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Melatonin combined with antineoplastic drugs or natural products for cancer treatment: An update

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ABSTRACT

Drug combinations have shown promise in suppressing drug resistance, improving drug efficacy, and reducing side effects in anticancer therapy. Considering that the anticancer activity of melatonin may be due to its antiproliferative, antioxidant, and immunomodulatory activities, the combined administration of this endogenous indoleamine with anticancer drugs has been extensively explored. This review provides an overview of the advances in the last five years in the anticancer activity of melatonin in combination with synthetic drugs and natural products. Papers on this topic were searched in PubMed, Google Scholar, Cochrane, and Scopus within the period 2018–2024. A total of 47 papers were retrieved showing a synergistic antitumor effect of melatonin combined with different drugs in the treatment of breast, colorectal, prostate, gastric, thyroid, and pancreatic cancer, as well as in head and neck squamous cell carcinoma, melanoma, and glioblastoma. The evidence gathered in this review will contribute to our knowledge of the use of melatonin. In addition, it may allow us to develop novel approaches to the treatment of cancer to be evaluated in preclinical and/or clinical trials.

1. Introduction

Cancer remains a leading cause of morbidity and mortality worldwide. According to a World Health Organization (WHO) report (Globocan), the leading causes of malignancy-related deaths in 2020 were lungs, colon/rectum, liver, stomach, and breast cancer (Bray et al., 2024). While chemotherapy remains the first-line treatment for most cancers, adverse drug reactions and drug resistance are major obstacles to effective anticancer intervention. Resistance mechanisms include individual genetic differences, intratumor heterogeneity, cancer stem populations, drug inactivation, multidrug resistance by the ABC transporter family, enhancement of the DNA repair, band gene amplification (Pakkir Maideen et al., 2017). Combination therapy has been used in recent years to increase efficacy, reduce side effects, overcome multidrug resistance, and reduce toxicity associated with standard therapy.

Melatonin (MLT), a neurohormone, is a small lipophilic molecule produced by the pineal gland. It is secreted at night with a circadian rhythm. It is also synthesized in the skin, bone marrow, lymphocytes, retina, and gastrointestinal tract (Talib, 2018). MLT is involved in sleep induction, immune regulation, and modulation of pituitary and adrenal hormones (Reiter et al., 2020). MLT has been used to treat neurodegenerative disorders, cardiometabolic conditions, and cancer (Ahmad et al., 2023; Giri et al., 2024).

The anticancer activity of MLT, either alone or in combination with standard chemotherapeutic agents, has been attributed to its modulating effect on genetic and epi-genetic mechanisms, signaling pathways, tumor microenvironment, immune and redox systems. The crosstalk between these networks is known to regulate cancer cell survival, proliferation, angiogenesis, migration, invasion, metastasis, apoptosis and autophagy (Gurunathan et al., 2021; Iravani et al., 2020; Srinivasan et al., 2008). MLT exerts its anti-tumor activity by modulating signaling pathways induced by the MLT 1 and MLT 2 receptors (MT1 and MT2), platelet-derived growth factor receptor (PDGFR), epidermal growth factor receptor (EGFR), Fas ligand receptor (FASR), toll-like receptor 4

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(TRL4), inositol-requiring enzyme 1α (IRE1α), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6), as well as androgen and estrogen receptors (AR and ER) (Das and Samanta, 2021). Once activated, these receptors induce the activity of transcription factors, which in turn promote the synthesis and activity of antioxidant enzymes (catalase [CAT], superoxide dismutase [SOD]-1, −2, and glutathione peroxidase [GPx]) (Liu and Ng, 2000; Reiter et al., 2009; Samanta, 2020), anti-inflammatory cytokines (interleukin [IL]-4, IL-10, IL-27), and proapoptotic factors (Bid, Bax, Apaf, puma, noxa, caspase-8, -9, -3, and -7) (Li et al., 2009). MLT also exerts antiproliferative effects by inhibiting the expression and release of proinflammatory and proangiogenic factors, including IL-1β, IL-6, IL-8, IL-26, tumor necrosis factor α (TNFα), cyclooxygenase-2 (COX-2)/prostaglandin (PG)E2, inducible nitric oxide synthetase (iNOS)/nitric oxide (NO), and vascular endothelial growth factor (VEGF)/VEGFR (González et al., 2021; Haddadi and Fardid, 2015; Sánchez et al., 2015), as well as by downregulating the expression of proteins involved in cell survival (Bcl-2, Mcl-1, cellular inhibitors of apoptosis [cIAPs], survivin), proliferation (proliferating cell nuclear antigen [PCNA], Ki-67, cyclin-dependent kinases [CDKs], cyclins), and migration/invasion (fibronectin, collagenase, vimentin, N-cadherin, matrix metalloproteinase [MMP]-2, and MMP-9) (Maroufi et al., 2020; Mortezaee et al., 2019; Wang et al., 2012) (Fig. 1). On the other hand, MLT also removes tumor cells by inducing or inhibiting autophagia, an effect that depends on the type of cancer cell, the tumor microenvironment, the stage of carcinogenesis (initiation, promotion, or progression), and the dose of MLT (Boga et al., 2019; Fernández et al., 2015; Roohbakhsh et al., 2018).

Here, we discuss *in vitro* and *in vivo* studies on the anticancer effects of MLT when administered with synthetic antineoplastic drugs or natural products to treat various types of cancer, focusing on drug doses, type of pharmacological interaction (synergism, addition, or antagonism), use of stem and non-stem cancer cells, pharmacological resensitization of cancer cells, and side effects, as well as the molecular pathways associated with antineoplastic activity, including proliferation, angiogenesis, epithelial-mesenchymal transition (EMT), migration, invasion, apoptosis, autophagy, necrosis, oxidative stress, and endoplasmic stress. Only studies published between 2018 and 2024 were included.

2. Methods

A systematic search was performed in PubMed, MEDLINE, Embase, Google Scholar and Scopus databases. The keywords used were “cancer” “melatonin combination AND cancer” “combination”, “melatonin synergism AND cancer”, “adjuvants”, “plus”, “natural products”, “antitumor”, “drugs”, “chemotherapy”, and “melatonin chemotherapeutics AND cancer”. Only studies that reported the evaluation of MLT and other agents on cancer cell lines and cancer models, either *in vitro* or *in vivo,* were selected. The literature search and data extraction were performed by all authors.

3. Results

The database search yielded 47 publications on combined MLT treatment in cancer, including 26 drugs and four natural products. The most common drug combinations were MLT plus 5-fluorouracil (5-FU), doxorubicin (DOX), or cisplatin (CIS), accounting for 51 % of the reports. Among natural products, thymoquinone, resveratrol, retinoic acid, and docosahexaenoic acid were co-administered with MLT. Double combinations were usually evaluated, and there was only one report with three compounds (MLT plus DOX and dexamethasone).

The papers reviewed focused on breast cancer (21.2 %), colorectal cancer (17.4 %), head and neck cancer (10.6 %), and leukemia (8.5 %). Other neoplastic diseases accounted for 42.3 % of the publications. Of these studies, 22.2 % reported *in vivo* evaluation and 77.8 % reported *in vitro* experiments. The dose of MLT used for *in-vitro* assays was highly variable, ranging from 0.6 nM to 30 mM; the dose administered was highly dependent on the cell line used. Doses used for *in vivo* studies ranged from 1 to 300 mg/kg. Most of the drug combinations evaluated *in vivo* were administered intraperitoneally, by passing first-pass hepatic metabolism and increasing systemic concentrations.

Most studies on the combined administration of MLT in cancer reported a significant increase in cytotoxic activity compared to single drug treatments. This increase has been reported as a synergistic effect or an enhanced cytotoxicity of anticancer drugs by MLT. However, few studies evaluated pharmacologic interactions by estimating a median dose-response (CC_{50} or IC_{50}) or the combination index (IC), common parameters used to measure synergism (Chou, 2006, 2010). In general, drug synergy is rare, and only 4 out of 47 combinations (8.5 %) reported a synergistic interaction (as shown by a decrease in CC_{50} or IC_{50}, or by $IC < 1$). Those combinations were 5-FU plus MLT (esophageal cancer, decrease in IC_{50}), sorafenib plus MLT (leukemia, $I < 1$), albendazole plus MLT (glioblastoma, $IC < 1$) and thymoquinone plus MLT (breast cancer, $IC < 1$).

The reported benefits of co-administration of MLT with antineoplastic drugs include a significant decrease in cell viability and consequent decrease in tumor growth, as well as an increase in the rate of apoptosis and necrosis, autophagy modulation, and inhibition of drug resistance and angiogenesis.

A brief description of all the papers reviewed, including the cell lines or animal models used, the drug concentrations or doses evaluated, the effect of combined treatment, and the targets or pathways modulated, is shown in Table 1. The key findings of each study are described below.

3.1. MLT combinations in cancer

3.1.1. Breast cancer

Breast cancer (BC) is the most common malignancy in women, with high morbidity and mortality rates (Hulvat, 2020). Standard treatment includes chemotherapy, radiotherapy, and surgery. Hormone therapy and immunotherapy are often added as adjuvant treatment. Chemotherapeutic agents approved by the Food and Drug Administration (FDA) for BC include alpelisib, docetaxel, 5-FU, lapatinib, paclitaxel (PTX), tamoxifen and vinblastine (Baranova et al., 2022). However, current therapies have limited efficacy and undesirable side effects. In recent years, the benefits of combining anticancer agents with MLT have been investigated.

Thus, the co-administration of MLT (either 1 nM or 10 nM) with low doses of PTX (1 or 10 nM) was reported by El-Sokkary et al. MLT enhanced the cytotoxic effects of taxol in MCF-7 and MDA-MB-231 cells. Co-treatment increased the rates of invasion inhibition in MDA-MB-231 cells compared to single drug treatment. These effects were mediated through the deglycase-1/transcription factor 17/inhibitor of DNA binding (Id) protein (DJ-1/KLF17/ID-1) pathway. The combined treatment also inhibited the release of reactive oxygen species (ROS) induced by PTX, thereby reducing the side effects of single-agent chemotherapy (El-Sokkary et al., 2019).

On other hand, Alonso-González et al. (2017) demonstrated that MLT (1 nM) enhanced the antiproliferative and apoptotic responses to docetaxel at low doses (0.1 nM or 1 nM) in human BC cells (MCF-7, MDA-MB-435, MDA-MB-234, SKBR3 and T-47D). Interestingly, these effects were more marked when MLT (1 nM) was added prior to docetaxel (0.1 nM or 1 nM). The combined treatment showed a synergistic effect by reducing cell proliferation and inducing apoptosis in MCF-7 cells by downregulating the genic expression of TP53, cyclin-dependent kinase inhibitor 1A (CDKN1A), and cadherin 13 (CDH13), and upregulating mucin 1 (MUC1), GATA binding protein 3 (GATA3), and C-Myc. The combination also promoted the expression of the pro-apoptotic genes *Bad* and *Bax* and enhanced the docetaxel-induced inhibition of the anti-apoptotic gene *Bcl-2* (Alonso-González et al., 2017). This combination allowed the dose of docetaxel to be reduced from the order of

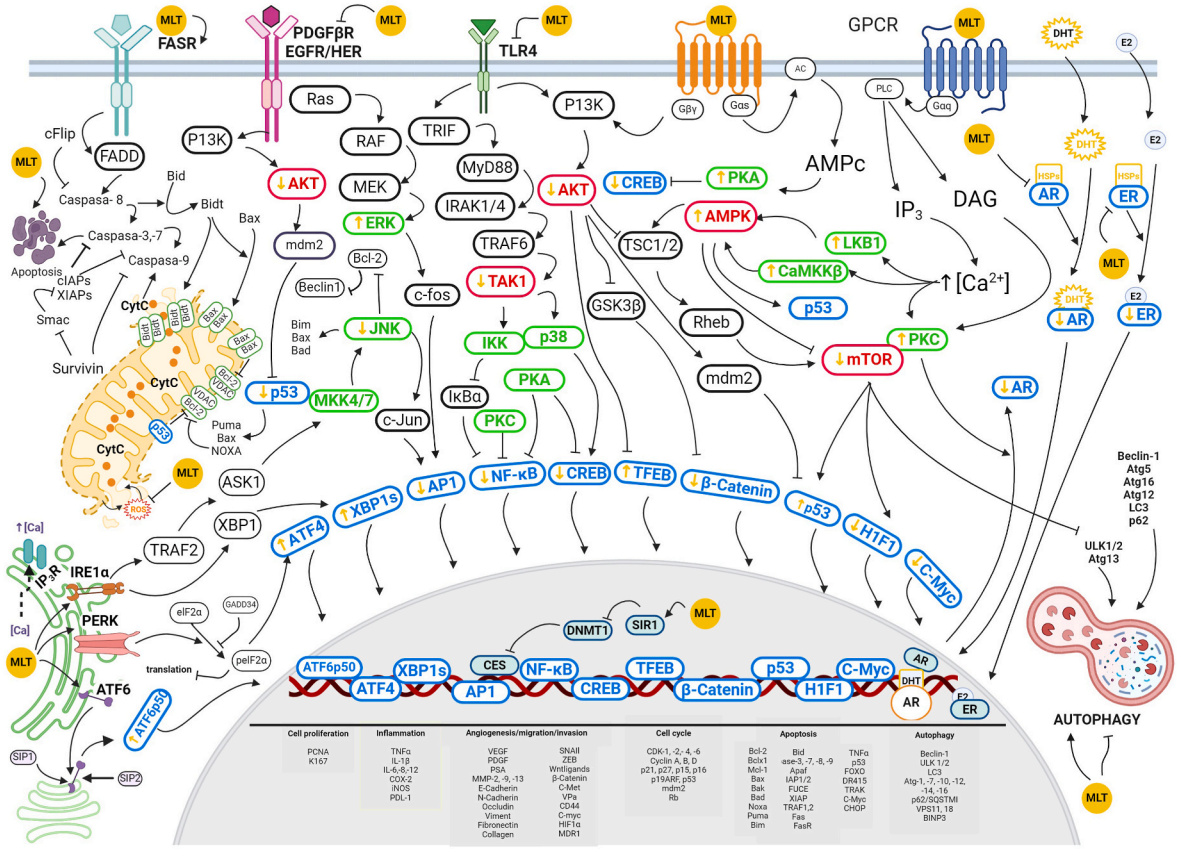

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Fig. 1. Modulation of IRE1α, PERK, ATF6, TLR4, MT1R, GPCR, PDGFβR, EGFR, ER, AR and TNFα signaling pathway by melatonin (MLT) cancer cells. The activation of these proteins promotes signaling pathways that regulates the activity of MAPK (ERK1/2, JNK and P38), IKK complex, PKC, PKA, AKT, AMPK and mTOR, which transduce signals into the nucleus through the modulation of transcription factors such as ATF4 and ATF3, XBP1s, CHOP, ATF6p50, AP-1, NF-κB, TFEB, β-Catenin, HIF-1α, and C-Myc and in consequence the regulation in the expression of genes that are important for cell proliferation, survival, cell cycle progression, resistance to the cell death (autophagy and apoptosis), inflammation, metabolism, angiogenesis, migration and invasion. ER stress induces by redox and Ca^{2+} homeostasis imbalance as well as misfolded or unfolded proteins in the ER lumen, can induce cell death by apoptosis and autophagy under prolonged or severe ER stress through sensors such as IRE1α, PERK and ATF6 pathway and Ca^{2+}, which had been regulated by MLT. Activated IRE1α forms a complex with TRAF2 and ASK1, which induces the activation of MKK4/7 with the subsequent activation of JNK. JNK promotes the inactivation of Bcl-2 by phosphorylation lead at the releases of Beclin-1 from Beclin-1/Bcl-2 complex, and in turn the association of Beclin-1 with Vps34, Vps15, and Atg-14L to promote autophagy. Also, JNK activates the apoptosis by phosphorylates at pro-apoptotic proteins such as BIM, Bax and Bad or induces the formation Bidt. In addition, JNK can up-regulate the expression of pro-apoptotic (*Bax* and *puma*) and autophagic (*Beclin-1*, LC3, *Atg-5* and -7) genes via c-jun/AP-1 transactivation. Furthermore, IRE1α/TRAF2 activates the IKK complex the promotes the activation of NF-κB through the phosphorylation and inactivation of IκBα an inhibitor of NF-κB. Concomitantly, IRE1α mediates the formation of XBP1s transcription factor by a splicing of XBP1 mRNA. Also, XBP1s promotes the transcription of Beclin-1, Atg-5 and CHOP a transcription factor that regulates the positive transcription of Atg5, DR5, Bim, and ERO1α, and down-regulates the genic expression of Bcl-2 inducing the cell death. Activated PERK mediated the phosphorylation of elF2α, which promotes its inactivation and in turn an increase of ATF4 transcriptional factor and a decrease in the IκBα synthesis. ATF4 transcriptionally induces CHOP, Atg-12, noxa, Bim and GADD34. GADD34 is activated by dephosphorylation at elF2α inducing the translation. ATF6 is translocated to the Golgi apparatus, whereas it is activated (ATF6p50) by S1P and S2P. ATF6p50 indirectly regulates apoptosis and autophagy by to transcribe at XBP1s and CHOP. For other hand, Ca^{2+} released from ER through the activation of IP_3R via IP_3 lead at the activation of LKB and CAMKKβ, which activates at AMPK and this kinase inactive at mTOR through TSC 1/2. mTOR inhibits the process of initiation of the autophagy via the inactivation of the ULK1 complex. Furthermore, the Ca^{2+} cytosolic activates DAPK, which induces Beclin-1 phosphorylation and in turn its dissociation of Bcl-2. Also, Ca^{2+} and DAG activates to PKC and subsequently promotes the inactivation of NF-κB and the exclusion of the androgen receptor (AR) from nucleus to cytoplasm. AR can be activated by DHT, which induces the release of AR from chaperons and in turn its nuclear translocation. Similarly, E2 can activate at ER by promoting its release of chaperons. MLT can bind to AR and ER inducing its inactivation. In addition, TLR4 leads to the recruitment of TIRAP, which promotes adaptor molecules to bind the receptor complex, then MyD88/IRAK1/4/TRAF6/TAK1 signaling induces the activation of MAPK (ERK1/2, p38, and JNK) and IKK and in turn the modulation of transcriptional factors such as AP-1, NF-κB and CREB. TLR4, also recruitment of PI3K, thus PI3K activates to AKT and AKT promotes the nuclear translocation of β-Catenin, HIF1 and C-Myc through the inactivation of GSK3 and TSC1/2, respectively. AKT inhibits TFEB by phosphorylation and at p53 by mdm2. In addition, MLT receptor1 (MT1R) induces the PI3K/AKT/mTOR via protein $G_{\beta\gamma}$ as well as $G_{\alpha s}$/AC/AMPc/PKA, whereas PKA inhibits at NF-κB and CREB. GPCR, also induced by MLT, promotes the activity of PKC through Gαq/PLC, which hydrolyzes PIP_3 to generate DAG and Ca^{2+}. TRKs (PDGFβR, EGFR and HER) inhibited by MLT induces the PI3K/Akt/mTOR and RAF/MEK/ERK signaling, thus ERK transactivate at c-jun/AP-1. FASR induces by MLT activates recruit at adaptor protein FADD, which stimulates the auto-activation of initiation caspases including −8 and-10, which induces the activation of effector caspases such as −3 and −7. Caspases-3 and-7 induce the cleavage of PARP, lamins and ICAD, essential proteins by cell survival. Caspase-8 hydrolyzes at the pro-apoptotic protein Bid generates a tBid, which induces its oligomerization and translocation of Bax to mitochondria and in consequence the release of Cyt *c* and Smac from mitochondria to cytosol. Cyt *c* induces the activation of caspase-9. P53, also modulates the cell death by regulates transcriptionally pro-apoptotic and autophagic genes like *LKB1*, *ULK1/2, Atg-4*, *Atg-7*, *Atg-10, Bax*, *puma* and *noxa*. Furthermore, p53 directly binds at anti-apoptotic protein Bcl-2 and stimulates the apoptosis. Additionally, the MLT modulates epigenetic modification. **Abbreviations:** 5′-AMP-activated protein kinase (**AMPK**), activator protein 1 (**AP1);** Apoptotic protease activating factor **(Apaf);** Apoptosis signal-regulating kinase 1 (**ASK1**); Activating transcription factor 6 (**ATF6**); Autophagy-related genes (**Atg);** protein kinase B (**AKT**); Diacylglycero (**DAG);** Calmodulin-dependent kinase kinase β (**CaMKKβ**); carboxylesterase 1 (**CES1**); Cyclin-dependent kinases **(CDKs);** CCAAT enhancer-binding protein (C/EBP) homologous protein (**CHOP**); Cluster of differentiation 44 **(CD44),** Cellular Inhibitors of Apoptosis **(cIAPs)**; Cyclooxygenase-2 (**COX-2**); Cyclic-AMP-responsive-element-binding protein (**CREB**); Cytochrome *c* (C**yt *c***); Damage-associated Molecular Patterns (**DAMP**s), Death-associated protein kinase 2 (**DAPK2**); DNA methyltransferases (**DNMT1**); Death receptor 4/5(**DR4/5);** Epidermal growth factor receptor (**EGFR**); Eukaryotic initiation factor 2 Alpha (**eIF2α**); Endoplasmic reticulum (**ER**); Epithelial-mesenchymal transition (**EMT**); Estrogen receptor (**ER**); Extracellular-signal-regulated kinase (**ERK**); Fas-associated death domain (**FADD**); Fas ligand (**FASL);** Growth arrest and DNA damage protein (**GADD34);** G protein coupled receptors **(GPCRs);** glucose-regulated protein 75 (**Grp75**; also known as binding immunoglobulin protein **(BiP**)); Glycogen synthase kinase 3-beta **(GSK3β);** Hypoxia inducible factor 1 **(HIF1);** Heat shock protein chaperon (Hsp), Inhibitor of caspase activated DNase (**ICAD**); inositol-1,4,5-triphosphate (**IP_3**), Interleukin-6 (**IL-6**); Interleukin 2 receptor (**IL-2R**); Inositol triphosphate receptor (**IP_3R**); Inositol requiring enzyme 1α (**IRE1α**); c-jun N-terminal kinases (**JNK**); Microtubule-associated protein light chain-II (**LC3-II);** Mitogen-activated protein kinases (**MAPK**); Mitogen-activated protein kinase (**MEK**); Matrix metalloproteinase-9 (**MPP);** MLT 1 receptor **(MT1R);** mammalian target of rapamycin (**mTOR**); nuclear factor kappa-light-chain-enhancer of activated B cells (**NF-κB**); Nitric oxide synthetase **(NOS);** Platelet-derived growth factor receptor (**PDGR**); Poly (ADP-ribose) polymerase (**PARP**); Proliferating cell nuclear antigen **(PCNA);** death protein-ligand1 (**PDL-1);** phosphoinositide 3-kinase (**PI3K**); Protein kinase A (**PKA**); Protein kinase C (**PKC**); Protein kinase RNA-like endoplasmic reticulum kinase (**PERK**); Prostate Specific Antigen **(PSA);** Ras homolog enriched in brain **(Rheb);** Reactive oxygen species (**ROS**); site1 and site2 proteases (**S1P and S2P**); Transforming growth factor-β-activating kinase 1 (**TAK1**); Toll-like receptor 4 (**TLR4**); tyrosine kinase receptors (**TKRs**); Tumour necrosis factorα (**TNFα**); Tumor Necrosis Factor receptors (**TNFR**); Tumour necrosis factor (TNF)-receptor associated receptor 2, 6 (**TRAF2, 6**); Tuberous sclerosis complex **(TSC ½);** Unc-51-like kinase 1 and 2 (**ULK1/2**); urokinase plasminogen activator **(uPA),** Voltage-dependent anion channel (**VDAC**); Vascular endothelial growth factor (**VEGF**); Spliced X-box binding protein 1 (**xbp1**); X-linked **IAP** (**XIAPs**), E-box-binding homeobox (**ZEB**).

μM to nM, which could result in better tolerability of the drug and fewer side effects of chemotherapy. Docetaxel is administered to BC patients at doses of 75–200 mg/m^2, which correspond to 1 μM in BC cells (Mann et al., 2020).

In recent decades, there has been considerable interest in studying the anticancer effects of bioactive phytochemicals administered with standard therapies (Talib, 2017). Odeh et al. evaluated the *in vitro* and *in vivo* effect of a combination of MLT and thymoquinone on the proliferation of the EMT6/P cell line. The combination showed a synergistic antiproliferative effect *in vitro* (IC = 0.55). Whereas in tumor-bearing mice, the combined administration of thymoquinone (10 mg/kg/day) and MLT (2 mg/kg/day) showed a significant reduction in tumor growth compared with single drug treatments. This antitumor effect *in vivo* was associated with the induction of apoptosis and necrosis; inhibition of angiogenesis (decrease in VEGF expression) and activation of a Th1 response. On the other hand, serum levels of IL-4 and IFNγ were increased in mice treated with the combined therapy, while aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were close to their normal values (Odeh et al., 2018). This work correlated for the first time the effect *in vitro* and *in vivo* of MLT in combination with thymoquinone against EMT6/P cells.

The potential of MLT to enhance the efficacy of DOX in BC cell lines (MCF-7, MDA-MB157, and MDA-MB231) was investigated by Tran et al. The combination of DOX (1 μM) and MLT (3 mM) induced a synergistic effect on apoptosis in MCF-7, MDA-MB157and MDA-MB231 cells. Autophagy was synergistically enhanced in MDA-MB157 cells by decreasing the levels of 5′-AMP-activated protein kinase (AMPK) α1 (Tran et al., 2021).

The combination of MLT and low-dose DOX was also evaluated in MCF-7 and MDA-MB-231 cells. Co-administration of DOX (1 nM or 10

Table 1
Summary of *in vitro-in vivo* studies of MLT combinations (drugs and natural compounds) and new delivery approaches of co-treatments.

Drug Combined	Model experimental	Dose of MLT	Dose of combined drug	Effect	Target/Pathway	Reference
Breast Cancer						
Paclitaxel	*In vitro* MCF-7 MDA-MB-231	1 nM 10 nM	1 nM 10 nM	-Increase the cytotoxic effect of paclitaxel -Inhibition of cell invasion	↓[DJ-1 mRNA, ID-1 mRNA] ↑[KLF17 mRNA]	El-Sokkary et al. (2019)
Docetaxel	*In vitro* MCF-7	1 nM	1 nM	-Increase of anti-proliferative and apoptotic effect	↑[p53, Bad, CDKN1A, CDH13, Bax] ↓[MUC1, Bcl-2, GATA3, C-Myc]	Alonso-González et al. (2017)
Thymoquinone	*In vitro* EMT6/P	0.1–5 mM	10–800 μM	Synergistic antiproliferative effect (IC = 0.55)		Odeh et al. (2018)
	In vivo EMT6/P cells xenograft mice model	2 mg/kg	10 mg/kg	-Increase of apoptosis and necrosis -Inhibition of angiogenesis	↑[Th 1 response, IFNγ] ↓[VEGF, IL-4, AST, ALT]	
Doxorubicin	*In vitro* MCF-7 MDA-MB157 MDA-MB231	3 mM	1 μM	-Synergistic cytotoxic effect. -Increase of apoptosis and autophagia	↑[cleaved caspase-3, cleaved PARP, LC3-II] ↓[AMPKα1]	Tran et al. (2021)
Doxorubicin	*In vitro* MCF-7 MDA-MB-231	1 nM	1 nM and 10 nM	-Increased anti-proliferative effect	↓[TWIST1]	Menéndez-Menéndez et al. (2019)
Lapatinib	*In vitro* HCC1954 MDA-MB-453 MDA-MB-361 MCF7/HER2	2 mM	1 and 2 μM	-Increase of cytotoxicity	↑[ROS, UPR pathway]	Sang et al. (2021)
	In vivo HCC1954-xenograft mice	50 mg/kg	100 mg/kg	-Increase of anti-tumor effect and apoptosis	↑[DNA damage, γH2AX cleaved PARP]	,
Neratinib	*In vitro* HCC1954 MDA-MB-453, MDA-MB-361 MCF7/HER2	1 and 2 mM	50 and 100 nM	-Synergistic cytotoxic and apoptotic effect	↓[HER2 stability]	Liu et al. (2021)
	In vivo HCC1954 cells xenograft mice model	50 mg/kg	5 mg/kg	-Inhibition of the growth of tumor		
Apatinib	*In vitro* MCF-7 MDA-MB-231	100 mM	1 μM	-Increase the apoptosis -Decrease of VM and the invasion of CSCs	↓[VE-cadherin, EPHA2, PI3K, p-AKT, Wnt5a]	Maroufi et al. (2022)
Platinum II + diphenylpyrazol (PtDPhPzTn)	*In vitro* TNBC MDA-MB-231	1 mM	10.4 μM	-Increase of apoptosis in TNBC cells and the anti-migratory effect	↑[ROS, % cells with hypodiploid DNA content]	Estirado et al. (2022)
Alpelisib	*In vitro* MDA-MB-453 T-47D	1 mM	1 mM	-Reduction in viability and cell migration	↑[caspase-3] ↓[PI3K, p-AKT, mTOR, HIF-1α]	de Godoy et al. (2023)
Colorectal Cancer						
5-fluorouracil	*In vitro* SNU-C5/WT SNU-C5/5FUR SNU-C5/OXAL CSCs S707	500 μM	1 μM	-Inhibition of cancer stem cell proliferation. -Increase of cancer stem cell apoptosis.	↑[Bax, cleaved caspase-3, cleaved PARP-1, LCB3-II, Atg7, Beclin1] ↓[Bcl-2, Oct4, Nanog, Sox2, ALDH1, p62, PrPC]	(Lee et al., 2018a)
	In vivo S707 cells xenograft mice model			-Decreased tumor volume -Inhibition of angiogenesis.	↓[PrPC]	
5-fluorouracil	*In vitro* HCT116 SW480 COLO320 DLD-1 HT29 RKO CaCO2 SW620 HCT116-5FU-R SW480-5FU-R	200 μM	100 μM	-Increase of cytotoxicity. -Increase of cytotoxicity in 5-FU resistant cells (resensitize).	↑[miR-215-5p] ↓[TYMS]	Sakatani et al. (2019)
5-fluorouracil	*In vitro* SW-480	150 μM	150 μM	-Decrease of cell proliferation -Increase of apoptosis and intracellular ROS levels -Suppression of CAT and SOD activities.	↑[Bax] ↓[Bcl-2, XIAP, survivin]	Mihanfar et al. (2020)

(*continued on next page*)

Table 1 (*continued*)

Drug Combined	Model experimental	Dose of MLT	Dose of combined drug	Effect	Target/Pathway	Reference
5-fluorouracil	*In vitro* HT-29	1 mM	1 mM	-Increase of cytotoxicity and apoptosis	↑[ROS, caspase-3]	Pariente et al. (2018)
Cisplatin	*In vitro* HT-29	1 mM	20 μM	-Moderate chemosensi-tizing effects in CIS-treated cells	↑[caspase-3]	Pariente et al. (2018)
Cisplatin	*In vitro* HT-29	5 μM	50 μM	-Increase of cytotoxicity, apoptosis and autophagy	↑[p53, p27, Beclin-1, Atg-4, LC3] ↓[mdm2, mRNA]	Polat et al. (2022)
Oxaliplatin	*In vitro* SNU-C5 SNU-C5/OXAL-R	500 μM	1 μM	- Increase of apoptosis and endoplasmic reticulum stress.	↑[Bax, caspase-3, pPERK, CAT, IRE1α, ATF4, CHOP, O_2] ↓[Bcl-2, SOD, CAT, PrPC]	Lee et al. (2018b)
Doxorubicin	*In vitro* Caco-2	0.8 mM	0.8 μM	-Increase of early and late apoptosis rate -Reduction of tumor spheroid formation, proliferation, viability, invasion, and migration.	↑[Bax, Smac] ↓[MMP-2, MMP-9, Bcl-2, survivin]	Jadid et al. (2021)
Leukemia						
Retinoic acid	*In vitro* HL-60	1 mM	10 nM	-Reduction of mitotic index -Increase of cytotoxicity	↑[CNPase, ETC complexes] ↓[Bcl-2, VDAC1, TSPO]	Krestinina et al. (2018)
Sorafenib	*Ex vivo* FLT3 wild type (ML-1 and HL-60) ITD mutated (MOLM-13 and MV4-11)	2 mM	5 and 100 nM	-Synergism (IC < 1) –Increase of apoptosis		Tian et al. (2019)
	In vivo MV4-11 cells xenograft mice model	20 mg/kg	3 mg/kg	-Synergistic therapeutic activity	↑[ROS]	
Arsenic trioxide	*In vitro* NB4	1 mM	2 μM	-Increase the inhibition of cell viability and early and late apoptosis	↑[Atg7, LDH, Bax, caspase-3, LC3-II] ↓[Bcl-2]	Wei et al. (2019)
Navitoclax	*In vitro* HL-60	1 mM	0.2 μM	-Reduction of the index of mitotic activity -Increase of autophagy	↑[ROS, PERK, CHOP, Bax] ↓[Ca^{2+}, Bip, mitochondrial membrane potential, Bcl_{xL}, Bcl_w, Mcl-1]	Lomovsky et al. (2020)
Prostate Cancer						
Docosahexaenoic acid	*In vitro* PNT1A	1 μM	100 μM	-Increase the anti-proliferative effect and the mitochondrial function	↑[ROS, p-ERK, GSTP1] ↓[p-AKT, p-mTOR]	Tamarindo et al. (2019)
Enzalutamide	*In vitro* C4-2 22RV1	1 mM		-MLT induced apoptotic cell death in both cell lines by increases the ER stress	↑[CES1, MT1, SIRT1, PPARα, p-PERK, p-IREα, p-elF2α, IRE1α, ATF6] ↓[DNMT1, STAR4, CYP11A144, lipids, cholesterol, testosterone, dihydrotestosterone]	Zhou et al. (2021)
	In vivo C4-2 cells xenograft mice model	200 mg/kg	10 mg/kg	-MLT reduced the tumoral volume and induced apoptosis reversing the resistance to ENZ of castration-resistant prostate cancer	↑[CES1, $TUNEL^+$] ↓[$Ki67^+$, CYP11A144, lipids, cholesterol]	
Pancreatic Cancer						
Sorafenib	*In vitro* PANC-1 MIAPaCa-2	2 mM	10 μM	-Synergically inhibited cell proliferation and induces apoptosis via mitochondrial	↑[Cyt *c* cytosolic, caspase-3 activity, PARP hydrolysis] ↓[pPDGFβ, pSTAT3, Bcl-2, Mcl-1, surviving, XIAP]	Fang et al. (2018)
	In vivo MIAPaCa-2 cells xenograft mice model	40 mg/kg	10 mg/kg	-Synergically reduced tumoral growth by induces apoptosis	↑[caspase-3 activity, $TUNEL^+$] ↓[PCNA, pPDGFβ, pSTAT3]	
Gemcitabine	*In vitro* PANC-1	10^{-10} and 10^{-12} M	10^{-6} M	-Synergically increases the apoptosis via intrinsic pathway.	↑[Bax, caspase-9, -3 activation] ↓[Bcl-2, cIAP1, HSP70]	Leja-Szpak et al. (2018)
Cisplatin	*In vitro* PANC-1	10 nM	50 μM	-Modulates tumor suppressors and oncogenes.	↑[21, p53, p57, mdm2, KRAS] ↓[p27]	Gür and Özkanlar (2021)
Ovarian Cancer						
Paclitaxel	*In vitro* SK-OV-3	3.2 mM	0.625 μM	-Decrease viability and cell invasion -Increase apoptosis and necrosis -MLT increases chemosensitivity of SK-OV-3 to paclitaxel	↓[TLR4, TRIF, MyD88, p-PI3K, p-AKT, p38, ERK½, JNK, p70s6K, PD-L1, NF-kB, CREB, STAT5]	Gaiotte et al. (2022)

(*continued on next page*)

Table 1 (*continued*)

Drug Combined	Model experimental	Dose of MLT	Dose of combined drug	Effect	Target/Pathway	Reference
Cisplatin	*In vitro* OVCAR3	4 mM	–	-MLT Increases of pro-apoptotic effect of cis-platin.	↑[ROS, p53, caspase-3 activation, and AKT] ↓[p-AKT, p-GSK3β, HIF1, VEGF]	Baghal-Sadriforoush et al. (2022)
Cisplatin	*In vitro* SK-OV-3	1.841 mM	117.5 μM	-MLT reduces the resistance to cisplatin by decreasing the cell proliferation and induces apoptosis	↑[CTR1, E-cadherin] ↓[ERCC1, GSH, Pgp]	Adeya et al. (2023)
Head, neck and oral cancer						
Rapamycin	*In vitro* Cal-27 SCC-9	0.1, 0.5, 1.0 mM	1 nM	-Increase of mitophagy and apoptosis at MLT high dose	↑[ROS, NIX, LC3-II Bax] ↓[p-AKT, p-mTOR, Bcl-2, p62]	Shen et al. (2018)
	In vivo Cal-27 cells xenograft mice model	300 mg/kg	300 mg/kg	-Significantly greater accumulation of apoptotic bodies and more tumor cell necrosis. -Toxicity reduction		
Verteporfin	*In vitro* SCC-25 SCC-1 SCC-104	1 mM	2.5 μM	-Increase of apoptosis. -Decrease of migration capacity of cells, sphere-forming ability and stem cell population	↑[ROS] ↓[Parkin, PINK1, MMP-2, MMP-9]	Shin et al. (2022)
Erastin	*In vitro* SCC-15	0.5–2 mM	0.5 μM	-Increase of apoptosis and ferroptosis levels. -Decrease autophagy	↑[Lipid-peroxidation, ROS, PARP-1, caspase-3, p62, LC3-II] ↓[Glutamate, GSH]	Wang et al. (2023)
	In vivo SCC-15 cells xenograft mice model	100 mg/kg	30 mg/kg	-Decreased tumor size -Increase of apoptosis and ferroptosis levels. -Decrease autophagy	↑[Lipid-peroxidation, TUNEL^{+}]	
Glioblastoma						
Vorinostat	*In vitro* U87MG, GSC267	1 mM	8 μM	-Increase of apoptosis increased. -Decrease of tumor-sphere formation and size.	↑[PARP hydrolysis, p-γH2AX] ↓[TFEB]	Sung et al. (2019)
	In vivo GSC267 cells orthotopic mice model	15 mg/kg	25 mg/kg	-Reduction in tumor volume -Median survival of the mice increased		
Albendazole Albendazole sulphoxide	*In vitro* C6 RG2 U87 cells C6 RG2 U87 cells	0.6 mM 0.6 mM 0.45 mM 1 mM 0.9 mM 0.45 mM	0.6 μM 0.6 μM 0.45 μM 20 μM 20 μM 0.45 μM	-Increase of apoptosis and autophagy -Increase of apoptosis and autophagy.		Hernández-Cerón et al. (2023)
Cervical cancer						
Cisplatin	*In vitro* HeLa	1 mM	20 μM	-MLT Increases of apoptotic capacity of cisplatin through the inhibition of mitophagy.	↑[ROS, Cyt *c* cytoplasmatic, Bad, Bax, caspase-9, -3 activation] ↓[p-JNK, p-Parkin, cIAP, Atg5, Beclin-1, p62, LC3-II]	Chen et al. (2018)
Docetaxel	*In vitro* HeLa	2 mM	10 and 20 nM	-MLT enhances the sensitivity to docetaxel.	↑[CHOP, GPR78] ↓[p-IκBα, p-NF-κB/p65]	Song and Wang (2023)
Melanoma						
Vemurafenib	*In vitro* SK-Mel-28 A375 A431 G361	1 mM	2 μM	-Decrease of proliferation, colony formation, migration and invasion. -Increase of apoptosis, cell cycle arresting, stemness weakening.	↓[NF-κB, iNOS, hTERT]	Hao et al. (2019)
	In vivo Melanoma cells xenografts mice model	25 mg/kg	20 mg/kg	-Inhibition of tumor growth		
Thyroid cancer						
Dabrafenib	*In vitro* SW1736 OCUT1 KHM-5M CAL-62	1 mM	0.1 μM	-Inhibition of cell proliferation, migration and invasion. -Increase of apoptosis and cell cycle arrest.	↓[AKT, EMT]	Liao et al. (2020)
Esophageal cancer						
5-fluorouracil	*In vitro* EC-9706 EC-109 HET 1A	1 mM	60 mM	-Increase of apoptosis. -IC_{50} value of 5-FU was decreased	↑[caspase-3] ↓ [EZH2, Bcl-2, Mcl-1]	Zhang et al. (2021)
Hepatocellular carcinoma						

(*continued on next page*)

Table 1 (*continued*)

Drug Combined	Model experimental	Dose of MLT	Dose of combined drug	Effect	Target/Pathway	Reference
Doxorubicin	*In vitro* HePG2 HuH7	30 mM	1 μM	-Increase of apoptosis and autophagia.	↓[AMPKα1 mRNA]	Tran et al. (2021)
Lymphoma						
Doxorubicin and dexamethasone	*In vitro* Toledo CRL-2631	1.25 mM	Doxorubicin 10 ng/mL, dexamethasone 4 μg/mL	-Increase of cytotoxicity and pro-apoptotic activity. -Modulation of the cell cycle after the combination of MLT with doxorubicin and dexamethasone.	↑[mitochondrial membrane potential, caspase-3, -8, -9 activation]	Mańka et al. (2023)
Renal cancer						
Sunitibit	*In vitro* 786-O 769-P SW839	2 mM	10 μM	-Inhibition cell growth. -Affectation of mitochondrial homeostasis. -Reversion of Warburg effect induced by sunitibit.	↑[OCR] ↓[Pyruvate, ECAR]	Xue et al. (2023)
Gastric cancer						
Cisplatin	*In vitro* SGC-7901	2.5 mM	0.5 μg/mL	-Promotes arrest in G0/G1 phase of the cell cycle and apoptosis.	↑[LC3-II, Beclin-1, Bip, p-p38]	Cheng et al. (2023)
New delivery approaches for MLT drug combinations						
Graphene dendrimeric system Doxorubicin-Melatonin	*In vitro* Saos-2 MG-63 hBM-MSC			-Inhibition of cell proliferation and increase of apoptosis.	↓[XIAP, surviving. hTERT]	Niu et al. (2021)
Nanocarriers of MEL and resveratrol (Sericin based nanocarriers)	*In vitro* MCF-7			-Increase of cytotoxicity.	↑[Caspase-3, Bax, Bcl-2]	Aghaz et al. (2023)

nM) and MLT (1 nM) enhanced the anti-proliferative effect of DOX, but only in MCF-7 cells. This effect was mediated by a downregulation of twist-related protein 1 (TWIST1) by MLT. This work was the first to report the ability of MLT to modulate the expression of the *TWIST1* gene in cancer, which is known to evade p53-induced growth arrest (Menéndez-Menéndez et al., 2019).

Lapatinib (a tyrosine kinase inhibitor, TKI) exerts its anti-tumor effects by competing with intracellular ATP to block the HER2 signal (Moreira and Kaklamani, 2010). This mechanism of action has some advantages in overcoming drug resistance and has been considered in drug combinations against BC. Recently, Sang et al. reported a beneficial effect of MLT (2 mM) in combination with lapatinib (1 μM or 2 μM) (Sang et al., 2021). MLT enhanced the cytotoxic effects of lapatinib in both primary and therapy-resistant BC with oncogenic HER2 signaling. The combination improved the cytotoxicity of lapatinib on MCF7/HER2 and MDA-MB-361 cells. The effect was due to the stimulation of the endoplasmic reticulum (ER) stress-induced unfolded protein response (UPR) and ROS overaccumulation. The *in vivo* effect of MLT (50 mg/kg/day) co-administered with lapatinib (100 mg/kg/day) in an HCC1954/HER2-xenografted mouse model (BC cells resistant to lapatinib) resulted in a significant enhancement of the anti-tumor effect of lapatinib. This study demonstrated for the first time the modulatory effect of this combination on UPR activation and HER2 signaling in BC cell lines, both *in vitro* and *in vivo*.

Other *HER2* mutations have been detected in HER2+ BC patients treated with neratinib (a TKI), suggesting hyperactivation of kinases in the HER family, which may contribute to resistance to neratinib (Hyman et al., 2018). One approach to overcome this problem is the use of MLT in combination with neratinib, which was investigated by Liu et al. This study demonstrated that MLT (1 mM or 2 mM) synergized the cytotoxic and proapoptotic effects of neratinib (50 nM or 100 nM) on HER2+ BC cell lines (HCC1954, MDA-MB-453 and MDA-MB-361). *In vivo,* a combination of MLT (50 mg/kg/day) and neratinib (5 mg/kg/day) inhibited HCC1954 tumor growth in a mouse xenograft model without altering mouse body weight. These results suggested for the first time that MLT inhibits the formation of the HER2/HSP90 complex and, in turn, the lysosomal degradation of HER2, enhancing the anti-tumor effect of neratinib and supporting the potential of MLT as an adjuvant in the treatment of HER2+ BC (Liu et al., 2021).

Co-treatment of MCF-7 and MDA-MB-231 cells with MLT (100 mM) and apatinib (1 μM) induced apoptosis, decreasing cell viability and vasculogenic mimicry (VM) formation. The combined treatment also reduced proliferation, VM formation, and migration and invasion of cancer stem cells (CSCs) from MDA-MB-231 cells in a dose- and time-dependent manner. The authors suggested that the inhibition of VM formation is related to a decreased expression of vascular endothelial (VE) cadherin, which in turn is due to the inhibition of the ephrinA2 receptor (EPHA2)/phosphor-inositide-3 kinase (p-PI3K)/phospho-protein kinase B (p-AKT) signaling pathway. VM formation has been associated with tumor grade, progression, invasion, metastasis, and a poor prognosis (Maroufi et al., 2022). This drug combination could be a novel approach to improve the anti-angiogenic effect of apatinib in BC patients.

Recently, new metallodrugs have been synthesized and used to improve the lipophilicity of anticancer drugs and their permeability into tumor cells. Estirado et al., reported that MLT (1 mM) enhanced the cytotoxic effect of platinum (II) complex coordinated with the ligand 2-(3,5-diphenylpyrazol-1-yl)-2-thiazoline (PtDPhPzTn, 10.4 μM) on MDA-MB-231 cells, increasing apoptosis and the antimigratory effect of PtDPhPzTn. These effects were attributed to an increase in ROS levels, cell cycle arrest in the S phase, and activation of caspase-9 and -3. MLT potentiated the cytotoxic properties of the platinum complex through multiple mechanisms, including oxidative stress and mitochondrial injury, which may be useful to overcome the resistance of BC cells (Estirado et al., 2022).

In another study, a combination of MLT (1 mM) and alpelisib (a PI3K inhibitor, 1 μM) decreased cell viability and migration of MDA-MB-453 (H1047R PIK3CA, HER2+) and T-47D (H1047R PIK3CA, ER+/PR+) cells, while increasing apoptotic cell death in both lines. These effects were associated with downregulation of PI3K, p-AKT, mammalian target of rapamycin (mTOR) and HIF-1α and activation of caspase-3. MLT enhanced the oncostatic effect of alpelisib, reduced tumor cell migration compared to either treatment alone; also, reduced the collateral toxicity of chemotherapy. As such, it may improve the quality of life for patients, particularly those who carry a mutation in *PIK3CA* (de Godoy et al., 2023).

3.1.2. Colorectal cancer

Morbidity and mortality from colorectal cancer (CRC) have increased significantly worldwide. According to recent data, it is the third most common malignant neoplasm and the fourth leading cause of death worldwide (Bray et al., 2024). Standard treatment includes surgery, chemotherapy, and radiotherapy. The currently used chemotherapeutic drugs 5-FU, oxaliplatin (OXAL), irinotecan, leucovorin, and capecitabine (Kuipers et al., 2015; McQuade et al., 2017) cause severe inflammation, toxicity, and resistance (Dariya et al., 2020; Lee, 2014). Therefore, the search for more effective and less toxic alternatives is urgent.

Gao et al. investigated for the first time the effect of the combined administration of MLT (1 mM) and 5-FU (a pyrimidine analog with a narrow therapeutic index, 30 μM) on SW620 and LOVO CRC cells. The authors reported that MLT synergized the cytotoxic effect of 5-FU by suppressing the PI3K/AKT and NF-κB/iNOS signaling pathways (Gao et al., 2017). More recently, Lee et al. investigated the effect of co-treatment with MLT (500 μM) and 5-FU (1 μM) on CSCs (human colorectal S707). The combined treatment significantly inhibited cell proliferation and induced apoptosis and autophagy by decreasing the expression of CSCs markers octamer-binding transcription factor 4 (Oct4), Nanog homeobox (Nanog), sex determining region Y-box 2 (Sox2), aldehyde dehydrogenase 1 A1 (ALDH1A1), Bcl-2, and p62, while increasing the levels of Bax, LC3B-II, ATG7, Beclin 1, cleaved caspase-3, and PARP-1 in S707 cells. In a human CSCs xenograft model, co-treatment with MLT and 5-FU treatment significantly reduced tumor volume, cell proliferation, and angiogenesis. The authors suggested that the antitumor effect of the co-treatment was due to modulation of the cellular prion protein (PrP^C)/heat shock 70-kDa protein-1-like (HSPA1L)/Oct4 signaling pathway. This combination may be a valuable therapeutic approach for this cancer by inhibiting PrP^C (Lee et al., 2018a,b), a glycoprotein with an important role in CSCs proliferation and therapeutic resistance (Go and Lee, 2020; Mouillet-Richard et al., 2021).

In turn, Sakatani et al. investigated the association between co-treatment with MLT (200 μM) and 5-FU (100 μM) in 5-FU-resistant CRC cells (HTC116-5FU and SW480-5FU). MLT resensitized resistant cells to 5-FU by increasing the level of miR-215-5p, thereby downregulating the expression of thymidylate synthase (TYMS) (Sakatani et al., 2019). This paper was the first to report a possible genetic modulation of TYMS by miR-215-5p to overcome the resistance of CRC cells to 5-FU.

In another study, Mihanfar et al. showed that MLT (150 μM) potentiated the cytotoxic effect of 5-FU (150 μM) and decreased proliferation in SW-480 cells. These effects were associated with an increase in ROS levels, mediated by a downregulation of the enzymatic activity of CAT and SOD, and a significant increase in the rate of apoptosis (Mihanfar et al., 2020). This pro-apoptotic effect of this drug combination may be explained by a negative modulation of the mRNA and protein expression of Bcl-2, X-linked inhibitor of apoptosis (XIAP) and survivin, which have been implicated in the carcinogenic process of CRC (Hehlgans et al., 2013). Therefore, XIAP and survivin may be novel therapeutic targets in this malignancy.

Similarly, Pariente et al. investigated the effect of co-treatment with MLT (1 mM) and either 5-FU (1 mM) or CIS (20 μM) on human colorectal adenocarcinoma HT-29 cells. MLT significantly improved the cytotoxic effect of 5-FU, inhibited cell proliferation, and induced apoptosis via the mitochondrial pathway by activating caspase-9 and -3. Meanwhile, co-treatment with MLT and CIS showed a moderate increase in apoptosis compared with the MLT and 5-FU combination, which was attributed to caspase-3 activation. The authors suggested that the combination of MLT and 5-FU may be a promising approach for the treatment of CRC (Pariente et al., 2018).

On the other hand, Polat et al. reported that a combination of MLT (5 μM) and CIS (50 μM) enhanced apoptotic death and autophagy in HT-29 cells by increasing the transcription of *p53, p27, Beclin-1, Atg-4,* and *LC3* and downregulating *mdm2* mRNA (Polat et al., 2022). Therefore, co-administration of MLT and CIS may be useful for CRC treatment.

Lee et al. evaluated the effect of co-administration of MLT (500 μM) and OXAL (1 μM) on SNU-C5 and SNU-C5/OXAL-R cells. Co-treatment increased apoptosis rates in both cell lines by inducing ER stress through inhibition of PrP^C. This inhibition induced an increase in the expression of Bax, active caspase-3, pPERK, and IRE1α, activating the transcription factor 4 (ATF4), C/EBP homologous protein (CHOP), and superoxide ion, while downregulating Bcl-2, SOD, and CAT (Lee JH; Yoon YM; Han YS; Yun CW; Lee SH, 2018). These results confirm previous reports on the role of PrP^C in the development of chemoresistance.

Finally, Jadid et al. demonstrated that a combination of MLT (0.8 mM) and DOX (0.8 μM) increased apoptotic cell death and decreased cell proliferation, migration, and invasion in Caco-2 cells, as well as the number and size of spheroids. These effects were due to a decrease in MMP-2, MMP-9, Bcl-2, and survivin mRNA and expression levels, and an increase in the transcription and translation of Bax and Diablo IAP-binding mitochondrial protein (Smac). In all cases, the effects of the combination were greater than those of monotherapy (Jadid et al., 2021). This combination may be an alternative for patients with DOX-resistant CRC.

While the capability of MLT to increase the cytotoxic efficacy of different antineoplastic drugs for CRC, has been reported, it is important to highlight that in most of the studies MLT was combined with antineoplastic agents at lower concentrations of than those commonly used in single form. This could limit some undesirable side effects in normal cells; in fact, it has been found that the use of MLT, suppresses CIS-induced nephrotoxicity (Kilic et al., 2013). Likewise, some studies have shown that MLT decreases the side effects produced by anticancer agents by protecting against the mitochondrial oxidation related with the chemotherapy (Espino et al., 2011; Madhu et al., 2015).

3.1.3. Leukemia

Leukemia is a cancer that affects blood-forming tissues, including bone marrow and the lymphatic system. It is the leading cause of malignant death in children (Salama et al., 2023). Standard chemotherapy includes purine analogues such as 6-mercaptopurine, vinblastine, vincristine, and vinorelbine. Recently, the FDA approved three new drugs for all leukemia types: asciminib, brexucabtagene autoleucel, and asparaginase *Erwinia chrysanthemi* (recombinant)(Kent and Pollyea, 2023). However, the side effects and toxicity of current treatments persist, and new approaches are focused on optimizing efficacy and minimizing toxicity.

The combined effect of MLT (1 mM) and low-dose retinoic acid (10 nM) used in clinical practice was evaluated in acute promyelocytic leukemia HL-60 cells. This combination increased cytotoxicity against HL-60 cells compared to monotherapy by reducing the mitotic index, the activity of electron transport chain (ETC) complexes, and by downregulating the expression of Bcl-2 and voltage-dependent anion selective channel 1 (VDAC1). MLT improved the effect of retinoic acid at a subtoxic concentration for cells, reducing the side effects of this drug (Krestinina et al., 2018).

Approximately 33 % of leukemia patients overexpress the type III receptor Fms-like tyrosine kinase 3 (FLT3). In this context, MLT (2 mM) and sorafenib (a multikinase inhibitor, 5 or 100 nM) decreased cell viability in a synergistic manner ($CI < 1$) by increasing apoptosis rates in primary FLT3/ITD acute AML cells (MOLM-13 and MV4-11). These effects were correlated with ROS generation, loss of mitochondrial membrane potential, and increased release of cytochrome C from mitochondria into the cytosol. When tested *in vivo,* the combination of MLT (20 mg/kg) and sorafenib (3 mg/kg) showed synergistic antiproliferative and pro-apoptotic activity in MV4-11 xenografts and a mouse model of FLT3/ITD leukemia (Tian et al., 2019). Modulation of redox status by MLT in combination with sorafenib may provide a novel approach to improve the outcome of FLT3/ITD leukemia.

In another study, the effect of MLT on the cytotoxicity of arsenic

trioxide on human leukemia NB4 cells was investigated. Pretreatment (24 h) with MLT (1 mM) enhanced the cytotoxic effect of arsenic trioxide (2 μM) by increasing apoptosis and lactate dehydrogenase (LDH) release in NB4 cells through overregulation of Bax, downregulation of Bcl-2, and increase in caspase-3 activation, as well as an increase in LC3-II levels (Wei et al., 2019). These findings suggest that MLT may be a valuable adjuvant to arsenic trioxide in the treatment of leukemia by modulating autophagy.

Similarly, the cytotoxic effect of MLT (1 mM) co-administered with navitoclax (a Bcl-xL, Bcl-2, and Bcl-w inhibitor, 0.2 μM) on HL-60 cells was recently reported. The combination led to a reduction in cell viability and mitotic index by increasing ROS production and Bax, PERK, and CHOP expression. The combined treatment enhanced the suppression of B-cell lymphoma-extra-large (Bcl-XL), B-cell lymphoma-wide (Bcl-w), myeloid cell leukemia-1 (Mcl-1), binding immunoglobulin protein (Bip), ERO1, and protein disulfide isomerase (PDI). Thus, MLT may enhance the cytotoxicity of navitoclax by modulating ER stress, autophagy, and apoptosis (Lomovsky et al., 2020).

3.1.4. Prostate cancer

Prostate cancer is one of the most common and malignant neoplasms in men. It is the fifth leading cause of death worldwide and the second leading cause of death in the United States, with an overall survival rate of 5 years (Steele et al., 2017). Chemotherapeutic agents approved for prostate cancer include abiraterone acetate, apalutamide, bicalutamide, cabazitaxel, darolutamide, degarelix, docetaxel, leuprolide acetate, enzalutamide, flutamide, goserelin acetate, olaparib, mitoxantrone, nilutamide, niraparib, relugolix, rucaparib, sipuleucel, and talazoparib. Several studies have reported that high concentrations of MLT decrease the risk of developing prostate cancer and its progression to castration-resistant prostate cancer. Therefore, a combination of chemotherapeutic drugs and MLT may provide an alternative for improving the antitumor effect of available drugs (Papantoniou et al., 2015; Reiter et al., 2017; Steele et al., 2017).

Tamarindo et al. reported that co-administration of MLT (1 μM) and docosahexaenoic acid (100 μM) induced a synergistic anti-proliferative effect in PNT1A prostate cancer cells, improved mitochondrial bioenergetic capacity and function, and increased the expression of glutathione S-transferase Pi (GSTP1). The effects of MLT were due to modulation of ROS produced by docosahexaenoic acid, inactivation of AKT/mTOR signaling, and activation of ERK1/2 (Tamarindo et al., 2019). Higher ROS levels in PC3 prostate cells promote AKT inactivation and GSTP1 expression via ERK phosphorylation, resulting in decreased cell viability (Yan et al., 2013). The authors suggested that MLT may modulate mitochondrial bioenergetics of prostate cancer cells, preventing their development or inducing cell death in patients older than 65 years who showed low MLT serum levels, through its antioxidant activity and ability to modulate proliferative pathways. In addition, low levels of MLT and high levels of total cholesterol and lipids are associated with a higher risk of prostate cancer (Li et al., 2017). On the other hand, Jahn et al. reported no association between night work and the development of prostate cancer (Jahn et al., 2024).

The combined administration of MLT (1 mM) and enzalutamide (ENZ) to C4-2 and 22RV1 enzalutamide-resistant prostate cancer cells increased the expression of carboxylesterase 1 (CES1) by increasing the levels of MT1, sirtuin 1 (SIRT1), peroxisome proliferator-activated receptors (PPARα), pPERK, pIREα, pelF2α, Bip, and ATF6, while decreasing the levels of DNA methyltransferases (DNMT1), STARD4, and CYP11A144, promoting apoptosis and decreasing the levels of lipids, cholesterol, testosterone, and dihydrotestosterone in both cell lines. Furthermore, MLT reverted the resistance of C4-2 (ENZ-R) and 22RV1 cells to ENZ. *In vivo,* the co-administration of MLT (200 mg/kg) and ENZ (10 mg/kg) in C4-2 (ENZ-R) cell xenograft NCG mice significantly reduced cell proliferation, tumor growth, CYP11A144 levels, and intra-tumor concentrations of triglycerides and cholesterol compared to the group treated with ENZ alone. MLN-ENZ co-treatment increased CES1 levels and apoptosis rates (TUNEL+), suggesting that MLT improves the sensitivity of tumor cells to ENZ. The authors reported that MLT induced CES demethylation and, in turn, its overexpression by decreasing the activity of DNMT1 through SIRT1. CES1 reduces lipid levels to promote a reduction in androgen biosynthesis and apoptosis via PPARα/ER stress, which reverses the resistance to ENZ and inhibits prostate cancer progression, respectively. Reduced CES1 expression in human PCa samples compared to normal tissue is negatively associated with tumor progression and metastasis (Zhou et al., 2021). Therefore, co-administration of MLT and ENZ may be a promising therapy for advanced prostate cancer.

3.1.5. Pancreatic ductal adenocarcinoma

Pancreatic ductal adenocarcinoma (PDAC) is the fourteenth most common neoplasm worldwide and the seventh leading cause of death in cancer patients. It is highly invasive, recurrent and metastatic. PDAC mortality rates vary by country. In North America, the mortality rate is 6.5 per 100,000 people, with higher incidence and mortality in men than in women (Bray et al., 2024; Ushio et al., 2021). Current therapy for this malignancy includes surgery followed by standard chemotherapy (gemcitabine alone or in combination with albumin-bound PTX, capecitabine, or erlotinib) or a multidrug regimen of 5-FU, irinotecan, leucovorin, and OXAL, which has failed due to drug resistance and severe side effects (Kang et al., 2016; Koltai et al., 2022; Principe et al., 2021). Preclinical and clinical studies are underway to develop a safer and more effective therapy for pancreatic cancer patients.

Fang et al. reported for the first time that co-administration of MLT (2 mM) and sorafenib (10 μM) synergistically inhibited cell viability of human PANC-1 and MIAPaCa-2 PDAC cells. Similarly, the combined treatment synergistically induced cell cycle arrest in the G1 phase and apoptosis via mitochondrial pathways in the MIAPaCa-2 cell line by downregulating anti-apoptotic proteins such as Bcl-2, Mcl-1, survivin, and XIAP, and by promoting mitochondrial translocation of Cyt *c* to the cytosol, caspase-3 activation, and PARP hydrolysis. Furthermore, the combined treatment decreased the levels of pPDGFβ and phosphosignal transducer and activator of transcription (pSTAT3), as well as their nuclear localization, but did not inhibit the RAF/MEK/ERK signaling pathway in PANC-1 and MIAPaCa-2 cell lines. *In vivo,* the combination of MLT (40 mg/kg) and sorafenib (10 mg/kg) decreased tumor proliferation and growth, induced apoptosis by activating caspase-3, and decreased PCNA, pPDGFβ, and pSTAT3 levels in MIAPaCa-2 xenograft models. These results suggest that co-treatment enhances the anti-proliferative and pro-apoptotic effects of sorafenib by inactivating the transcription factor STAT3 via PDGFR-β and MT1/2 in PDAC cells. Interestingly, these effects were independent of the RAF/MEK/ERK pathway (Fang et al., 2018). Therefore, MLT may improve the anti-tumor efficacy of sorafenib while reducing its side effects and may be a promising therapeutic approach for the treatment of PDAC in the future.

Leja-Szpak et al. demonstrated that either MLT (10^{-10} or 10^{-12} M) or its metabolite N^1-acetyl-N^2-formyl-5-methoxy kynuramine (AFMK, 10^{-10} or 10^{-12} M) synergistically enhanced the cytotoxicity and pro-apoptotic effect of gemcitabine (GEM, 10^{-6} M) in the PANC-1 cell line. Both treatments (MLT/GEM and AFMK/GEM) modulated the mitochondrial apoptotic pathway by inducing the overexpression of Bax and the activation of caspase-9 and -3, and by decreasing the expression of Bcl-2, cIAP1, and HSP70. Thus, MLT and AFMK could enhance the chemosensitivity of cancer cells to gemcitabine (Leja-Szpak et al., 2018).

In the same line, Gür and Özkanlar investigated the antiproliferative effect and the ability to modulate tumor suppressors (p21, p27, p53, and p57) and oncogenes (*mdm2* and KRAS) of MLT (10 nM) combined with CIS (50 μM) in the PANC-1 cell line. Cell viability was significantly reduced in the CIS and MLT/CIS groups compared to the control (untreated) group. Both monotherapy and combination treatment induced the genic expression of *p21, p53, p57, mdm2*, and *KRAS,* and downregulated the expression of *p27* compared to controls (Gür and Özkanlar,

2021).

The latter studies suggest that MLT may enhance the therapeutic efficacy of antineoplastic drugs by promoting mitochondrial apoptosis and tumor suppressor expression.

3.1.6. Ovarian cancer

Advanced-stage ovarian cancer is the deadliest gynecologic neoplasm. It is the seventh most common neoplasia in women. In 2018, it was associated with 4.4 % of cancer-related mortality because it was often detected at a late stage. First-line treatment includes surgical removal of the tumor, usually followed by chemotherapy with bevacizumab, carboplatin, CIS, cyclophosphamide, DOX, gemcitabine hydrochloride, melphalan, soravtansine-gynx, niraparib tosylate, olaparib, PTX, rucaparib, thiotepa, or topotecan (Goff et al., 2000; Momenimovahed et al., 2019; Siegel et al., 2016).

Gaiotte et al. also showed for the first time that co-treatment with MLT (3.2 mM) and PTX (0.625 μM) significantly reduced viability and cell invasion and increased cell death by apoptosis and necrosis in human ovarian cancer cells SK-OV-3. These effects were due to decreased levels of TLR-4, Toll/interleukin-1 receptor (TIR)-domain-containing adaptor inducing interferon-beta (TRIF), myeloid differentiation primary response gene 88 (MyD88), pPI3K, p-AKT, MAPKs (p38, ERK1/2 and JNK), p70s6K, death protein ligand 1 (PD-L1) and transcription factors (NF-kB, CREB and STAT5), all of which are associated with cell viability, inflammation, cell invasion, chemoresistance and metastasis. Thus, by restoring the chemosensitivity of SK-OV-3 cells to PTX, MLT may be a valuable adjuvant in the treatment of ovarian cancer (Gaiotte et al., 2022). Previously, the TLR4/MyD88/NF-κB pathway (inhibited by MLT) was found to be closely associated with tumor progression and poor prognosis in ovarian cancer by increasing chemoresistance to PTX and other chemotherapeutic agents (Wang et al., 2009).

Baghal-Sadriforoush et al. reported that co-treatment of MLT (4 mM) and CIS to human ovarian adenocarcinoma cell line OVCAR-3, significantly increased ROS generation, p53 stability, and caspase-3 activation, as well as AKT and glycogen synthase kinase 3-beta (GSK3β) dephosphorylation. It also decreased HIF1 and VEGF levels. The authors suggested that MLT enhanced the pro-apoptotic effect of CIS in OVCAR3 cells through ROS production and modulation of PI3K/AKT signaling. On the other hand, co-treatment with MLT and CIS significantly decreased the IC_{50} of CIS compared to CIS alone (Baghal-Sadriforoush et al., 2022).

Adeya et al. found that the co-administration of MLT (1.841 mM) and CIS (117.5 μM) to SK-OV-3 cells (CIS-resistant) reduced the resistance to CIS, decreased cell proliferation, and induced apoptosis. It also inhibited DNA repair, CIS inactivation, and drug efflux by downregulating the expression of excision repair cross-complementation 1 (ERCC1), gamma-glutamyl cysteinyl glycine (GSH) and p-glycoprotein (Pgp). The combination also increased CIS uptake and cell-cell adhesion by upregulating copper-transporting ATPase-1 (CTR1) and E-cadherin expression (Adeya et al., 2023).

The latter results suggest that MLT may sensitize ovarian cancer cells to CIS by inactivating AKT, HIF1, ERCC, and Pgp, and by generating ROS, promoting the pro-apoptotic activity of CIS and inhibiting EMT.

3.1.7. Head and neck squamous cell carcinoma

Head and neck squamous cell carcinoma (HNSCC) is a broad group of epithelial malignancies affecting the oral cavity, pharynx, hypopharynx, larynx, nasal cavity, and salivary glands. Together, they represent the seventh most common cancer diagnosis worldwide. HNSCC is more common in men than in women (2:1 ratio) (Bray et al., 2024). Oral squamous cell carcinoma, the most common type, has a 5-year survival rate of only 50 % (Thavarajah et al., 2006). In the primary stages (I and II), the standard treatment for HNSCC includes surgery and/or radiation therapy. A combination of surgery, radiation, or chemotherapy is used to treat stage III or IV cases. Drugs approved for the treatment of HNSCC include bleomycin sulfate, docetaxel, hydroxyurea, sodium methotrexate, imatinib, sunitinib, gefitinib, erlotinib, and afatinib (Goerner et al., 2010). Some combination regimens (carboplatin-taxol and carboplatin-cetuximab-5-FU) have been approved (Marur and Forastiere, 2016) All types of HNSCC are highly aggressive and associated with a poor prognosis despite current treatments. Therefore, better alternatives are urgently needed.

Shen et al. evaluated the effect of MLT (0.5 or 1 mM) in combination with rapamycin (mTOR inhibitor, 20 nM) on Cal-27 and SCC-9 cells *in vitro*. MLT enhanced the cytotoxic effect of rapamycin, reduced the clonogenic capacity of the cells, and induced apoptosis and mitophagy. These effects were associated with increased levels of Bax, LC3-II and mitochondrial outer membrane-anchored protein (NIX), and with downregulation of Bcl-2 and p62. MLT also inhibited rapamycin-induced feedback activation of AKT signaling and increased ROS levels. Tumors harvested from Cal-27 xenografted mice and treated with MLT (300 mg/kg) and rapamycin (1 mg/kg) showed increased apoptosis and cell differentiation rates compared to MLT and rapamycin monotherapy. MLT protected normal tissues in the liver, lung and kidney from rapamycin toxicity (Shen et al., 2018).

In another study, the effect of co-administration of MLT (1 mM) and verteporfin (an inhibitor of Yes-associated protein 1 [YAP]/WW domain-containing transcriptional regulator 1 [TAZ], 2.5 μM) was evaluated in the SCC-25 cell line. This combination synergistically inhibited cell viability, migration, mitophagy, sphere formation, EMT and CSC (CD44+/CD24-) populations in SCC-25 cells. The combined treatment induced apoptosis by downregulating pAKT, phosphatase and tensin homolog-induced kinase 1 (PINK), Parkin, MMP2, MMP9, N-cadherin, vimentin, and the Cellular Communication Factor 1 (CCN1), and by activating caspase-3 through inhibition of the Hippo/Last1/2/YAP pathway, independent of ROS generation. These results suggest that this co-treatment may be useful to reduce HNSCC metastasis by inhibiting multiple steps in the carcinogenic process (Shin et al., 2022).

On the other hand, Wang et al. showed that co-treatment with MLT (2 mM) and erastin (a ferroptosis inhibitor, 5 μM) on the SCC-15 cell line synergistically reduced cell viability, increased apoptosis and ferroptosis rates, and blocked late-stage autophagy through ROS modulation. This drug combination increased the levels of ROS, malonic dialdehyde (MDA), lipid peroxidation, iron, LC3A/B and SQSTM1/p62. It also cleaved caspase-3 and PARP1 and decreased glutamate and glutathione levels compared to cells treated with MLT or erastin alone. *In vivo*, combined administration of MLT (100 mg/kg) and erastin (30 mg/kg) to subcutaneously xenografted SCC-15 mice reduced tumor growth by inhibiting autophagy and promoting apoptosis and ferroptosis, without side effects on kidney, liver, and lung (Wang et al., 2023). The authors suggest that autophagy inhibition by MLT and erastin may enhance the antineoplastic effect and overcome drug resistance in oral cancer cells.

3.1.8. Glioblastoma

Glioblastoma (GB) is the most aggressive tumor of the central nervous system, with a poor prognosis in adults. The average incidence is 3.19/100000 population (Thakkar et al., 2014). The incidence of GB is 1.6 times higher in men than in women, and 2 times higher in individuals of white race and non-Hispanic ethnicity (Tamimi and Juweid, 2017). Standard treatment is maximal surgical resection followed by radiotherapy and concurrent chemotherapy with temozolomide; however, median overall survival is 12–15 months, and 5-year survival is less than 10 %. The most recently approved drugs for recurrent glioblastoma are lomustine and carmustine, which are highly toxic. Therefore, the search for alternative therapies that improve patient survival is critical (Poon et al., 2020).

Sung et al. investigated the effect of combined administration of MLT and vorinostat (a histone deacetylase inhibitor) both *in vitro* and *in vivo*. A combination of MLT (1 mM) and vorinostat (8 μM) was evaluated in the U87MG glioma cell line, and a combination of MLT (1 mM) and vorinostat (4 μM) was evaluated in GSC 267 cells. The combination

inhibited cell viability in both cell lines and induced apoptosis more efficiently than either MLT or vorinostat alone. The combined treatment promoted PARP and caspase-3 cleavage; it also increased p-γH2AX levels by inhibiting the expression and activation of the transcription factor EB (TFEB). TFEB is overexpressed in human GB tissues and in cell lines such as U87 and A172 (Sung et al., 2019). *In vivo*, co-treatment with MLT (15 mg/kg) and vorinostat (25 mg/kg) in orthotopic GSC267 nude mice significantly reduced tumor growth and resulted in prolonged median survival (Sung et al., 2019). In contrast, neither vorinostat nor MLT monotherapy suppressed tumor growth. The authors suggested that the combination may be useful to inhibit tumorigenesis and suppress resistance to standard treatment by modulating TFEB activation in glioma cells and GSCs (Sung et al., 2019).

Recently, Hernández-Cerón et al. reported the effect of MLT (0.18–6 mM) in combination with albendazole (0.16–1.25 μM) or albendazole sulfoxide (2–64 μM) on C6, RG2, and U87 glioma cell lines. Most combinations showed a synergistic cytotoxic effect on all cell lines compared to monotherapy, promoting apoptotic and autophagic cell death by increasing the proportion of annexin V-positive cells, the expression level of LC3, and the formation of acidic vesicular organelles (Hernández-Cerón et al., 2023). The authors suggested that the good therapeutic index and availability of these drugs in the brain may open a valuable treatment strategy against glioma cells.

3.1.9. Cervical cancer

Cervical cancer is the fourth most common malignancy in women, with an incidence of 13.3/100,000 women and a mortality rate of 7.2/100,000 women. The prevalence of cervical cancer is higher in developing countries (Bhatla et al., 2021). Surgery, radiotherapy, and CIS-based drugs are the standard treatment for the disease (Singh et al., 2023). Carboplatin, bleomycin sulfate, gemcitabine, ifosfamide, irinotecan, topotecan hydrochloride, PTX, and vinorelbine are also approved for cervical cancer (Liontos et al., 2019; Oza et al., 2015).

Chen et al. demonstrated that co-administration of MLT (1 mM) and CIS (20 μM) significantly enhanced the pro-apoptotic effect of CIS on HeLa human cervical cancer cells through mitochondrial inhibition of mitophagy, as evidenced by an increase in ROS generation, collapse of mitochondrial membrane potential, opening of the mitochondrial permeability transition pore, release of Cyt *c* from mitochondria into the cytosol, activation of caspase-9 and -3, overexpression of Bad and Bax, and dephosphorylation of c-Jun N-terminal kinase (JNK) and Parkin, as well as downregulation of cIAP, Atg-5, Beclin-1, p62, and LC3-II. Mechanistically, MLT inhibits JNK/Parkin-dependent mitophagy induced by CIS, thereby promoting apoptosis. Activation of JNK/Parkin-dependent mitophagy suppressed mitochondrial apoptosis by removing damaged mitochondria (Chen et al., 2018).

Similarly, Song et al. reported that MLT (1 mM) potentiated the effect of DOX (10 nM) on HeLa and SiHa cells by inhibiting cell proliferation, colony formation, and adherence to fibronectin. In HeLa cells, MLT (2 mM) inhibited the transcriptional activation of NF-κB, thereby enhancing DOX-induced ER stress and apoptotic cell death by inhibiting the phosphorylation of IκBα (an NF-κB inhibitor) and p-NF-κB/p65, increasing the levels of C/EBP homologous protein (CHOP) and GPR78. Thus, MLT increased the sensitivity of cervical cancer cells to DOX by increasing IκBα levels, which blocked NF-κB activation. NF-κB suppressed the expression of growth arrest and DNA damage-inducible gene 153 (GADD153) and CHOP, both of which offset ER stress and, in turn, reduce apoptosis (Song and Wang, 2023).

3.1.10. Melanoma

Melanoma is one of the most lethal malignancies due to its high metastatic potential, with a mortality rate of one in four patients (Ahmed et al., 2020). Significant progress has been made in the treatment of melanoma in recent years with the emergence and widespread application of combinatorial immunotherapy, particularly with the use of ipilimumab, the first immune checkpoint inhibitor, and vemurafenib, a first-in-class v-Raf murine sarcoma viral oncogene homolog B1 (BRAF) tyrosine kinase inhibitor (Hao et al., 2019; Teixido et al., 2021). However, other options are still needed to achieve a better clinical outcome.

In this context, Hao et al. investigated the effect of co-treatment with MLT (0.5–8 mM) and vemurafenib (0.5–8 mM) on SK-Mel-28 and A375 human melanoma cell lines. MLT synergistically enhanced the inhibitory effects of vemurafenib on cell proliferation, colony formation, and migration, and enhanced the promotion of G1-phase cell cycle arrest, apoptosis, and stemness attenuation. These effects were attributed to a decrease in the levels of Bcl-2, Cyc B, Cyc D3, CDK2, MMP-1, vimentin, pPDK, pAKT, and β-Catenin, while increasing the levels of phosphatase and tensin homolog (PTEN) and cleaved capase-3 and -9 by inhibiting the phosphorylation of IKKα, ERK, and MSK1, suppressing nuclear translocation and DNA binding of NF-κB, thereby suppressing transcription and activation of iNOS and telomerase reverse transcriptase (hTERT) signaling. *In vivo,* co-administration of MLT (25 mg/kg) and vemurafenib (25 mg/kg) regulated melanoma growth and CSC expansion in mice with subcutaneous xenografts of A375 cells, significantly delaying tumor growth. Suppression of the expression of p65, iNOS, hTERT, CD44, epithelial cell adhesion molecule (EpCAM), and PCNA were also demonstrated. The authors demonstrated the ability of MLT to increase the sensitivity of melanoma cells to vemurafenib while reducing the toxicity of the drug to normal tissue (Hao et al., 2019).

3.1.11. Thyroid cancer

Thyroid cancer, the ninth most common malignancy worldwide, is most common in adolescents and adults aged 16–33 years. It has a median survival of 3–6 months due to its aggressive growth, invasive and metastatic capacity, and resistance to standard drugs, including cabozantinib, lenvatinib, sorafenib, and vandetanib. It is therefore necessary to identify novel biological targets and therapeutic approaches for this neoplasia (Chen et al., 2023).

Liao et al. investigated the effect of combining MLT (1 mM) and dabrafenib (a BRAFV600E inhibitor, 0.01–10 mM) on the human anaplastic thyroid cancer cell lines SW1736, OCUT1, KHM-5M (mutant BRAFV600E), and CAL-62 (BRAFV600E WT). The authors demonstrated that mutant BRAFV600E cell lines were significantly more sensitive to the combined treatment than CAL-62 cells. MLT (1 mM) also enhanced dabrafenib (0. 1 μM)-mediated inhibition of cell proliferation and EMT and promotion of G1 cell cycle arrest and apoptosis on SW1736 and OCUT1 cells by increasing the activation of Cyc D1, CDK2, Bax, caspase-3, cleaved PARP, E-cadherin, and PTEN, while downregulating the expression of MMP9, N-cadherin, and vimentin by decreasing pAKT and hTERT (transcript and protein) levels. These results suggest that the combination of MLT and dabrafenib has a synergistic anti-tumorigenic effect on thyroid cancer cells expressing BRAFV600E by modulating the hTERT/PTEN/AKT pathway (Liao et al., 2020).

3.1.12. Esophageal cancer

Esophageal cancer (EC) is the seventh most common cancer worldwide. With a higher incidence in men than in women, its prognosis and survival data are concerning (Stabellini et al., 2022). Standard treatment for this malignancy includes radiotherapy or chemotherapy (CIS, cetuximab, capecitabine, docetaxel, 5-FU, ipilimumab, nivolumab, pertuzumab, or pembrolizumab) (Huang and Yu, 2018). As chemoresistance is a common cause of treatment failure, there is an urgent need to find new therapeutic approaches against EC.

Zhang et al. evaluated the cytotoxic effect of MLT (1 mM) and 5-FLU (40 or 60 mM) on the EC-9706 and EC-109 cell lines. The combination showed a synergistic cytotoxic effect in both cell lines, significantly reducing cell viability (IC_{50} for 5-FU was significantly lower when co-administered with MLT), migration, and invasion. The cotreatment induced apoptosis by downregulating the expression of Bcl-2, Mcl-1 and histone lysine N-methyltransferase (both mRNA and protein) and increased caspase-3 activity. MLT also improved the antineoplastic effects of 5-FU by negatively regulating the expression of EZH2, which is

highly associated with chemoresistance in several cancer lines (Zhang et al., 2021). Therefore, this combination may be a promising strategy against EC.

3.1.13. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC), the sixth most common malignancy worldwide and the third leading cause of cancer death (Bray et al., 2024) has a higher incidence in men than in women (Wu et al., 2018). Treatment that results in long-term survival includes surgical resection, liver transplantation, and ablation. Antibodies such as atezolizumab, bevacizumab, durvalumab, ramucirumab, and ipilimumab, and kinase tyrosine inhibitors such as lenvatinib, regorafenib, sorafenib, and cabozantinib have been approved for the treatment of unresectable or advanced HCC (Vogel et al., 2022).

Recently Tran et al. (2021), evaluated the combination of MLT (3 mM) and DOX (1 μM) on the hepatoma cell lines HepG2 and HuH7. The combination induced apoptosis, as evidenced by increased levels of cleaved caspase-7 and PARP, and autophagic cell death by downregulating p62 and increasing the processing of LC3-I to LC3-II, thereby reducing the expression of AMP-activated protein kinase α1 (AMPKα1), both mRNA and protein (Tran et al., 2021) Therefore, this combination may be a promising therapeutic approach to improve the sensitivity of liver cancer cells to chemotherapy.

3.1.14. Lymphoma

Lymphoma is one of the most common forms of hematologic malignancy (Khanmohammadi et al., 2020). Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma, accounting for 30–40 % of newly diagnosed cases. The average age for diagnosis is 65 years. The standard first-line treatment is based on a multidrug chemotherapy protocol using the R-CHOP regimen (rituximab, cyclophosphamide, hydroxydaunorubicin hydrochloride—DOX, Oncovin®—vincristine, and prednisone). However, this regimen is only effective in about 60 % of cases (Mańka et al., 2023).

Mańka et al. investigated the effect of co-treatment with MLT (1.25 mM), DOX (10 ng/mL) and dexamethasone (4 mg/mL) on the CRL-2631 lymphoma cell line. Co-treatment increased cytotoxicity, cell cycle modulation, and pro-apoptotic activity compared to monotherapy. Higher proportions of cells in the sub-G0 and G0/G1 cell cycle phases, increased caspase-8, -9, and -3 activation, and lower mitochondrial membrane potential were also observed. The authors suggested that MLT may be a valuable adjuvant in the treatment of DLBCL (Mańka et al., 2023).

3.1.15. Renal cancer

Renal cell carcinoma (RCC) is the 13th cause of cancer death worldwide. Although many effective treatments have been approved (avelumab, bevacizumab, ipilimumab, nivolumab, pembrolizumab, axitinib, cabozantinib-s-malate, lenvatinib, pazopanib, sorafenib, temsirolimus, tivozanib, everolimus, sunitinib, belzutifan), the survival rate of patients with this disease has not been effectively improved (Bahadoram et al., 2022; Capitanio et al., 2019).

Xue et al. investigated the effect of co-treatment with MLT (2 mM) and sunitinib (10 μM) on 786-O, 769-P, and SW839 RCC cell lines. MLT and sunitinib synergistically inhibited cell viability and counteracted the Warburg effect induced by sunitinib in RCC cells by reducing pyruvate activity and extracellular acidification (ECAR) and increasing oxygen consumption rate (OCR). These results suggest that MLT may modulate metabolic reprogramming and help overcome therapeutic resistance to sunitinib (Xue et al., 2023).

3.1.16. Gastric cancer

Gastric cancer (GC) is the fifth most diagnosed cancer and the fourth leading cause of cancer death worldwide. Standard therapy for GC includes capecitabine, 5-FU, CIS, docetaxel, PTX, and irinotecan. DOX, epirubicin, leucovorin, mitomycin, nivolumab, OXAL, pembrolizumab, ramucirumab, fam-trastuzumab deruxtecan-nxki, and trifluridine/tipiracil are also approved for GC (Guan et al., 2023; Sexton et al., 2020).

Cheng et al. reported that a combination of MLT (2.5 mM) and CIS (0.5 μg/mL) on the gastric cancer cell line SGC-7901 induced apoptosis, G0/G1 phase cell cycle arrest, and significantly increased levels of autophagy markers such as Beclin-1 and LC3-II compared to monotherapy. The authors suggested that this therapeutic combination may be promising for the treatment of GC (Cheng et al., 2023).

3.2. Novel delivery approaches for MLT combinations in cancer

Therapeutic strategies such as nanostructured lipid carriers and dendrimeric systems have been developed to maximize the anticancer effect of MLT combinations and reduce the non-specific toxicity of standard drugs.

In this context, a functionalized graphene dendrimeric system formed with Fe_3O_4 nanoparticles (NP) as magnetic nanocarrier for co-delivery of MLT and DOX was used to evaluate the cytotoxic effect of MLT/DOX combination on Saos-2 and MG-63 osteosarcoma cell lines and on a bone marrow mesenchymal stem cell (hBM-MSC) line. Saos-2 and MG-63 cells treated with free MLT/DOX or MLT/DOX-loaded NP showed changes in cell morphology, shrunken nuclei, and DNA fragmentation, as well as higher apoptotic rates compared to cells treated with single agents, either free or loaded in NP. Meanwhile, hBM-MSC normal cells did not show any morphological changes or DNA damage; instead, they showed higher cell viability after the treatments. The synergistic apoptotic effect demonstrated with the nanoformulation co-delivering MLT and DOX on Saos-2 and MG-63 cell lines was due to downregulation of XIAP, survivin and hTERT. The authors suggested that MLT inhibited the cytotoxic effect of DOX on non-transformed cells but, at the same time, improved the antitumor capacity of DOX on osteosarcoma cell lines. Therefore, the magnetic nanocarrier may be a useful approach (Niu et al., 2021).

Recently, a combination of MLT and resveratrol encapsulated in sericin-based nanocarriers (MR-SNC) was developed as an antioxidant therapy and evaluated in MCF-7 cells. The study demonstrated a synergistic effect of the carrier, which decreased cell viability, increased chromatin condensation and DNA fragmentation of MCF-7 cells at pH 6.0 compared to the non-encapsulated combination. These results suggested that the pro-efficient release of MLT and resveratrol from nanocarriers in acidic microenvironment may be valuable for eliminating cancer cells (Aghaz et al., 2023).

4. Conclusion and perspectives

The aggressiveness and lethality of cancer are due to its high genetic instability, heterogeneity, epigenetic modifications, tumor microenvironment, metabolic reprogramming, and migratory and invasive capacity. CSCs, which have a higher proliferation and self-renewal capacity than normal cells, contribute to tumor growth and resistance to radiotherapy, immunotherapy and chemotherapy. To date, these treatments have only been able to prolong patient survival, but the antitumor effects are often transient, as most tumors eventually progress and exhibit high migratory and invasive capacity, recurrence and metastasis.

The goal of chemotherapy is to promote the death of cancer cells. In this sense, the combined administration of MLT and antineoplastic drugs may be a promising approach. Several papers have reported the use of MLT as a resensitizing agent, particularly with 5-FU, CIS, and DOX in BC and CRC, leukemia, prostate, pancreatic and ovarian cancer, head and neck cancer, GB, cervical cancer, melanoma, thyroid, esophageal and hepatocellular cancer, lymphoma, and renal and gastric cancer. These effects are mediated by a variety of mechanisms, including oxidative stress, mitochondrial injury, cellular metabolic reprogramming and DNA damage. MLT also modulates the activation of transcription factors such as ATF4, ATF6p5, ATF3, AP-1, CHOP, C-Myc, HIF-1α, NF-κB, TFEB,

and XBP1s, which are associated with various human pathologies, including cancer. In addition, in combination with apatinib, 5-FU, verteporfin, or vorinostat, MLT inhibited the proliferation, migration, and invasion of CSCs by decreasing the expression of Oct4, Nanog, Sox2, and ALDH1A1. These selective inhibitory effects may result in the suppression of various steps of carcinogenesis, thereby inhibiting metastasis.

In the case of MLT combinations with natural products, the preclinical evidence about antineoplastic activity, mechanism of action and toxicity in healthy cells, is still relatively limited. In this review we found only four studies (thymoquinone, resveratrol, retinoic acid, and docosahexaenoic acid) and only one included *in vivo* evaluation. More research is required to support its potential to the clinical field.

On the other hand, it is important to consider that the effect of antineoplastic drugs, including MLT, depends on the dose that reaches the tumor and the route of administration. Therefore, novel delivery systems such as nanocarriers based on graphene dendrimers and sericin (biodegradable, biocompatible, highly stable, and non-immunogenic) are under development. Loaded with DOX/MLT or resveratrol/MLT combinations, respectively, these delivery systems improve their effect on cancer cell lines compared to cells treated with drugs or nanocarriers alone or with single drug loaded nanocarriers. These delivery systems should be evaluated *in vivo* to confirm their therapeutic potential.

In summary, *in vitro* and *in vivo* reports provide ample evidence that drug combinations with MLT have the potential to improve the therapeutic efficacy of antineoplastic drugs, reduce chemoresistance, shorten treatment and consequently reduce the incidence of side effects. Several studies have shown that MLT alone can inhibit all stages of the carcinogenic process by modulating various signaling pathways induced by chemotherapeutic agents (Fig. 1), regulating the expression of genes involved in cell proliferation, survival, cell cycle progression, resistance to cell death (autophagy and apoptosis), inflammation, metabolism, angiogenesis, migration, and invasion.

As discussed, the antineoplastic potential of MLT, both as an individual treatment and in combination with chemotherapy, is well-documented in the literature. However, further research is needed to determine its translational potential. To date, preclinical and clinical evaluations of treatments have shown significant variability in survival rates, tumor regression, and side effects (Alshehri and Althobaiti, 2024; Kartini et al., 2020; Novik et al., 2021; Schernhammer et al., 2012; Seely et al., 2021; Sookprasert et al., 2014). In this context, randomized controlled preclinical trials have been proposed to bridge the gap between experimental and clinical research (Llovera et al., 2015; Llovera and Liesz, 2016). These studies must comply with rigorous guidelines, including a large sample size; selection of an appropriate drug dose and formulation; long periods of administration and evaluation; and the cancer type and its tumoral stage (Alshehri and Althobaiti, 2024b; Boutin et al., 2023). Standardizing these parameters could improve the evaluation process and provide more robust evidence of MLT's antineoplastic efficacy, either alone or in combination with anticancer drugs; this could increase the successful translation to the clinic.

Informed consent statement

Not applicable.

Author Contributions

Conceptualization, I.S.R.-T., H.J.-C., C.T.-S. and F.P.-A.; methodology, I.S.R.-T., H.J.-C., C.T.-S. and F.P.-A.; investigation, I.S.R.-T., H.J.-C., C.T.-S. and F.P.-A.; writing—original draft preparation, I.S.R.-T., H.J.-C., C.T.-S. and F.P.-A.; writing—review and editing, I.S.R.-T., H.J.-C., C.T.-S. and F.P.-A. All authors have read and agreed to the published version of the manuscript.

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Cristina Trejo-Solís: Conceptualization, methodology, Investigation, writing, original draft preparation, writing-review and editing.

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All authors have read and agreed to the published version of the manuscript.

On behalf of the co-authors.

PhD Francisca Palomares-Alonso.

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