Silibinin against lung cancer and COVID-19: A molecular journey from the laboratory to the clinic

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The flavonolignan silibinin, the major bioactive component of the silymarin extract of *Silybum marianum* (milk thistle) seeds, is gaining traction as a novel anti-cancer therapeutic [1-3]. Here, we survey a two-way clinico-molecular street connecting the *bedside* effects of bioavailable formulations of silibinin in the therapeutic management of lung cancer patients with the basic science-discovery *bench* aspects of silibinin underlying its molecular capacity to target brain metastasis traits in lung cancer. First, we update the survival analyses of our clinical series demonstrating that Legasil™ –an oral nutraceutical product containing silibinin– is a safe treatment that provides a highly significant advantage in overall survival over all the standard-of care treatments (surgery, stereotactic radiosurgery, whole brain radiotherapy, systemic therapy) of brain metastases [4-6]. Second, we revisit the transcription factor STAT3 as a central tumor-cell intrinsic and microenvironmental target of silibinin in primary lung tumors and brain metastasis [7]. Third, we provide preliminary insights into unforeseen molecular targets through which silibinin might regulate brain-metastasis initiating and immune-escape traits at the primary tumor site as well as blood-brain-barrier (BBB) extravasation, colonization, and adaptation of disseminated tumor cells to the activated brain microenvironment. Fourth, we briefly explore the similarities between STAT3-driven lung cancer brain metastasis and the pathophysiology of SARS-CoV-2, which has inspired silibinin-based clinical trials in oncological and non-oncological populations of COVID-19 patients [8]. We anticipate that silibinin and/or next-generation silibinin derivatives will be integrated into the scarce armamentarium currently available for the prevention and treatment of biologically aggressive lung cancer subtypes prone to brain metastasis.

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