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Editorial

How far we have gone in realizing true potential of *Viscum album* as versatile regulator of cell signaling pathways

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It will not be wrong if we say that *Viscum album* (Mistletoe) has attracted extra-ordinary attention of clinicians because of its encouraging results in various phases of clinical trials. Surprisingly, the clinical trials associated with *Viscum album* outnumber the studies uncovering the mechanisms used by *Viscum album* extract or bioactive components to inhibit/prevent cancer. Therefore, in this editorial we will emphasize on the need to concentrate on the mechanisms and pathways regulated by *Viscum album* to induce apoptosis, inhibit epithelial to mesenchymal transition (EMT) and metastatic spread in different cancers.

Viscum album extracts are known under several trade names, such as Iscador, Helixor, AbnobaVISCUM and others which are mainly available in European countries. Composition and concentration of the compounds in different *Viscum album* extracts is dependent on the host tree mistletoe is growing on, season in which the plant is harvested as well as on the techniques used for preparation of the drug.

Different biologically active constituents obtained from *Viscum album* have been shown to induce apoptosis in different cancers. Mistletoe lectin-II worked effectively with interferon-gamma and induced apoptosis in myeloid U937 cells (1). However, we still have insufficient information about potential of bioactive components to induce apoptosis in TRAIL-resistant cancers. TRAIL-based therapeutics have entered into clinical trials and it will be advantageous to explore *Viscum album*-mediated apoptosis in TRAIL-resistant cancer cell lines and xenografted mice. Mistletoe lectin I (ML-I) has been shown to activate extrinsic and intrinsic apoptotic pathway in cancer cell lines (2). *Viscum album* preparation has been shown to inhibit anti-apoptotic proteins (3). However, these aspects have to be tested in more details.

Additionally, Viscum album mediated regulation of non-coding RNAs has also been incompletely studied. Mistletoe lectin-I exerted repressive effects on miR-135a and miR-135b in colorectal cancer cells (4). More importantly, adenomatous polyposis coli and the phosphorylated levels of β-catenin were found to be enhanced in Mistletoe lectin-I-treated colorectal cancer cells (4). Rapidly accumulating high-impact research is continuously broadening our understanding about regulation of microRNAs and long non-coding RNAs by phytochemicals, however, we have yet to wait to conceptually and experimentally evaluate the ability of *Viscum album* to modulate tumor suppressor and oncogenic non-coding RNAs in different cancers.

Likewise, there has been an explosion in the field of molecular oncology and scientists have witnessed landmark discoveries in context dependent role of cell signaling pathways in various cancers. Overwhelmingly increasing cutting-edge research is improving our understanding about remarkable potential of natural products to therapeutically target deregulated signal transduction cascades. However, *Viscum album* mediated regulation of deregulated pathways has not yet been extensively explored. Wide ranging signaling pathways (Wnt/β-catenin, JAK/STAT, SHH/GLI, TGF/SMAD, NOTCH, VEGF/VEGFR, EGF/EGFR, PDGF/PDGFR) have been shown to play instrumental role in cancer onset and progression. However, surprisingly, there are visible knowledge gaps related to ability of *Viscum album* and its constituents to target these pathways. Mistletoe preparation inhibited tumor growth in xenografted and in the syngeneic mouse models (5). Iscador Qu rich in mistletoe lectins effectively reduced the levels of TGF-β, TGF-β receptor type II and SMAD2 in LNT-229 glioma cells (6). ViscumTT, a whole mistletoe preparation induced dephosphorylation of STAT3 at Tyr705 and Ser727. Intratumoral administration of ViscumTT considerably reduced tumor growth in mice subcutaneously injected with Saos-2 cells (7).

Viscum album-mediated pharmacological effects have not been extensively explored in different cancers. Better understanding of the mechanistic regulation of signaling pathways by *Viscum album* will be helpful in getting a step closer to individualized medicine.

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