

Title: Alkaloid-based modulators of the PI3K/Akt/mTOR pathway for cancer therapy: Understandings from pharmacological point of view

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Abstract: This review aims to summarize the role of alkaloids as potential modulators of the PI3K/Akt/mTOR (PAMT) pathway in cancer therapy. The PAMT pathway plays a critical role in cell growth, survival, and metabolism, and its dysregulation contributes to cancer hallmarks. In healthy cells, this pathway is tightly controlled. However, this pathway is frequently dysregulated in cancers and becomes abnormally active. This can happen due to mutations in genes within the pathway itself or due to other factors. This chronic overactivity promotes cancer hallmarks such as uncontrolled cell division, resistance to cell death, and increased blood vessel formation to nourish the tumor. As a result, the PAMT pathway is a crucial therapeutic target for cancer. Researchers are developing drugs that specifically target different components of this pathway, aiming to turn it off and slow cancer progression. Alkaloids, a class of naturally occurring nitrogen-containing molecules found in plants, have emerged as potential therapeutic agents. These alkaloids can target different points within the PAMT pathway, inhibiting its activity and potentially resulting in cancer cell death or suppression of tumor growth. Research is ongoing to explore the role of various alkaloids in cancer treatment. [Berberine](#) reduces mTOR activity and increases apoptosis by targeting the PAMT pathway, inhibiting cancer cell proliferation. [Lycorine](#) inhibits Akt phosphorylation and mTOR activation, increasing pro-apoptotic protein production and decreasing [cell viability](#). In [glioblastoma](#) models, [harmine](#) suppresses mTORC1. This review focuses on alkaloids such as [evodiamine](#), [hirsuteine](#), chaetocochin J, indole-3-carbinol, [noscapine](#), berberine, piperlongumine, and so on, which have shown promise in targeting the PAMT pathway. Clinical studies evaluating alkaloids as part of cancer treatment are underway, and their potential impact on patient outcomes is being investigated. In summary, alkaloids represent a promising avenue for targeting the dysregulated PAMT pathway in cancer, and further research is warranted.

Keywords: Alkaloids PI3K/Akt/mTOR pathway Cancer therapy Natural bioactive compounds Targeted molecular signaling

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