The unprecedented rates of resistance of cancer cells to traditional chemotherapeutic medications necessitated relentless exploration and drug design in an attempt to introduce safe and effective new antineoplastic agents. The latter is a particular pivotal to the treatment of solid tumors malignancies which represent the top causes of cancer deaths. Our laboratory has established a line of research to investigate potential cytotoxic agents of native plant origins. Folkloric anecdotal evidence and initial screening led us to investigate the cytotoxicity of *Mercurialis annua* L. (Euphorbiaceae) methanolic extract against a variety of cancer cell lines. In total, six different cell lines representing three types of common cancers were used to determine the potential antineoplastic activity of the plant extract. Our results show that the *M. annua* extract exhibited potent cytotoxic effect on both HRT-18 and T47D cell lines in a dose-dependent manner. HRT-18 is a colorectal adenocarcinoma cell line, while T47D is a breast cancer cell line. The calculated IC50 values of the plant extract against HRT-18 and T47D cell lines were 41 and 270 µg/ml, respectively. On the other hand, there was no appreciable inhibitory effect of the plant extract on the growth of Caco-2, MCF-7, A375-S, and WM136-1A cell lines. The inhibition of cellular growth was cell-type specific. Among the breast cancer cell lines, MCF7 and T47D, only T47D which is a human ductal breast epithelial was sensitive to the plant extract. Likewise, the human epithelial colorectal adenocarcinoma cells (Caco-2) was resistant, while the human rectum adenocarcinoma (HRT-18) was sensitive to the plant extract. Interestingly, the two human malignant melanoma cell lines; A375.S2 and WM136 1A were both resistant to the plant extract. This work is a first step towards unraveling the full pharmacologic potential of *M. annua* in cancer treatment.