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The Dual Role of the Natural Compound Cardamonin in Triple Negative Breast Cancer

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Breast cancer is the leading cause of malignancy-related death in women, with increasing prevalence worldwide. Triple-negative breast cancer (TNBC) accounts for about 10% of all breast cancers. It has an aggressive nature and is highly metastatic, and because of the lack of therapies, it continues to be a challenge. Unlike other forms of breast cancer, TNBC does not express estrogen, progesterone, or HER2 receptors. These cancer cells instead employ mechanisms to escape the immune system. One such mechanism involves the upregulation of the expression of PD-L1, a ligand encoded by the CD274 gene. Because cancer cells tend to produce higher levels of PD-L1 compared to normal cells, therapies that inhibit PD-L1 may be helpful. Evidence also shows that high levels of oxidative stress and inflammation may participate in the initiation and progression of cancer. Many dietary flavonoids found in fruits and vegetables are attracting great interest in the prevention and treatment of TNBC due to their anti-carcinogenic, anti-oxidative, and anti-inflammatory properties. Cardamonin, an aromatic enone flavonoid found in cardamom spice, has displayed an array of pharmacological activities, including modulation of different signaling molecules involved in the development and progression of cancer. Despite evidentiary support for cardamonin in tumor suppression, there is a lack of research regarding its influence on the tumor microenvironment. This work aimed to investigate the ability of cardamonin to modulate the expression of PD-L1 and Nrf2 in genetically different MDA-MB-231 (Caucasian) and MDA-MB-468 (African American) TNBC cell lines. The results show that cardamonin treatment caused a dose-dependent decrease in cell viability in both cell lines, ranging from 3.12 μM to 200μM. ELISA data showed that even though MDA-MB-231 cells show a higher expression of PD-L1, cardamonin reduced protein expression in both cell lines. Furthermore, RT-PCR assays demonstrated that cardamonin downregulated PD-L1 expression in MDA-MB-231 cells in the presence or absence of IFN-γ, showing more effectiveness after the cells were stimulated. In MDA-MB-468 cells, a cardamonin inhibitory effect was observed in the presence of IFN-γ because of the lower levels in the non-stimulated cells. Additionally, cardamonin upregulated the expression of Nrf2 and downregulated the expression of Keap1 in both cell lines' transcription and protein levels. The results show that cardamonin may downregulate the production of PD-L1 and block the evasion of the immune system. Still, on the other hand, it may also induce the activation of Nrf2, which has a controversial role in cancer development. In conclusion, the results suggest that cardamonin may have a therapeutic potential to decrease the levels of PD-L1 in the tumor microenvironment combating the cancer cells' effectiveness in evading the immune system; however, its role in the activation of Nrf2 needs to be further investigated.