Abstract

INDEX No.: 42/19/Life Sc./26

Thesis title: **Studies on anti-breast cancer and anti-colon cancer activities in *Bergenia ligulata (Wall.) Engl.***

Submitted by: **Samhita De.**

Cancer is the prime cause of mortality worldwide. Globally, there were 19.9 million new cases of cancer, which took about 10 million lives in 2020. Colorectal cancer (CRC), the 2nd most diagnosed cancer, claimed about 0.9 million lives. Breast cancer, on the other hand, the most diagnosed cancer in women, with an estimated 2.3 million new cases globally, has claimed 69000 deaths. Overall, the incidence is 2 to 3 times higher in developed than the developing countries. Per current trends, both cancer incidences deaths are predicted to rise in the coming decades. Drug resistance, recurrence, general toxicity, and unaffordability to many have always been major concerns with current cancer therapy. These signify the importance of alternate treatment strategies that would overcome/reduce these limitations of the current treatments. An increasing number of in vitro and in vivo studies with phytochemicals highlighted their great potential as chemotherapy agents alone or in combination with existing therapies. *Bergenia ligulata* is known for its various medicinal properties in Indian traditional and folk medicine. In this study, an HPLC-purified fraction, with the highest activity against CRC and breast cancer cells was isolated from *Bergenia ligulata* rhizome. This fraction is termed PFBL (polyphenol-rich fraction of *Bergenia ligulata*). LC-MS analysis detected a group of eleven compounds in PFBL. The molecular basis of anti-breast and anti-CRC-specific activities of PFBL was investigated in both in vitro and in mice models. PFBL sensitized both CRC (HCT116 and HT29) and breast cancer (MCF7 and MDAMB231) cells at a concentration that is not toxic to normal cells, such as NKE. Notably, PFBL induced death in CRC and breast cancer cells by distinct mechanisms. The HCT116 cells died majorly by autophagy, as suggested by the alteration of the cellular level of several characteristic markers, such as upregulation of LC3-II levels and downregulation of mTORC1 activities. The major involvement of apoptosis was detected in the MCF7 cells, characterized by the dose-dependent increase of cleaved PARP1, caspase 7, 8, and 9, and other associated markers. Elevation of cellular reactive oxygen species (ROS) levels was evidenced by DCFDA staining. Abrogation of PFBL-induced anti-cancer activity by n-acetyl cysteine (NAC) pre-treatment, indicating the elevation of intracellular ROS levels as a key mediator of PFBL action. Surprisingly, shRNA-mediated downregulation of AMPK protected these cells from PFBL action, suggesting the role of AMPK in PFBL-induced death in both cell types. PFBL treatments regressed both CT26- and 4T1-induced solid tumors in BALB/c mice majorly by induction of autophagic and apoptotic cell death, respectively. Consistent with in vitro results, PFBL efficiently reduced lung metastasis of CF26 and 4T1 cells in pre-clinical (mice) models without affecting the healthy animals. Altogether, the present study highlighted PFBL as a potent anti-colon and anti-breast cancer agent that can be considered for clinical trials for future use in cancer treatment.

Samhita De.
23.11.23

23.11.23

Mahadeb Pal, Ph.D.
Professor
Division of Molecular Medicine
BOSE INSTITUTE
P-1/12, C.I.T. SCHEME VIIM
Kolkata-700 054, India