like receptor)4-dependent pathway and can induce cell death via apoptosis. Additional testing revealed that the treatment with cinnamaldehyde led to an increase in the expression of Bax (Bcl-2-associated X protein) and caspase-9, while the expression of Bcl-2 (B-cell lymphoma 2) was reduced, indicating that cinnamaldehyde induced apoptosis in myeloid-derived suppressor cells by following an intrinsic pathway [10].

The research aims to investigate whether or not cinnamaldehyde, which has been hypothesised to have anticancer properties, has any impact on human HL-60 cell lines. The study showed that cinnamaldehyde, at concentrations ranging from 0 to 0.8 mg/mL, significantly raised the number of cells in the G<sub>2</sub>/M phase of the cell cycle and revealed significant suppression of the growth of tumour cells. In response to the cinnamaldehyde treatment, the expression of cyclin A, cyclin B1, ERK2 (mitogen-activated protein kinase 1), and p-ERK was shown to be decreased by Western blotting. Cinnamaldehyde, in particular, has been demonstrated to reduce the viability of tumour cells by down-regulating the target molecules that are involved in the control of the cell cycle and mitotic regulation [11].

### 3. Cinnamaldehyde on Brain Cancer

An in vitro and in vivo study was conducted utilizing glioblastoma TS14-15, TS15-88 cells, and the mouse orthotopic xenograft model, respectively, to evaluate the anticancer properties of 2'-hydroxycinnamaldehyde, a natural congener of cinnamaldehyde. Combination treatment with 2'-hydroxycinnamaldehyde at a concentration of 5 µM and commercially available temozolomide at a concentration of 250 µM significantly reduced cellular growth, invasiveness, and cell survival while increasing cytotoxicity. In addition, the combined treatment dramatically decreased the levels of invasiveness, cell differentiation, and mesenchymal transition markers N-cadherin, Zeb1, and β-catenin. Additionally, the combination therapy with 2'-hydroxycinnamaldehyde (50 mg kg<sup>-1</sup>) and temozolomide (30 mg kg<sup>-1</sup>) prevented tumour growth in an orthotopic xenograft model carried out on mice. According to the findings of this research, the combination of temozolomide and 2'-hydroxycinnamaldehyde showed a promising effect on glioblastoma [12].

A current study attempted to determine, for the very first time, if cinnamaldehyde could be co-administered with doxorubicin (an anticancer agent) against U87MG glioma cells to enhance doxorubicin's lethal impact and overcome or lessen its adverse effects. The MTT assay was performed to establish the potential of doxorubicin and cinnamaldehyde as a single performer or in combination using U87MG cells. Several postulations, viz., caspase-3

and -9 activation, and mitochondrial membrane potential, were made to ascertain the etiology of cell death. Additionally, an investigation on the levels of apoptotic gene expression was carried out (Bax and Bcl-2). The fact that the IC<sub>50</sub> values for cinnamaldehyde and doxorubicin were 11.6 and 5 µg/mL, respectively, in a cellular toxicity assay suggests that both components may have a detrimental effect on the survival of U87MG cells. Cinnamaldehyde, when combined with doxorubicin, produced a significant increase in the cytotoxic effect of doxorubicin on U87MG cells. Cinnamaldehyde has the potential to induce programmed cell death, i.e., apoptosis in U87MG cells. This was discovered by the use of SUB-G<sub>1</sub>, MMP, caspase-3, and -9 activity assays, as well as Bcl-2 and Bax gene expressions, where all the levels were enhanced. In addition to this, it has been shown that doxorubicin's apoptotic effects were amplified in the presence of cinnamaldehyde. Therefore, cinnamaldehyde seemed to have an effect on the level of doxorubicin-induced apoptosis in human glioblastoma cells by reducing cell proliferation. Overall, the data suggested that treating glioblastoma with a combination of doxorubicin and cinnamaldehyde might be effective [13].

It is still unknown how cinnamaldehydes are effective against glioma. Therefore, to investigate the effects of cinnamaldehyde on the viability of temozolomide-treated T98G glioma cells, as well as the expression of chemokine receptors CXCR4 and CXCR7, Chen et al. designed an experiment in 2020 and observed that cell viability was considerably lower following the combination treatment with cinnamaldehyde (75 µM) and temozolomide (300 µM) than treatment with temozolomide or cinnamaldehyde alone. CXCR4 and CXCR7 expressions were evaluated using western blotting. As a consequence of this, it suppresses the expression of CXCR4. Cinnamaldehyde, while co-administering with temozolomide, showed a sharp reduction in the viability of glioma cells, most likely through inhibiting CXCR4 expression [14].

## 4. Cinnamaldehyde on Breast Cancer

Breast cancer is the second most common cancer in women after skin cancer. It is a malignant tumor that starts in the breast tissue and spreads throughout the breast. Although women are more likely to be diagnosed with breast cancer, males are not immune to the disease. The presence of a lump in the breast, a change in the breast's form or texture, and a bloody discharge from the nipple are all symptoms that can be associated with breast cancer. To get rid of this issue numerous phytochemicals have already been recognized as effective and safe in use, and cinnamaldehyde is one of them. An attempt by Lu et al. was adopted in the year 2010 where cinnamaldehyde, in terms of the cinnamon extract, seemed to be successful in inhibiting the effects of vascular endothelial growth factor (VEGF) on HUVEC and bovine capillary endothelial cell proliferation, migration, and tube formation (32 µg/mL) in vitro and in vivo formation of tumours. Cinnamaldehyde (IC<sub>50</sub>: 30 ng/mL) possesses those activities by inhibiting the kinase activity of purified VEGFR2 as well as the mitogen-activated protein kinase- and STAT3-mediated signalling cascade in endothelial cells [15].

Protein tyrosine phosphatase 1B (PTP1B) has the potential to be a useful therapeutic target for cancer; thus, cinnamaldehyde's impact on PTP1B enzyme activity and MCF-7 cancer cell survival is examined. After performing the experiment, it was observed that cinnamaldehyde decreased the activity of PTP1B at a concentration of 500 µM (IC<sub>50</sub>: 1 mM), which resulted in an inhibition of the growth of MCF-7 cancer cells at 50 µM [16].

One of the most recently discovered adipokines, nicotinamide phosphoribosyl transferase (NAMPT, visfatin), has not only been connected to metabolic syndrome and obesity but it has also been associated to the proliferation of cancer. Therefore, inhibiting NAMPT and reducing the synthesis of nicotinamide adenine dinucleotide might be a viable treatment for cancer. In order to accomplish this, the researchers of this experiment used the breast cancer MDA-MB-231-GFP (GFP: Green fluorescent protein) cell line for an in vitro study and the female Balb/c nude xenograft animal model for an in vivo study, where tumors were implanted by the subcutaneous injection of MDA-MB-231-GFP cells. They treated both models with varying concentrations of visfatin combined with cinnamaldehyde and FK866 (a visfatin inhibitor) to evaluate cellular toxicity. This was the first study to demonstrate that a naturally occurring molecule may block NAMPT both extracellularly and intracellularly. In this experiment, the cinnamaldehyde at concentration 25–100  $\mu\text{M}$  showed significant inhibitory activity against the breast cancer cell line, which led to severe cell death. On the other hand, as compared to the group that had been treated with visfatin, the amount of cinnamaldehyde (75  $\mu\text{M}$ ) and FK866 (100 nM) that dramatically decreased cell viability by reducing visfatin-induced proliferative mediated proteins, such as mTOR (mammalian target of rapamycin), p-mTOR, p-PI3K, PCNA, and PI3K. This combination was also found to have reduced intra- and extra-cellular NAMPT protein expressions. However, in the same experiment, the in vivo study revealed that a combination of cinnamaldehyde (100  $\text{mg kg}^{-1}$ ) and FK866 (4  $\text{mg kg}^{-1}$ ) results in a tumour with a reduced weight compared to the control. It also demonstrated that the combination reduced the visfatin-induced luminescence signal in tumour luminescence tests. Lower proliferating cell nuclear antigen was also observed in the animal group treated with cinnamaldehyde and FK866 combination [17].

In a different experiment, cinnamaldehyde at 2.5, 5, 10, 20, and 40  $\mu\text{g/mL}$  concentration resulted in a suppression of the proliferation of MDA-MB-231 cells. After 24 h, the  $\text{IC}_{50}$  concentration of cinnamaldehyde was measured to be 16.9  $\mu\text{g/mL}$ , and after 48 h, it was measured to be 12.23  $\mu\text{g/mL}$ . The effect of cinnamaldehyde on apoptosis was evaluated using flow cytometry at a range of different concentrations. In MDA-MB-231 cells, induction of apoptosis occurred at rates of 9.5, 10.5, and 22.5% when the cells were treated with cinnamaldehyde at doses of 10, 15, and 20  $\mu\text{g/mL}$ , respectively. The results of Trans well testing demonstrated that cinnamaldehyde at doses 15 and 20  $\mu\text{g/mL}$  were adequate to suppress the invasiveness of MDA-MB-231 cells. In a wound healing test, the same concentration of the compound significantly decreased the migration capability of MDA-MB-231 cells. These findings suggest that cinnamaldehyde may be able to significantly inhibit the invasion of MDA-MB-231 breast cancer cells [18].

Oncolytic virotherapy, a relatively new approach to cancer treatment, has promise as an anticancer therapy because of its capacity to boost antitumor adaptive immunity. The oncolytic measles virus is ideally suited for targeting breast cancer because of upregulating the measles virus receptor known as nectin-4. Cinnamaldehyde at concentrations of 60 and 80  $\mu\text{M}$  and the measles virus at a MOI (multiplicity of infection) of 0.1 exhibited a greater antitumor activity against breast cancer MCF-7 cells when combined than treated alone. Additional mechanistic research revealed that the combination of the measles virus and cinnamaldehyde has a synergistic antibreast cancer activity. This activity is mediated by enhanced apoptosis in the cancer cells. Cinnamaldehyde, on the other hand, did not have an effect to enhance the infection in MCF-7 cells with the oncolytic measles virus. It was also shown that cinnamaldehyde displayed greater cytotoxicity at concentrations ranging from 60–400  $\mu\text{M}$ , although to

a lower degree than the measles viral combinational treatment. As a result, the findings of this research provided the first evidence that using an oncolytic measles virus in conjunction with cinnamaldehyde could be an effective treatment strategy for breast cancer cells that have been marked with the protein nectin-4 [\[19\]](#).

In malignant cells, the transcription factor known as STAT3 (signal transducer and activator of transcription 3) often has an elevated level of activity. A downstream target of STAT3, the cMyc gene is an important site in treating cancer. As a result, the objective of the study was to establish whether or not cinnamaldehyde has the potential to cause apoptosis in breast cancer cells by the means of the STAT3/cMyc pathway. Cinnamaldehyde (5, 10, 20, 40, and 80 µg/mL) was shown to have a significant inhibitory effect on cell growth and migration in MDA-MB-231, MCF-7, and 4T1 cells when tested over time and in a dose-dependent way. Cinnamaldehyde, at the same dosage as the cMyc inhibitor 10074-G5, was shown to have a promising effect, according to the findings of the research. It was also able to restrict the proliferation and migration of breast cancer cells, which may be connected to the upregulating of the mitochondrial apoptosis in those cells via downregulating apoptosis-mediated proteins through the STAT3/cMyc pathway [\[20\]](#).

## 5. Cinnamaldehyde on Cervical Cancer

The global mortality rate for female cancer patients remains the highest due to cervical cancer. HPV (human papillomavirus), namely HPV16, is the prime accuse in this development. The antitumor effect of a natural congener of cinnamaldehyde, i.e., 4-methoxycinnamaldehyde, was investigated on C-33A human cervical cancer cell lines. By using the MTT (3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide) assay, it was discovered that 4-methoxycinnamaldehyde (IC<sub>50</sub>: 110 µM) had a dose-dependent impact on these C-33A cells. Flow cytometry indicated that it significantly induced apoptosis with the same IC<sub>50</sub>. In addition, non-toxic doses of 4-methoxycinnamaldehyde were sufficient to substantially inhibit the invasive capacity of C-33A cells. Cell invasion of HPV16-expressing C-33A cervical cancer cells was considerably decreased by 4-methoxycinnamaldehyde, as demonstrated by a considerable drop in the MMP(Matrix metalloproteinases)14 expression as determined by the real-time polymerase chain reaction (PCR), although MMP9 expression was unaffected by the treatment [\[21\]](#).

To investigate the anticancer effects of cinnamaldehyde on human HeLa cell lines, Xie et al., in the year 2018, noticed that at concentrations ranging from 0 to 0.8 mg per mL, it dramatically increased the number of cells in the G<sub>2</sub>/M phase of the cell cycle and demonstrated substantial inhibition of tumour cell growth. Western blotting revealed that the expression of cyclin A, cyclin B1, ERK2, and p-ERK was suppressed in response to cinnamaldehyde treatment. Specifically, cinnamaldehyde was shown to decrease tumour cell viability by down regulating target molecules involved in cell cycle control and mitotic regulation [\[11\]](#).

## 6. Cinnamaldehyde on Colon Cancer

When it comes to malignant growth, colorectal cancer is one of the most common reasons for both morbidity and death. A pharmacological intervention that makes use of dietary components that activate the redox-sensitive



Nrf2/Keap1-ARE signalling pathway has recently shown a promising method for the chemoprevention of human cancers, including colorectal cancer. In the quest for dietary Nrf2 (nuclear factor erythroid 2-related factor 2) activators that may have chemo-preventive effects targeting colorectal cancer, researchers have been concentrating their attention on *trans*-cinnamaldehyde since it is the principal flavour molecule found in cinnamon essential oil. The treatment of human colon cancer HT29, HCT116 cells with *trans*-cinnamaldehyde (10  $\mu$ M) led to an increase in the cellular protein levels of Nrf2 and the identification of Nrf2 targets, i.e.,  $\gamma$ -glutamyl-cysteine synthetase and heme oxygenase 1 (HO-1), which are involved in the antioxidant response. After being pre-treated with *trans*-cinnamaldehyde when a strong upregulation of cellular glutathione level occurs, the HCT116 cells seemed to have protected activity against the genotoxicity generated by hydrogen peroxide as well as the oxidative stress caused by arsenic. In human epithelial colon culture cells, all of these findings indicate that cinnamaldehyde has a potent stimulating effect on the antioxidant response mediated by Nrf2. Because of this, cinnamaldehyde may be an underappreciated chemo-preventive component in the diet that suppresses the development of colorectal cancer [22].

In continuation to the previous study, another group of researchers contributed their effort to investigate the chemo-preventive potential and the molecular mechanism behind cinnamaldehyde-induced Nrf2 activation in colorectal epithelial HCT116 cells in vitro and the comparison of Nrf2<sup>+/+</sup> with Nrf2<sup>-/-</sup> mice in vivo. In HCT116 cells, the addition of cinnamaldehyde at a concentration of 20  $\mu$ mol per litre prolonged the half-life of the Nrf2 protein by inhibiting ubiquitination. This resulted in the activation of cytoprotective Nrf2 target genes and an increase in the amount of cellular glutathione. Cinnamaldehyde was demonstrated to minimize the amount of AOM/DSS-induced inflammatory colon carcinogenesis by modifying the molecular markers of colorectal carcinogenesis. Cinnamaldehyde was able to reduce colorectal cancer in Nrf2<sup>+/+</sup> mice, but it did not have this effect on Nrf2<sup>-/-</sup> mice, which shows that the chemo-preventive effects of cinnamaldehyde are reliant on Nrf2 [23].

BAG3, also known as B-cell lymphoma 2-associated anthanogene, is a protein that belongs to the BAG co-chaperone family. This protein has been investigated for the possibility that it plays a role in the adaptive responses of normal cells and cancer cells to stressful events. It was shown that 2'-hydroxycinnamaldehyde (50  $\mu$ M) was responsible for the death of SW620 and SW480 colon cancer cells by the activation of caspase-7, -9, and poly (ADP-ribose) polymerase (PARP), as well as the confirmation of apoptosis by staining with Annexin V. Notably, 2'-Hydroxycinnamaldehyde was able to considerably raise BAG3 mRNA and protein levels in both time- and dose-dependent way. Through its ability to stimulate the activity of HSF1, 2'-hydroxycinnamaldehyde is responsible for the enhanced expression of BAG3. When the expression of BAG3 was suppressed using siRNA, more evidence that BAG3 was directly involved in 2'-Hydroxycinnamaldehyde-induced cancer cell death was discovered. In light of the fact that the body's stress response system contributes to the development of cancer, the findings strongly suggest that BAG3 might be an effective therapeutic target for cancer therapy [24].

Cinnamaldehyde (100  $\mu$ g/mL) was found to decrease cyclin D1 protein level through cyclin D1 degradation via GSK3 $\beta$ -dependent threonine-286 (T286) phosphorylation of cyclin D1. These findings suggest that cyclin D1 degradation may contribute to cinnamaldehyde-mediated decrease of cyclin D1 protein level in human colorectal cancer LoVo, HCT116, HT-29, and SW480 cells. In addition, cinnamaldehyde was able to lower the amount of

cyclin D1 mRNA and prevent the activation of the Wnt pathway by inhibiting  $\beta$ -catenin and TCF4 production. Additionally, it was shown that apoptosis might be caused by cinnamaldehyde via ROS-dependent DNA damage. Cinnamaldehyde was responsible for the production of ROS, which in turn increased the activity of the transcription factors nuclear factor-kappa B (NF- $\kappa$ B) and activating transcription factor 3 (ATF3). As a result, the findings suggest that cinnamaldehyde may limit cell proliferation by inhibiting the expression of cyclin D1 through proteasomal degradation and transcriptional inhibition, as well as by activating NF- $\kappa$ B and activating transcription factor ATF3 in a ROS-dependent manner to cause apoptosis. It is possible that the effects of cinnamaldehyde are to blame for the reduced viability of human colorectal cancer cells [25].

Using the MTT test, the effects of cinnamaldehyde (0.4  $\mu$ g/mL) on the proliferation of the HCT 116 colon cancer cell line were determined. Fluorescent labelling procedures Rhodamine-123 and MitoSOX were used to analyse the impact of cinnamaldehyde on mitochondrial membrane potential, ROS, and superoxide generation, respectively. Even at low doses, cinnamaldehyde exhibited cytotoxicity. Superoxide anion and ROS generation increased while mitochondrial membrane potential dropped, which inhibited the proliferation of cells. Based on these findings, cinnamaldehyde could be helpful for people with colon cancer [26].

A poor prognosis and resistance to radio-chemotherapy are both associated with hypoxia in the surrounding microenvironment of solid tumours, which is one of the most important pathological markers of solid tumours. According to the findings of a study, hypoxia makes colorectal cancer cells more stem-like and causes them to undergo an epithelial-mesenchymal transition, both of which reduce the cells' susceptibility to oxaliplatin. On the other hand, cinnamaldehyde at a concentration of 40  $\mu$ g/mL increased the rate of apoptosis in colon cancer HCT116 and SW480 cells both in vitro and in vivo, using a tumour xenograft model in BALB/c/nu/nu nude mice. This had the effect of enhancing the curative effect of oxaliplatin. Cinnamaldehyde and oxaliplatin were able to effectively upregulate Bax, cleave caspase-3 and PARP, and downregulate Bcl-2. An in vivo investigation showed that the combination of cinnamaldehyde (50 mg kg<sup>-1</sup> with oxaliplatin (7.5 mg kg<sup>-1</sup>)) resulted in antitumor action. This activity was shown by a decrease in Bcl-2 expression and an increase in the expression of the pro-apoptotic marker Bax. Immunohistochemistry performed on tumour tissue demonstrated increasing amounts of the protein Bax and decreasing levels of the protein  $\beta$ -catenin. Cinnamaldehyde and oxaliplatin worked synergistically to inhibit cell proliferation in colorectal cancer cells by reversing hypoxia-induced epithelial-mesenchymal transition and stemness in these cells. This was accomplished on a mechanistic level. These findings not only demonstrated the potential therapeutic benefit of cinnamaldehyde but also offered novel recommendations for increasing the sensitivity of oxaliplatin in the treatment of colorectal cancer [27].

## 7. Cinnamaldehyde on Ehrlich Ascites Carcinoma

Cinnamaldehyde, at a dose of 50 mg kg<sup>-1</sup> of body weight, delayed the progression of Ehrlich ascites carcinoma tumours in mice by reducing the number of tumour cells by 45 percent, their viability by 53 percent, and their rate of proliferation by 53 percent. In addition to this, a significant arrest in the G<sub>0</sub>/G<sub>1</sub> phase of the cell cycle was seen. After treatment with cinnamaldehyde, there was an increase in the percentage of splenic T helper cells (CD3<sup>+</sup>CD4<sup>+</sup>) and T cytotoxic cells (CD3<sup>+</sup>CD8<sup>+</sup>), both of which are indicators that cinnamaldehyde successfully



initiated an immune response against cancer. In light of these data, it would seem that cinnamaldehyde has a potent anticancer effect against Ehrlich ascites carcinoma in vivo [28].

## 8. Cinnamaldehyde on Gastric Cancer

Gastric cancer is a term that refers to cancer that develops in the lining of the stomach. It is possible for stomach cancer to grow in any of the tissues that make up the stomach. In the majority of instances, the first sign of cancer will show up in the primary chamber of the stomach, which is also referred to as the stomach body. An experiment was carried out by Milani and colleagues to investigate the effects of *trans*-cinnamaldehyde on AGS cells. After the study was completed, it was shown that *trans*-cinnamaldehyde, at a concentration of 2 mg/mL, was able to significantly inhibit the development of AGS cells in a dose-dependent way. According to the findings of this study, *trans*-cinnamaldehyde produced profound impacts on the AGS cell line [29].

Lee and Jung investigated the antiproliferative effects of *trans*-cinnamaldehyde in AGS cells derived from stomach cancer and the mechanisms behind these effects. *trans*-cinnamaldehyde inhibits the viability of AGS cells dose dependently. According to the results, *trans*-cinnamaldehyde (100 µM) has the potential to trigger apoptosis by modifying the structure of cells. In order to get a better understanding of the process of apoptosis, researchers investigated the quantities of proteins that were involved. *trans*-cinnamaldehyde was able to increase the amount of cleaved caspase-9 as well as the amount of cleaved PARP. Additionally, it was able to stimulate the synthesis of p53 and Bax proteins. According to these findings, apoptosis was triggered in AGS cells by *trans*-cinnamaldehyde via a mechanism including p53. According to the findings, *trans*-cinnamaldehyde showed potential as an alternative for an anticancer pharmaceutical treatment in the case of stomach cancer [30].

Cinnamaldehyde, at a concentration of 50 µg/mL, was shown in studies to induce ER stress and cell death in gastric cancer, including SNU-216, SNU-638, AGS, MKN-45, NCI-N87, and MKN-74 cells. This was accomplished via the PERK-CHOP axis and the release of calcium ions. Intriguingly, autophagy inhibition decreased cinnamaldehyde-induced cell death, while cinnamaldehyde treatment resulted in autophagic cell death by increasing ATG5, Beclin-1, and LC3B expressions and by reducing p62 expression. Additionally, cinnamaldehyde was shown to activate LC3B while simultaneously inhibiting G9a function. In addition, cinnamaldehyde was able to prevent G9a from binding to the promoters of both LC3B and Beclin-1. The combination of these studies demonstrated that cinnamaldehyde regulates PERK-CHOP signalling and that suppression of G9a promotes autophagic cell death in gastric cancer cells through ER stress [31].

## 9. Cinnamaldehyde on Head and Neck Cancer

Cancers of the head and neck may occur in a variety of places, including the oral cavity, the pharynx, and other areas. The most common symptom is a painful and scratchy throat. p53-mutant (YD-10B) and p53-wild (SGT) human head and neck cancer cells were used to evaluate the apoptosis-inducing effects of the cinnamaldehyde derivative 2'-hydroxycinnamaldehyde and the signalling pathways that were involved. It was discovered that YD-

10B and SGT cells are more sensitive to the antiproliferative effects of 2'-hydroxycinnamaldehyde. The apoptotic effect that was caused by 2'-hydroxycinnamaldehyde (50  $\mu$ M) was verified by double staining with annexin V-FITC and PI, and this result was supported by the activation of caspase-3, -7, and -9 in addition to PARP. Following treatment with 2'-hydroxycinnamaldehyde, p21 expression was shown to be significantly elevated in both SGT and YD-10B cells. Furthermore, 2'-hydroxycinnamaldehyde boosted the cell death pathway in a p53-independent manner, as shown by the fact that it raised the expression of pro-apoptotic Bak1 and lowered the expression of antiapoptotic Bcl-2 in both of the cell lines tested. In addition to that, it led to an increase in the expression of LC3B in both SGT and YD-10B cells. When compared to YD-10B cells, SGT cells showed a significant increase in 2'-hydroxycinnamaldehyde-induced apoptosis after pre-incubation with the autophagy inhibitor 3-MA. This suggests that autophagy may actively contribute to 2'-hydroxycinnamaldehyde-induced apoptosis. YD-10B cells did not show this significant increase. In general, the findings of this study suggest that 2'-hydroxycinnamaldehyde, regardless of its impact on the p53 gene, has potential as a therapeutic agent for the treatment of head and neck cancer [32].

## 10. Cinnamaldehyde on Liver Cancer

Primary liver cancer is a significant public health problem and a subtype of cancer that is growing at an increasing rate in the United States. Both cancer of the liver and cancer of the bile ducts are considered to be the main forms of liver cancer. The underlying causes, risk factors, symptoms, and treatments for cancers that affect both sexes are the same. Medical practitioners focus on identifying those individuals who are at an increased risk in order to diagnose and treat primary liver cancer in its earlier stages when it is more treatable. Cinnamaldehyde was investigated in a work with the intention of determining whether or not it was able to decrease the growth of human hepatoma Hep G2 cells. Cinnamaldehyde exhibited antiproliferative action with an  $IC_{50}$  value of 9.76  $\mu$ M, which was equivalent to that of the cancer drug 5-fluorouracil ( $IC_{50}$ : 9.57  $\mu$ M). Additional study into the apoptotic pathways of cinnamaldehyde found that it cleaves PARP and, over time, upregulates CD95 (APO-1), p53, and Bax proteins while concurrently downregulating the expression of Bcl-X<sub>L</sub>. Cinnamaldehyde effectively prevented CD95 (APO-1), p53 expression and PARP cleavage in cells. On the basis of these findings, it would seem that the apoptotic mechanism induced by cinnamaldehyde in Hep G2 cells is perhaps mediated via the p53 activation and CD95 (APO-1) signalling pathways [33].

In search of the antiapoptotic property of cinnamaldehyde, Lin et al., in the year 2013, conducted a study on PLC/PRF/5 cells. Cinnamaldehyde was found to stimulate the activation of caspase-3, which in turn, led to the cleavage of PARP. This was accomplished by increasing the production of ROS, disrupting the mitochondria membrane potential, and releasing cytochrome c and Smac/DIABLO from the mitochondria into the cytosol. Cinnamaldehyde treatment also resulted in a decrease in the levels of the anti-apoptotic proteins XIAP and Bcl-2, whilst the levels of the pro-apoptotic protein Bax increased in a time-dependent way. Consequently, on the basis of these data, cinnamaldehyde seems to be a mitochondrial death pathway apoptosis inducer in PLC/PRF/5 cells [34].

Considering the importance of the Wnt/ $\beta$ -catenin pathway in aggravating cancer, Abd El Salam et al. in the year of 2022, introduced cinnamaldehyde in thioacetamide-induced hepatocellular carcinoma in male Sprague Dawley rats. For the purpose of analysing the Wnt/ $\beta$ -catenin pathway, the protein concentrations of  $\beta$ -catenin, Wnt-3a,

MMP-9, cyclin D, and VEGF were assessed in the liver. Cinnamaldehyde (70 mg kg<sup>-1</sup>) exhibited an intense inhibitory effect on the Wnt/ $\beta$ -catenin pathway by lowering the levels of hepatic  $\beta$ -catenin, Wnt-3a, MMP-9, cyclin D, and VEGF, thus proven to be a potential candidate in hepatocellular carcinoma [35].

Cinnamaldehyde, according to research that was only recently released, was able to limit the proliferation of HepG2 cells in a dose-dependent way. Researchers observed that after being exposed to cinnamaldehyde, IL-1 levels surged while IL-10 levels dropped. Additionally, after being exposed to cinnamaldehyde, the activity of caspase-3 was shown to be significantly increased in HepG2 cells. As a consequence of this, the findings of the present experiment suggested that cinnamaldehyde exhibited potentially useful antitumor action against hepatocellular carcinoma cells [36].

## 11. Cinnamaldehyde on Lung Cancer

Lung cancer is the term used to describe the development of a tumour in the lining cells of the pulmonary airways of the lungs. It is responsible for the vast majority of fatal instances of cancer in people of both sexes. The most frequent types of lung cancer are small-cell and non-small-cell varieties. These two cultivars have different requirements, and their growth occurs at different speeds because of those requirements. The non-small cell subtype of lung cancer accounts for the vast majority of diagnosed cases. In a study, human lung adenocarcinoma A549 cells were utilized as the subject of an investigation into the anticancer properties of 2-methoxycinnamaldehyde. The findings show that 2-methoxycinnamaldehyde at a concentration of 32  $\mu$ M inhibited cell proliferation and induced apoptosis. This is demonstrated by the upregulation of pro-apoptotic Bax and Bak genes and the downregulation of anti-apoptotic Bcl-2 and Bcl-X<sub>L</sub> genes; the loss of mitochondrial membrane potential; the release of cytochrome c; and the activation of caspase-3 and -9. Additionally, 2-methoxycinnamaldehyde was shown to induce lysosomal vacuolation, which was followed by an increase in the volume of the acidic compartment, a downregulation of NF- $\kappa$ B, and a reduction in the activity of topoisomerases I and II. The data suggest that 2-methoxycinnamaldehyde's growth-inhibiting effect on A549 cells is accompanied by downregulations of NF- $\kappa$ B binding activity and proliferative control involving apoptosis and both topoisomerase I and II activities, as well as upregulations of lysosomal vacuolation and volume of the acidic compartment. Additional studies have shown that an A549 xenograft BALB/c nude mouse model is likewise susceptible to the tumour growth-inhibiting effects of 2-methoxycinnamaldehyde (20 mg kg<sup>-1</sup>). According to the results of our research, 2-methoxycinnamaldehyde has characteristics that are desirable in an anticancer drug [37].

Cinnamaldehyde and hyperthermia are two complementing cancer treatments, and research conducted by scientists has revealed that the A549 non-small cell lung cancer cell line reacts well to both of them. The A549 cells were subjected to a hyperthermia treatment at 43 °C, which resulted in an increase in the cytotoxicity of cinnamaldehyde (200  $\mu$ M). Cinnamaldehyde with high temperatures had a synergistic effect that resulted in increased generation of ROS and phosphorylation of MAPK. Cell cycle arrest at the G<sub>2</sub>/M phase was also observed in the combinational therapy at the same concentration. As a result of this, the use of cinnamaldehyde in conjunction with hyperthermia may prove to be an effective therapeutic strategy for the management of non-small cell lung cancer [38].

## 12. Cinnamaldehyde on Oral Cancer

Oral cancer gives the appearance of a chronic sore or growth inside the mouth. It affects approximately 50,000 people each year in the United States, the majority of whom are men (nearly 70% of all cases). Oral cancer refers to a group of diseases that can affect the lips, tongue, cheeks, floor of the mouth, both the hard and soft palates, sinuses, and pharynx (the throat). It is possible that death will result from a delay in diagnosis and treatment. Therefore, cinnamaldehyde's potential anticancer effects were investigated in a study using HSC-3 cells, which are derived from human oral squamous cell carcinoma. Cinnamaldehyde at a concentration of 10  $\mu\text{g/mL}$  was shown to arrest the cell cycle at the  $G_2/M$  phase as well as a significant reduction in the viability of HSC-3 cells was observed. In HSC-3 cells that had been treated with cinnamaldehyde, both DNA damage and apoptotic characteristics (DNA laddering and chromatin condensation) were found. Additionally, cinnamaldehyde caused the mitochondrial malfunction, activated cytochrome c release, and raised cytosolic  $\text{Ca}^{2+}$  levels in addition to these effects. The amount of cellular glutathione and the activity of glutathione peroxidase was discovered to be significantly decreased in HSC-3 cells. On the other hand, the formation of reactive oxygen species and the levels of thiobarbituric acid reactive material were found to be increased. As a result of these observations, it could be concluded that cinnamaldehyde might inhibit the growth of oral cancer in HSC-3 cells [39].

In the year 2020, Varadarajan et al. subjected cinnamaldehyde to the oral squamous cell carcinoma SCC25 cell line. The phytochemical with an  $\text{IC}_{50}$  20.21  $\mu\text{M}$  demonstrated anticancer activity via a variety of mechanisms, including the induction of apoptosis enhancing the cytotoxic activity and the progression of cell cycle arrest at the S-phase. By decreasing the potential of the mitochondria, cinnamaldehyde brought about an increase in the rate of apoptosis [40].

In the year 2022, Ahmed et al. determined the cytotoxicity and apoptotic activity of cinnamaldehyde, scorpion venom, and their combination on the oral squamous cell carcinoma SCC25 cell line. In the experiment, the  $\text{IC}_{50}$  values of cinnamaldehyde were found to be 90.40 (at 24 h) and 42.95  $\mu\text{g/mL}$  (at 48 h), which indicates that it has a powerful effect on cancer. Whereas the combination group had the lowest nuclear area factor, up regulated the pro-apoptotic genes p53 and Bax, and down regulated the anti-apoptotic gene Bcl-2 with  $\text{IC}_{50}$  values of 4.93 (at 24 h) and 4.40  $\mu\text{g/mL}$  (at 48 h). The combination of cinnamaldehyde and scorpion venom demonstrated potential cytotoxicity and enhanced cytotoxic activity on oral squamous cell carcinoma [41].

In the same year, Aggarwal et al. tried to explore the title compound's potential against oral cancer. Several in vitro studies were conducted on oral cancer SCC-25, SCC-9, and SCC-4 cells. After treatment with 80  $\mu\text{M}$  cinnamaldehyde, it was shown that there was a dose-dependent reduction of the development and proliferation of oral cancer cells. These therapies further increased apoptosis and cytotoxicity as well as the arresting of the cell cycle at the  $G_2/M$  phase and autophagy. Cinnamaldehyde was able to prevent the invasion of these cell lines as well as the translocation of NF- $\kappa\text{B}$  into the cytoplasm. Therefore, in the cancer cells, there was a reduction in the expression of genes that were implicated in COX-2, VEGF, Bcl-2, and NF- $\kappa\text{B}$  [42].

## 13. Cinnamaldehyde on Osteosarcoma Cancer

Osteosarcoma is a kind of cancer that begins in the bone cells and spreads throughout the skeleton. Even while osteosarcoma most often starts in the long bones of the body, such as the legs or arms, it may also start in other parts of the skeleton. Extremely infrequently does it disseminate to non-skeletal soft tissue. According to the findings of a study, cinnamaldehyde significantly inhibited cell growth and induced apoptosis in a concentration-dependent manner by increasing the expression of the Bad gene and decreasing the expression of the Bcl-2 and PARP genes, respectively. It was found that it inhibited the migration and invasion of osteosarcoma cell lines 143B (IC<sub>50</sub>: 67.95  $\mu$ M) and MG63 (IC<sub>50</sub>: 56.68  $\mu$ M), respectively. Cinnamaldehyde was found to cause 143B cells to be arrested at the G<sub>2</sub>/M phase, whereas MG63 were cells arrested at G<sub>0</sub>/G<sub>1</sub> phase. In an in vivo Balb/c-nude female mouse xenograft model, the administration of cinnamaldehyde at a dose of 100 mg kg<sup>-1</sup> delayed the growth of osteosarcoma. Cinnamaldehyde's suggested approaches include lowering the amount of transcriptional activity associated with Wnt/ $\beta$ -catenin and PI3K/Akt, with the goal of preventing osteosarcoma from developing. Through its effects on the Wnt/ $\beta$ -catenin and PI3K/Akt signalling pathways, cinnamaldehyde may reduce osteosarcoma cell proliferation, migration, and invasion while simultaneously promoting their death [\[43\]](#).

## 14. Cinnamaldehyde on Ovarian Cancer

Ovarian cancer is by far the most dangerous kind of cancer that may affect a woman's reproductive system. It is seen in the tissues of the uterus that are responsible for egg production (ovaries). In many cases, the disorder is not recognized until it has already spread across the pelvis and into the belly. At this late stage, ovarian cancer is more difficult to treat, and it has a greater chance of becoming fatal. Ovarian cancer often does not produce any symptoms in its early stages. In later stages, patients may have symptoms that are not always clear, such as a loss of appetite and a reduction in their overall body weight. In most cases, chemotherapy and surgery are used in conjunction with one another to treat ovarian cancer. Cinnamaldehyde's potential uses were studied in a study that used human ovarian cancer SKOV3 cells in vitro and a SCID mice model in vivo. Cinnamaldehyde was shown to have an anticancer impact in vitro by lowering the expression and phosphorylation of AKT and STAT3, crucial factors in the control of HIF-1 $\alpha$  production, when it was utilized at a concentration of 10 mg/mL. This resulted in a significant decrease in the angiogenesis capacity of SKOV3 cells. Mice treated with cinnamaldehyde (300 mg kg<sup>-1</sup>) exhibited significant suppression of VEGF synthesis, blood vessel formation, and tumour growth in a human ovarian tumour model. The findings, considered overall, provide insight into the mechanisms by which cinnamaldehyde exerts its anti-angiogenic and antitumor actions and offer legitimacy to the possibility that the phytocomponent may be used in the treatment or prevention of cancer [\[44\]](#).

It was discovered by researchers that cinnamaldehyde and cisplatin combinedly demonstrated to have a synergistic effect on ovarian cancer cells, leading to an increase in ROS-mediated apoptosis and autophagy. The cell lines that will be studied are cisplatin-resistant A2780/cis cells and cisplatin-sensitive A2780/s cells. Throughout the course of the tests, cinnamaldehyde at IC<sub>50</sub> 43  $\mu$ M reduced cell growth for A2780/s. On the other hand, a dose of cisplatin as high as 10  $\mu$ M did not have any effect on A2780/cis. Therefore, cisplatin combined with cinnamaldehyde (51  $\mu$ M) was applied to the A2780/cis cells, which resulted in elevated synergistic growth-inhibiting action and ROS-mediated apoptosis and autophagy activity. As a result of this, it is possible to propose that the

combination of cinnamaldehyde and cisplatin may induce an excessive amount of ROS as a strategy for overcoming chemoresistance in ovarian cancer [45].

To explore cinnamaldehyde's ability to act against ovarian cancer, Boggiti et al., in the year 2021 administered cinnamaldehyde to female Wistar rats with the stated pathology. Cinnamaldehyde at a dose of 50 mg kg<sup>-1</sup> decrease the levels of estrogen, luteinizing hormone, and follicle-stimulating hormone in a dose-dependent manner. It also raises the level of progesterone. The results indicate that cinnamaldehyde could be a promising candidate in the near future to act against ovarian cancer [46].

## 15. Cinnamaldehyde on Prostate Cancer

One man in every six is diagnosed with prostate cancer in the United States, making it the second leading cause of death due to cancer among males. Due to the gradual nature of prostate cancer, diagnosing, and treating it before symptoms appear may not benefit men's health or lengthen their lives. In addition, recent studies have shown that fibroblasts that are present in malignancies assist in a variety of ways in the progression of cancer. Cinnamaldehyde's effect on cancer-associated fibroblasts hasn't been studied yet. Therefore, to address this cinnamaldehyde's effects on prostate cancer-associated fibroblasts hTERT PF179T cell line, as well as the method by which it exerts its effects, were the subject of an investigation. In fibroblasts taken from prostate cancer patients, it was shown that cinnamaldehyde (150 µM)-induced apoptosis and stopped the cell cycle at the G<sub>2</sub>/M phase via an inherent mechanism. One of the causes of lowering the proliferation was an increase in the amount of calcium ions as well as intracellular ROS. The examination of protein expression also demonstrated a decrease in mitochondrial membrane potential as well as in the expression levels of Bcl-2, caspase-9, PARP, and DEF-45, and, simultaneously, an increase in the expression of cytochrome c, Bax, cleaved caspase-3 and cleaved PARP. Thus, cinnamaldehyde seems to have the potential to be utilized as a treatment for cancer based on the findings of this analysis [47].

## 16. Cinnamaldehyde on Renal Cancer

A study of the anti-angiogenic activity of cinnamaldehyde and its effect on tumour progression was conducted by Bae et al., in the year of 2015. Cinnamaldehyde, when administered in vivo to BALB/c mice at a dose of 10 mg kg<sup>-1</sup>, significantly restricted the growth of tumours by preventing the new blood vessels in tumours. The expression of the HIF-1α protein and VEGF was suppressed in mouse tumours in vivo on treatment with cinnamaldehyde. On the other hand, the above two protein expressions were repressed in vitro in hypoxic Renca cells at a concentration of 100 µM. Interestingly, the treatment of cinnamaldehyde had no impact on the stability of HIF-1α that was coupled with the von Hippel-Lindau protein (pVHL), and it also reduced the activation of the mTOR pathway. Cinnamaldehyde's anti-angiogenic effect is presumed to be mediated in part by the mTOR pathway's inhibition, resulted in cessation of HIF-1α protein production. This revelation clearly indicates the pharmacological importance of cinnamaldehyde in cancer treatment [48].



Ahn et al., in the year 2020, presented the effectiveness of the combination of hyperthermia and cinnamaldehyde in the treatment of cancer. Following treatment with cinnamaldehyde, ACHN cell lines derived from patients with renal cell cancer were put through hyperthermia at a temperature of 43 °C. According to the results of Western blot experiments, both cinnamaldehyde (90 µM) and hyperthermia reduced the amount of heat shock protein 70. These treatments also increased the signalling of apoptosis with a sharp fall in the signalling of proliferation and metastasis. Flow cytometry revealed that ACHN cells underwent an arrest in the cell cycle at the G<sub>2</sub>/M phase. It was also observed that it induces apoptosis with a rise in mitochondrial membrane potential. It was also shown that the formation of ROS may be considerably boosted by combining cinnamaldehyde with hyperthermia at a temperature of 43 °C. In conclusion, it is reasonable to recommend cinnamaldehyde and hyperthermia combination treatment as a viable alternative option for anticancer medicines for renal cell carcinoma patients to consider [\[49\]](#).

## **17. Cinnamaldehyde on Skin Cancer**

The incidence of skin cancer is by far the most common form of cancer. Melanoma, squamous cell carcinoma, and basal cell carcinoma are the three basic subtypes of skin cancer that may be distinguished from one another. Melanoma is a kind of skin cancer that develops far less often than other types of skin cancer; nonetheless, it has a significantly greater tendency to invade neighbouring tissue and move to other parts of the body. Melanoma is the kind of skin cancer that has the highest mortality rate. A research paper that was released in 2009 found that *trans*-cinnamaldehyde suppresses the proliferation of melanoma cells as well as the formation of tumours. In a human A375 melanoma SCID mice xenograft model, it was shown that the therapeutic effectiveness of *trans*-cinnamaldehyde could be achieved at high doses (120 mg kg<sup>-1</sup>, daily oral dose for ten days). The human metastatic melanoma cell lines A375, G361, and LOX all inhibited their proliferation by *trans*-cinnamaldehyde, which resulted in G<sub>1</sub> cell-cycle arrest, higher intracellular ROS, and decreased invasiveness. The IC<sub>50</sub> values for these three cell lines are as follows: 6.3 µM, 8.1 µM, and 3.4 µM, respectively. *trans*-cinnamaldehyde was shown to have caused an oxidative stress response in A375 cells by up regulating genes, such as HO-1, sulfiredoxin 1 homolog, thioredoxin reductase 1, and the G<sub>1</sub>-arresting tumour-suppressor gene cyclin-dependent kinase inhibitor 1A (CDKN1A), as shown by an expression array. A reduction in TNF-induced IL-8 production and NF-κB transcriptional activity was seen in A375 cells when *trans*-cinnamaldehyde was present [\[50\]](#).

Cinnamaldehyde was examined against mouse melanoma cell lines Clone M3 and B16F10 (in vitro), as well as the C57BL/6 melanoma mice model in vivo. Cinnamaldehyde was shown, in both melanoma cell lines and an experimental melanoma mice model, to effectively suppress the production of pro-angiogenic factors (VEGF-α, EGF, FGF, and TGF-β) and master regulators of tumour growth (HIF-1 and Cox-2) at a dosage of 0.5 mg/mL. Cinnamaldehyde treatment resulted in an increase in both the cytotoxic activity of CD8<sup>+</sup> T lymphocytes as well as their production of cytolytic molecules, including interferon gamma and tumour necrosis factor alpha (TNF-α) [\[51\]](#).

Cinnamaldehyde's effect on hypoxia-induced angiogenesis and metastasis was investigated utilizing in vitro experiments with melanoma B16F10 cell lines and in vivo investigations using melanoma C57BL/6 mice models. Utilization of cinnamaldehyde (100 µM for in vitro and 30 mg kg<sup>-1</sup> for in vivo) seems to inhibit tumour angiogenesis, epithelial–mesenchymal transition, and metastasis, as shown by the findings of the study. This was followed by a

drop in epithelial–mesenchymal transition-related markers TWIST and ZEB1, as well as a decrease in VEGF secretion, VEGF receptor phosphorylation, and MMP expression. The next part of the investigation focused on the ways in which cinnamaldehyde influences HIF-1 $\alpha$ . The findings demonstrated that cinnamaldehyde decreased the HIF-1 $\alpha$  protein level by inhibiting its synthesis while having no effect on the rate at which it was degraded by the proteasome. Cinnamaldehyde was also able to obstruct the PI3K/Akt/m-TOR pathway, which is essential for the transcription and translation of HIF-1 $\alpha$  both in vivo and in vitro. In conclusion, cinnamaldehyde suppressed the formation of HIF-1 $\alpha$  protein in tumour cells, most likely by targeting the PI3K/Akt/mTOR pathway. As a result, angiogenesis and metastasis were both reduced [52].

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