Determining the Cytotoxicity and Mechanism of Novel Piperlongumine Analogs

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Piperlongumine (PLM) is a compound derived from the long pepper that can selectively kill cancer cells and cancer stem cells, which are often responsible for relapses. PLM has the potential to be a valuable cancer treatment, as mice treated with PLM at a dosage 30 mg/kg/day showed strong antitumor effects on breast cancer. Recent studies have shown that PLM is also a senolytic agent, a compound that targets aging cells. As potent anticancer agents, senolytic compounds can be used to target the mutated aging stem cells of elderly cancer patients so that the newer stem cells can produce cells that can survive more debilitating treatments such as chemotherapy. However, PLM has a high half-maximal effective concentration (EC50) value of 6.8 mM, suggesting that analogs of PLM may have higher cytotoxicity. The purpose of this study is to determine which of several novel analogs of PLM have the highest cytotoxicity and whether certain structures within the molecules of each compound contribute to the overall cytotoxicity while identifying possible mechanisms for PLM's selective cytotoxicity and senescent activity. If we understand which structures enhance the cytotoxicity of PLM, we can learn more about its mechanism of action. Here, I found that analogs of PLM with a sulfur dioxide, exocyclic alkyne, reversed orientation of the C7-C8 olefin, and a relocated C3-C4 olefin lowered the EC50 drastically. This suggests that combining these structural alterations may lead to the development of new analogs of PLM with an EC50 value in the optimal range for a clinical dose, while selectively targeting cancer stem cells and senescent cells.