1 **Table 1.**

Therapeutic platform	Agent	Targeting effects	Reference
Natural compounds	Withaferin A (Wi-A; withanolides from Ashwagandha)	- Induction of apoptosis - Inhibition of Notch-1 signaling - Downregulation of serine-threonine kinase (Akt)/nuclear factor (NF)-kB/B-cell lymphoma (Bcl)-2 pathways - Strong cytotoxicity to both cancer and normal cells - Potent anti-migratory, anti-invasive, and anti-angiogenic activities	[27-33]
	Withanone (Wi-N; withanolides from Ashwagandha)	- Interaction with p53, hmot-2, p21WAF1, and nuclear factor-erythroid 2-related factor 2 (Nrf2) (i-Extract) - Increased selective killing of cancer cells	[33, 37-40]
	CAPE (Ingredient of New Zealand honeybee propolis)	- Disruption of the mortalin–p53 complex - Increased translocation and activation of p53 in the nucleus - Enhancement of anti-tumor and anti-metastasis (γCD-complexed CAPE)	[41, 42, 44]
	Artepillin C (Ingredient of Brazilian green propolis)	- Abrogation of mortalin–p53 complexes, activation of p53 - Increased growth arrest of cancer cells - Increased cytotoxicity *in vitro* (green propolis-supercritical extract (GPSE) - conjugated with γCD) - Potent anticancer activity (GPSE-conjugated with γCD)	[45]
	Veratridine (VTD) (Alkaloid derived from Liliaceae plants)	- Increased transactivation of cytoplasmic UBX domain protein 2A (UBXN2A) - Inhibition of motalin - Increased tumor-specific toxicity - Induction of cancer chemosensitivity	[23]
	Embelin (natural quinone from *Embelia ribes*)	- Induction of cancer chemosensitivity - Increased nuclear translocation of p53 - Abolished activity of the mortalin–p53 complex - Downregulation of growth factor expression and metastatic signaling pathway - Inhibition of cancer cell growth	[46]
	Fucoxanthin (found in marine organisms)	- Suppression of the transcriptional activity of mortalin - Activation of p53 function in cancer cells - Decreased cancer cell proliferation and survival - Cancer cell-specific killing	[47]

		- Decreased migration and invasion of cancer cells	
Chemical compounds	MKT-077 ($C_{21}H_{22}ClN_3OS_2$)	- Elimination of mortalin–p53 interactions (no alteration of mortalin expression) - Binding to mot-2 and abrogation of its interaction with p53 - Enhancement of anti-tumor activity - Overcoming the limited efficacy of photodynamic therapy - Induction of apoptosis or necrosis - Decreased drug resistance of cancer cells	[48-52]
	Mortaparib	- Abrogation of cancer cell-specific mortalin–p53 interactions - Induction of growth arrest/apoptosis signaling - Inhibition of cancer cell migration, metastasis, and angiogenesis *in vitro* - Potent anti-tumor and anti-metastatic effects - A first dual inhibitor of mortalin and poly(ADP-ribose) polymerase 1 (PARP-1)	[53]
	Mortaparib^{Plus}	- Prevention of mortalin–p53 interaction - Induction of growth arrest and apoptosis - Induction of cancer cell death via multiple mechanisms	[54]
	SHetA2	- Disruption of mortalin–p53 complexes in ovarian cancer cells - Induction of apoptosis in cancer cells - Tumor growth inhibition in orthotopic ovarian tumor model (combination with PRIMA-1MET)	[55-59]
Peptide	SMR of Nef	- Disruption of the interaction of Nef with mortalin - Antagonization of the functions of mortalin (SMR-CLU) - Decrease in breast cancer cell metastasis (SMT-CLU) - Inhibition of growth (PEG-SMRwt-CLU) - Cell cycle arrest at G_2/M phase (PEG-SMRwt-CLU) - Increased sensitivity to cisplatin and paclitaxel (SMRwt)	[60, 61]
	Mot-P2 or Mot-P7	- Antibody-mediated and complement-dependent cell killing - Increased plasma membrane perforation and mitochondrial inner membrane depolarization - Decrease in ATP levels - Increased cell death on combination with rituximab	[62]
Antibody	i-mot Ab	- Enhanced transgene expression in mortalin-positive cells (i-mot Ab/PEI complex) - Increased cellular uptake of CAPE (CAPE-MotAb) - Stronger growth arrest/apoptosis (CAPE-MotAb) - Downregulation of the expression levels of proteins involved in cell migration (CAPE-MotAb)	[64, 66]

		- Significant suppression of tumor growth (CAPE-MotAb)	
Nucleic acid	shRNA against motalin	- Induction of mutant p53-mediated tumor-specific apoptosis - Increased responsiveness of cancer cells to chemotherapeutic drugs - Reduction in cancer cell stemness - Downregulation of the expression levels of ATP binding cassette subfamily G member 2 (ABCG2), POU class 5 homeobox 1 (POU5F1/OCT-4), CD133, aldehyde dehydrogenase 1 (ALDH1), CD9, ATP binding cassette subfamily C member 1 (ABCC1/MRP1), and connexin - Enhanced cancer cell-killing and anti-tumor effects on cancer cells (mot-Adon) - Enhanced apoptosis (mediated by reactivation of p53) (mot-Adon) - Suppression of microvessel formation (mot-Adon)	[9, 16, 67, 70-75]

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