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Melanoma, the most aggressive form of skin cancer, accounts for 75% of skin cancer mortality. The activation of the signaling cascade comprising BRAF-NRAS-MEK1/2-ERK1/2 is an important trigger for melanoma survival, growth and proliferation. Several studies have demonstrated the chemopreventive and/or chemotherapeutic effects of silybin, a major bioactive component of milk thistle (Silybum marianum), against various cancers. Virtual screening revealed that silybin is a potent inhibitor of the BRAF-MEK-ERK-RSK2 signaling pathway. The direct binding of silybin with RSK2 (ribbon structure shown) and MEK1/2 (not shown) was generated using the Schrödinger Induced Fit docking program. Silybin was shown to significantly inhibit melanoma cell growth in vitro and in vivo through its direct binding with MEK1/2 and RSK2, resulting in the inhibition of their catalytic kinase activities and subsequent reduction in the activation of NF-κB, AP-1 and STAT3—transcriptional regulators of a variety of proliferative genes in melanomas. See article by Lee and colleagues (beginning on page 455) for more information.