Curcumin and Ritonavir Synergy: A Review of Co-Loaded Nanocarriers for Reversing Multidrug Resistance in Skin Carcinoma

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Abstract

Skin carcinoma, including melanoma, basal cell carcinoma (BCC), and squamous cell carcinoma (SCC), remains a major global health concern due to increasing incidence, high recurrence rates, multidrug resistance (MDR), and limitations associated with conventional chemotherapy. Overexpression of ATP-binding cassette (ABC) transporters, poor drug penetration, tumor microenvironment-mediated resistance, and systemic toxicity significantly reduce therapeutic efficacy. Nanotechnology-based drug delivery systems have emerged as promising strategies to overcome these challenges by improving drug solubility, bioavailability, targeted delivery, and controlled release. Curcumin, a natural polyphenolic compound, exhibits potent anticancer activity through inhibition of NF-κB signaling, induction of apoptosis, anti-angiogenic effects, and modulation of MDR-related proteins. However, its poor aqueous solubility and limited bioavailability restrict clinical application. Ritonavir, originally developed as an HIV protease inhibitor, has recently gained attention as a repurposed anticancer agent due to its ability to inhibit P-glycoprotein (P-gp), CYP3A4, proteasome activity, and Akt signaling pathways. Co-loading curcumin and ritonavir within nanocarriers offers a synergistic strategy for reversing MDR by simultaneously enhancing intracellular drug accumulation, suppressing efflux pumps, and promoting apoptosis in resistant skin cancer cells. Various nanocarrier systems, including liposomes, niosomes, polymeric nanoparticles, solid lipid nanoparticles, and nanoemulsions, demonstrate improved therapeutic potential for co-delivery applications. This review highlights the pharmacological basis, nanocarrier design considerations, and MDR reversal mechanisms associated with curcumin–ritonavir co-loaded nanocarriers, emphasizing their potential as an advanced therapeutic approach for the management of resistant skin carcinomas.

Keywords: Curcumin; Ritonavir; Skin carcinoma; Multidrug resistance; Nanocarriers; Co-loaded nanoparticles; P-glycoprotein; Drug repurposing; Targeted drug delivery; Apoptosis.

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1. Introduction

Epidemiology of skin cancers (melanoma, SCC, BCC)

Skin cancer is the most frequently occurring malignant tumors in people with light skin; their incidence has reached outbreak levels worldwide (Naldi & Diepgen, 2002). The 2021 Global Burden of Disease (GBD) study reports that in 2021 there were 6.64 million skin cancer cases globally, with age-standardized rates of occurrence (ASIR) at 77.66 per 100,000 people and total disability-adjusted years of life lost (DALYs) reported at 2.89 million years (Zhou et al., 2025). The most

commonly diagnosed skin cancer type is basal cell carcinoma (BCC), which had an incidence rate of 525 per 100,000 people in the US in 2019. Squamous cell carcinoma (SCC) had an incidence rate of 262 per 100,000 people; and melanoma had an incidence of 17.0 per 100,000 people (Aggarwal et al., 2021). From 1990-2021, BCC rates increased by 291.85% worldwide; and SCC by 322.77% for older adults (Pan et al., 2025). SCC was observed to be the neoplasm with the greatest rate of increase (310%) from 1990-2017 among neoplasms tracked by GBD (Urban et al., 2021). For the entire year 2017, it is estimated that there were 3.3 million global cases of BCC, and 1.8 million cases of SCC; approximately 65,097 deaths were related to SCC (Zhang et al., 2020). The NMSC's age-standardized incidence rates (ASIR) increased from 54.08 per 100,000 in 1990 to 79.10 per 100,000 in 2019; projected new cases, deaths, and DALYs will be 1.50 times higher between 2020 and 2044 (Hu et al., 2022).

Challenges:-

1. **Drug Resistance**

While advancements have been seen in cancer treatment drugs are still often unsuccessful in treating patients that have developed a resistance (MDR) to chemotherapy medications. A classic pattern for developing a resistance is for the most frequently seen protein to be (P-glycoprotein or ABCB1), a pump that works with ATP as a source of energy to transport anticancer medications out of a cell by actively removing former drugs from a cell, thereby lessening the effectiveness of the medication being given (Bradshaw & Arceci). Members of the ATP-binding Cassette (ABC) transporter superfamily are also noted to contribute to the development of a resistance to chemotherapy medications and have been shown to show too much activity within a number of tumor types (Turner et al). Tumor cells in melanoma have previously been shown to resist both types of treatments due to the presence of multiple members within the ABC transporter superfamily (ABCB1, ABCB5, ABCC1-MRP1, and ABCC2) as well as experience greater amounts of resistance when treated with chemotherapy medications (Chen & Gottesman). A study using immunohistochemistry to check for the presence of drug resistance proteins in 191 melanoma tumor specimens found that 96.3% of samples tested were positive for MRP1, 82.7% of samples were positive for MDR P-g, and 79.5% of samples were positive for both types of resistance proteins with only 1 of 191 samples being negative for drug resistance proteins (Walsh et al). Melanoma has an extremely complex mechanism to develop chemotherapy drug resistance including genetic mutations, changes in apoptotic pathways, remodeling of the tumor microenvironment, cellular plasticity, and development of different cell types (Nigam et al). Approximately 10% of patients being treated by chemotherapeutic agents will be cured by their treatment.

2. **Poor Drug Penetration**

Topical therapies for skin cancer have limited efficacy because of the inadequate absorbance of medicines through the stratum corneum. Traditional styles of topical formulation (e.g. creams, gels/ointments) are occlusive and unable to penetrate into the dermis, remaining on the surface of the epidermis (Jain et al. 2020; Lalotra et al 2020). Presently available

topical treatments for NMSC and precursor lesions (5-fluorouracil, diclofenac, imiquimod) have adverse effects such as severe inflammation, discomfort, lengthy treatment times and unsightly scars causing patient noncompliance (Majumdar et al 2019).

3. Systemic Toxicity

Most traditional methods of treating skin cancers (chemotherapy, radiation therapy and immunotherapy) produce many systemic side effects and have a high recurrence rate; this greatly affects a patient's quality of life (Gomes et al, 2024) .The amount of drug that must be given to make up for low levels of drug reaching the tumour leads to increased total body drug toxicity and increased incidence of drug related side effects.

Introduction to Nanocarrier-Based Delivery

Nanotechnology-based drug delivery systems are a developing treatment to address issues with the way we currently treat skin cancer. The use of nanoparticles as drug carriers has demonstrated a multitude of advantages: the solubility of poorly soluble drugs may be improved; changing the way the drug is absorbed and/or metabolized may prolong the drug's duration in the body; the biovailability of the drug may be improved; metabolism may be reduced; the drug may be released from the nanocarrier at a controlled rate; and two or more drugs may be released and absorbed simultaneously (Dianzani et al., 2014). One of the major challenges to the penetration of nanoparticles into the tissue is the barrier function of the skin; however, in the setting of injury or inflammation, as occurs in skin cancer, this barrier may be compromised, allowing for the easier passage of the nanoparticles into the tissue (Krishnan & Mitragotri, 2020). A variety of systems have been studied as potential topical delivery systems for the treatment of skin cancer, mostly involving liposomes, niosomes, ethosomes, transferosomes, solid lipid nanoparticles, nanostructured lipid carriers, polymeric nanoparticles, nanoemulsions, dendrimers and nanofibres (Yadav et al., 2024; Adnan et al., 2023). As they cross the stratum corneum, the nanosized delivery systems will fuse with the cutaneous layer, thereby fluidizing membranes and allowing deeper penetration of the therapeutics to the target sites within the skin (Jain et al., 2020). There is evidence that the use of nanocarriers will significantly enhance the bioavailability of drugs, which may reduce dosing frequency and decrease the toxicity of the drugs (Adnan et al., 2023). Although there have been encouraging results during preclinical studies, there is limited research on the clinical applications of nanotechnology as a drug delivery system for topical treatment of skin cancers.

Introduction to Drug Repurposing: Ritonavir

Overall, drug repurposing is a cost-effective method to discover new therapeutic uses for existing drugs. An example of drug repurposing is the use of ritonavir as a pharmacokinetic enhancer for other antiretrovirals, as it was initially developed as a protease inhibitor for HIV-1 due to its strong inhibitory effects on CYP3A4 and P-glycoprotein (Pereira & Vale, 2024). Recent studies have shown that ritonavir has potent anticancer effects through several mechanisms. For instance, Ikezoe et al. (2004) have demonstrated that

ritonavir synergistically increases the antiproliferative and pro-apoptotic effects of docetaxel in androgen-independent prostate cancer cells in vitro and in vivo, through complete inhibition of CYP3A4 expression induced by docetaxel and inhibition of NF-κB DNA binding activity. Furthermore, Vadlapatla et al. (2014) showed that ritonavir co-treatment prevents the overexpression of efflux transporters and metabolizing enzymes in cancer cells. In addition, combining ritonavir with doxorubicin, paclitaxel, tamoxifen, or vinblastine significantly inhibits cell proliferation and promotes apoptosis. A polymer-ritonavir derivative nanomedicine using HPMA copolymer has exhibited significant antitumor activity in both CT26 and B16F10 tumor-bearing mice by inhibiting STAT3 phosphorylation, NF-κB signaling, and proteasome activity, with little systemic toxicity (Sivák et al., 2021). Moreover, Kumar et al. (2009) have demonstrated that ritonavir blocks AKT signaling and activates apoptosis while inhibiting the migration and invasion of ovarian cancer cells.

Why Combination Therapy Is Superior to Monotherapy

While monotherapy nanomedicines have shown promising results in preclinical studies, they have not proven to be more effective than conventional chemotherapy in various types of cancers during human clinical trials for a host of reasons, including the smaller degree of enhanced permeability and retention (EPR) effect seen in human tumors versus animal models with EPR, tumor heterogeneity, as well as intrinsic/acquired resistance towards the drug itself (He et al., 2015). Combination therapies that use multiple agents with different modes of action provide a greater degree of synergy and decrease the chance of developing resistance to the therapies themselves (Hu et al., 2010). Combination therapy involving nanoparticles has been reported to provide greater synergy and decreased resistance to both drugs than either drug alone (Gurunathan et al., 2018). The ability to combine multiple therapeutic agents in a single nanocarrier facilitates greater control over the timing and location of the release of the drugs, achieves the most optimal ratio of synergistic drugs at the tumor site, and limits the substrate interactions between the drugs that would be present if they were given as free drug combinations (Shrestha et al., 2019).

Scope of the Review

While many publications document the reversal of multidrug resistance (MDR) by curcumin-loaded nano carriers and with emerging data supporting the use of ritonavir as an anticancer agent, there are currently no reports of a combination curcumin/ritonavir formulation within a single nanocarrier system for use against skin carcinomas. Both agents have well-established properties as ABC transporter (P-glycoprotein; P-gp) modulators and act synergistically to reverse MDR via distinct mechanisms: curcumin down-regulates P-gp expression by inhibiting the nuclear factor kappa B (NF-kB) signaling pathway, while ritonavir inhibits the efflux function of P-gp and the activity of cytochrome P450 isoform 3A4 (CYP3A4), which mediates the metabolism of many drugs. This review will outline a rationale, formulation approaches, and potential therapeutic value of developing novel curcumin-ritonavir co-

loaded nanocarriers as a method for reversing MDR in skin carcinoma.

3. Multidrug Resistance (MDR) in Skin Carcinoma

3.1 Mechanisms of MDR

Overexpression of P-glycoprotein (P-gp)

The over-expression of ATP-binding cassette (ABC) transporters, P-glycoprotein (P-gp/ABCB1) in particular, contributes significantly to the development of multidrug resistance (MDR) in skin cancer. Both chemotherapy and radiotherapy do not work against melanoma cell lines since most of the time, the reason for MDR in human tumor cells results from the expression of energy-dependent multidrug pumps that pump chemotherapeutic agents from the cells (Chen and Gottesman, 2006). Melanoma cells express a group of ABC transporters, including ABCA 9, ABCB 1 (P-gp), ABCB 5, ABCB 8, ABCC 1, ABCC 2, and ABCD 1, that contribute to the resistance of several anticancer drugs and the detoxification of intermediate products of melanin biosynthesis (Chen et al. 2009). A study examining 191 melanoma samples with immunohistochemistry found that nearly all samples were positive for presence of drug efflux pumps: MRP-1 was found in 96.3% of specimens; MDR1 P-gp was found in 82.7% of specimens; and approximately 79.5% of specimens had expression of both pumps. Only one of the 191 samples did not have expression of either pump (Walsh et al . 2008).

In addition to P-glycoprotein (P-gp), ABCB5 represents a key transport protein involved in melanoma. In the article published in Cancer Research by Frank, et al. (2005), the authors show that ABCB5 can be detected in clinical melanoma and ABCB5 positive melanoma cells exhibit a CD133 positive stem cell phenotype. The authors further show that blocking ABCB5 significantly decreases doxorubicin resistance (by 43% based on LD50) and that the mechanism of resistance occurs through enhanced drug accumulation in the cells (Frank et al., 2005). Melanoma cells with MDR1 expression can also express both ABCB5 and ABCC2, and contain stem cell phenotype markers (Nanog and hTERT), providing evidence that MDR1+ melanoma cells have superior self-renewal and sphere-forming ability, and potentially providing support for the hypothesis that MDR1+ melanoma cells are melanoma stem cells and may be important as a unique cell target for anti-melanoma therapies (Keshet et al., 2008).

In addition to BRAF mutations, resistance to vemurafenib has also been related to the overexpression of the ABCG2 transporter, which has been shown to facilitate drug efflux and reduce BRAF kinase inhibition through interactions with the BRAF(V600E) mutant cells. In cells with SCC, ABCC1 has been found to be a target gene of the transcription factor, ΔNp63, with SCCs showing a statistically significant higher expression than normal skin. Utilization of nanomedicine-based delivery systems that are taken up by endocytosis from cancer cells (and therefore do not require ABC transporters to gain entry) provides a novel strategy to bypass transporter-mediated resistance mechanisms for melanoma.

Drug Efflux Pumps

The ABC transporter family serves as the main method used by skin cancers to remove drugs from cells. Melanoma cells utilize structures called melanosomes,

which are typically involved in making melanin, to create drug-sequestering compartments that hold cytotoxic drugs and release them through exocytosis. This mechanism is a different method of resistance that occurs in melanoma rather than the classical P-glycoprotein mediated efflux mechanism (Chen & Gottesman, 2006). In basal cell carcinoma, drug resistance caused by switching from basal to squamous cell carcinoma allows the cancer to bypass Smoothened inhibitor (SMOi) treatment. According to Jussila et al. (2023), tumors caused by Gorlin syndrome can also become resistant to SMOi treatment due to the switching from basal to squamous cell carcinoma; whole exome sequencing showed PCYT2 and the phosphatidylethanolamine biosynthetic pathway may suppress this resistance-related transition (Jussila et al., 2023). The occurrence of phenotypic switching was also documented in a case of a patient with basal cell carcinoma treated with vismodegib who had recurrent lesions that contained similar genetics as his original tumor but had become squamous in histology and resistant to vismodegib (Ransohoff et al., 2015).

Altered Apoptosis Pathways

Melanoma's capacity to resist treatment is substantially based on an inability to die (by apoptosis). Other factors that contribute to this resistance include inappropriate uptake of drugs by melanoma cells, improper detoxification of the drugs, and overexpression of proteins that help repair any damage done to the cells' DNA (Grossman & Altieri, 2004). The current 5-year survival rate for patients with advanced melanoma with distant metastases is only 10-20%, and this is largely attributed to the cells' ability to resist the cytotoxic effects of the drugs used to treat them.

A large number of proteins belonging to the BCL-2 "anti-apoptotic" family are central to the development of melanoma because of their role in enhancing cell survival through inappropriate signalling within cells and concurrently blocking the activation of cell death mechanisms. The primary anti-apoptotic proteins that regulate melanoma tumour F003 are BCL-2, BCL-xL, and MCL-1 (Anvekar et al., 2011). Work from Eberle et al. (2007) showed that constitutive activation of several pathways that lead to the activation of signal transduction molecules including mitogen activated protein kinases, AKT, and NF-kB, result in the prevention of successful melanoma treatment by drug therapy (Eberle et al., 2007). It appears that melanoma cells express very high levels of BCL-2 and BCL-xL and that the expression of MCL-1 is only down-regulated at late time points following the initiation of proteasome inhibitor treatment and therefore, bortezomib alone will not work as an effective therapeutic option for treating melanoma (Wolter et al., 2007).

The inhibitor of apoptosis known as survivin, which is overexpressed in melanoma cells, imparts a higher degree of resistance to apoptosis than is normally attributed to a healthy cell. Survivin is required to maintain both.

Tumor Microenvironment Influence

All skin cancer types exhibit a strong reliance on an environment called the tumor microenvironment (TME), which contributes to the formation of tumors and prevents drugs from treating them. The

TME consists not only of tumor cells but of all the components surrounding a tumor cell (e.g., immune cells, cytokines, stromal cells, and extracellular matrix) that create the appropriate conditions for a tumor to form and for that tumor to resist being treated (Georgescu et al., 2020). In melanoma, the TME produces mechanisms that cause resistance to chemotherapy, targeted therapy, and immune checkpoint inhibitors. Furthermore, several cells associated with the tumor (e.g., cancer-associated fibroblasts, tumor-associated macrophages, and regulatory T cells) participate in forming a microenvironment that suppresses the immune response to the tumor and promotes its development (Georgescu et al., 2020; Somasundaram et al., 2016).

Snail1(epithelial-to-mesenchymal transition transcription factor) has been activated in melanoma-associated fibroblasts by acting as a transcription factor that induces an epithelial-to-mesenchymal transition. In melanoma, Snail1 promotes an immunosuppressive microenvironment that reduces the amount of immunity directed against the tumor. When therapeutic blockade of Snail1 was administered in mouse models, there was a decrease in melanoma tumor growth and the number of melanomas that metastasized to lung tissue (Arumi-Planas et al., 2023). In non-melanoma skin cancers, the TME exerts immunosuppression by reducing the number of effectors T cells (CD4+ and CD8+) and increasing the production of oncogenic Th2 cytokines. Cancer-associated fibroblasts within squamous cell carcinoma (SCC) have an extremely diverse genetic make up (Chiang et al., 2023).

The TME is able to adapt its suppressive characteristics that allow for drug resistance through interactions involving immune cells, cytokines, immunomodulators, stromal cells, and the extracellular matrix, resulting in changes in immune and metabolic profiling of the TME that lead to changes resulting in less effective immune surveillance and promote drug resistance to tumors.

3.2 Clinical Impact

Chemotherapy Failure

MDR has a severe influence on skin cancer patients. After melanoma has spread, the average length of life before passing away is between 7 and 9 months. All chemotherapy drugs and/or combinations will not improve chances of living longer, unless there are no mechanisms in place for the cancer cells to resist chemotherapy, such as: the ability to resist cell death, be effective at repairing damaged DNA, express enzymes to remove drugs from inside, or if there is an existing population of cancer stem cells (Rass & Hassel, 2009).

A multicenter retrospective study including 463 metastatic melanoma patients treated with chemotherapy after failure of an immune checkpoint inhibitor was conducted to determine the effectiveness of chemotherapy after immune checkpoint inhibitors had failed. The results indicated that chemotherapy produced very poor responses (12.4 percent complete or partial) and that 67 percent had disease that progressed after starting chemotherapy treatments. The median progression-free period after starting chemotherapy was 2.6 months, and median overall survival from starting chemotherapy was 7.1 months

(Goldinger et al., 2021). The use of an immune checkpoint inhibitor combined with chemotherapy treatment after the failure of a PD-1 inhibitor produced improved results compared to chemotherapy alone; the median overall survival from starting therapy was 3.5 and 1.8 years for single drug versus combination therapies, respectively; the overall response rates were 59 percent for combination therapies and 15 for single-agent chemotherapy (Vera Aguilera et al., 2020) This indicates that the combination treatments are potentially able to partially overcome drug-resistant mechanisms.

Recurrence and Metastasis

The connection between drug resistance and tumor recurrence/metastatic advancement is extremely close. For example, in melanoma, there are chemoresistant populations of stem cells that have been shown to be responsible for melanoma recurrences seen in patients post-therapy. Frank et al. (2005) demonstrated that the expression levels of ABCB5 are increased in patients with lymph nodal metastasis and with distant metastasis when compared to that of primary melanoma and benign nevi, indicating chemoresistant stem cell populations accumulate through the progression of melanoma. Sharma et al. (2010) showed the increase in ABCB5 overexpression as the melanoma progressed through multiple sites.

In basal cell carcinoma, Smoothened inhibitors lead to resistance and subsequent tumor recurrence due to transition of the tumor from basal cell to squamous cell carcinoma. Jussila et al. (2023) showed that resistant clones progress more rapidly than others due to sustained inhibition post-long term inhibitor treatment.

In addition, there are many patients who do not respond to immune checkpoint inhibitors (ICIs) and therefore, will have recurrences after an initial response has occurred. Mechanisms of resistance to ICIs are still inadequately understood; however, it is thought that impaired antigen recognition, reduced T-cell migration and infiltration, and reduced function of effector T-cells in the TME may impede the success of these therapies (Kawashima & Togashi, 2022).

Epigenetic alterations, including DNA methylation and histone modification, are now thought of as playing a role in the mechanisms responsible for tumor progression and therapeutic resistance across basal cell, squamous cell, melanoma and cutaneous T-cell lymphoma (Gibson et al., 2023).

4. Pharmacological Basis of Curcumin–Ritonavir Synergy

4.1 Curcumin Mechanisms

- NF-kappa B Inhibition

Through its ability to block the activity of NF-kappa B signaling, curcumin has also been shown to have strong anti-cancer properties (Panahi et al. 2016). NF-kappa B plays a key role as the master controller of cancer development and progression by regulating many of the genes and pathways involved in tumor generation/maintenance (Singh & Khar 2006). By preventing the nuclear translocation of NF-kappa B p65 as well as blocking I kappa B kinase activity, curcumin down-regulates the expression of many of the genes encoded downstream from NF-kappa B that are known to promote cell proliferation (Bcl-2), survival

(survivin), and chemoresistance (cyclin D1, COX-2). Immunofluorescence studies conducted in tumor-bearing mouse models have also demonstrated that curcumin's inhibition of NF-kappa B p65 nuclear translocation results in the reduction of VEGF expression, thereby linking the inhibition of NF-kappa B with both anti-proliferative and anti-angiogenic activities (Belakavadi & Salimath 2005).

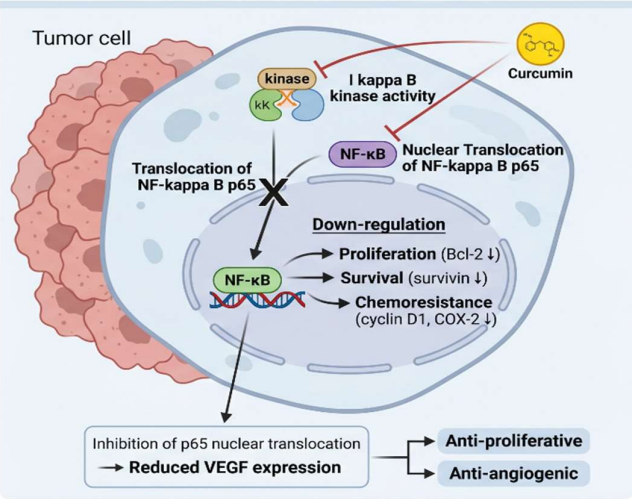

Fig 1:- *NF-kappa B Inhibition*

- Induction of apoptosis (caspase activation)

Curcumin Promotes Apoptosis (Caspase Activation). Various types of cancer cells are triggered to undergo cell death by curcumin via both intrinsic (mitochondria) and extrinsic (death receptors) pathways (Mortezaee, et al. 2019). From a mechanistic standpoint, curcumin promotes the activity of pro-apoptotic proteins (e.g. p53 and Bax) and decreases the activity of anti-apoptotic family of proteins (e.g. members of the Bcl-2 family), thus activating caspase-3, caspase-8, and caspase-9 resulting in DNA fragmentation and nuclear condensation (Kuttan et al. 2007). Curcumin has also been shown to induce apoptosis by increasing the generation of reactive oxygen species (ROS) in tumor cells, up-regulating the expression of apoptosis receptors located on the membranes of tumor cells, and modulating the PI3K/Akt and MAPK signaling pathways (Mortezaee, et al. 2019). Therefore, due to the multi-target apoptotic effects of curcumin, it can be used as a valuable adjuvant with both conventional cytotoxic and radiotoxic therapies (Chathoth, et al. 2008).

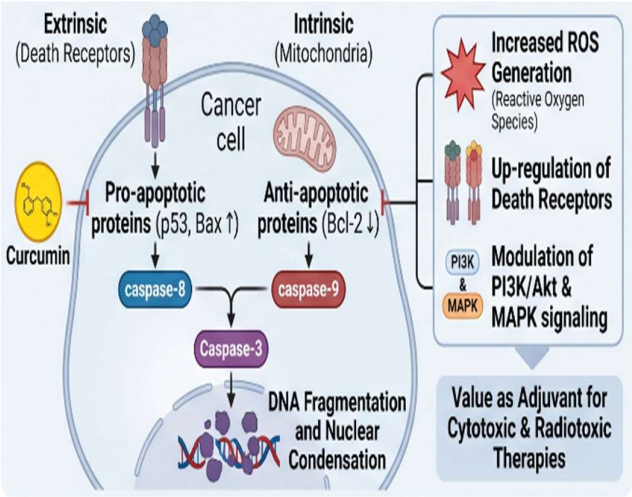

Fig 2:- *Induction of apoptosis*

- Anti-angiogenic effects

The anti-angiogenic effects of Curcumin are well-documented due to its ability to inhibit various pro-angiogenic growth factors such as the vascular endothelial growth factor (VEGF) and angiopoietins (Shakeri et al., 2019). In Ehrlich ascites tumor cells, Curcumin reduced VEGF secretion and inhibited endothelial cell proliferation in the peritoneal cavity, as confirmed by CD31 immunohistochemical staining (Belakavadi & Salimath, 2005). Additionally, Curcumin inhibits matrix metalloproteinases (MMPs) and intercellular adhesion molecules, thus preventing invasion/metastasis by tumors (Kuttan et al., 2007). Curcumin also has anti-angiogenic effects through inhibiting transcription factor pathways, including STAT3 and Sp-1, thereby increasing the number of different molecular targets through which Curcumin can inhibit tumor vasculature (Vallianou et al., 2015).

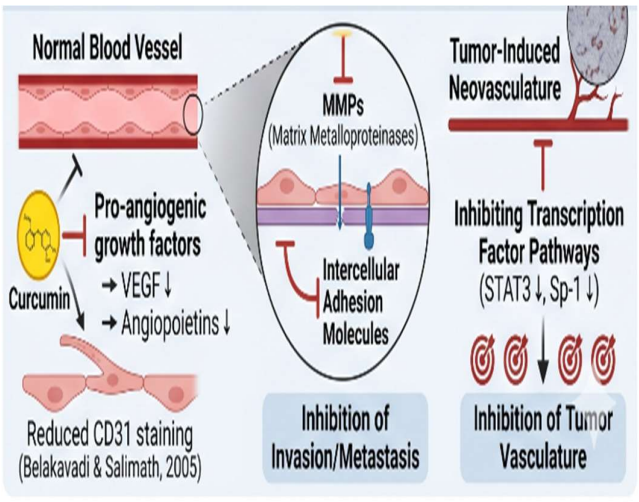

Fig 3:- *Anti-angiogenic effects*

4.2 Ritonavir Mechanisms

- Proteasome inhibition

Ritonavir, which was originally designed to be an HIV protease inhibitor, can be used to block the chymotrypsin-like activity of the proteasome (specifically, the 20S proteasome). This results in a buildup of the cyclin-dependent kinase inhibitor p21^WAF-1 in cancer cells and selective disruption of proteasome-mediated protein degradation. This cumulative effect of disrupting the proteasome ultimately causes endoplasmic reticulum (ER) stress, as shown by the phosphorylation of PERK and the increased expression of ATF4 and CHOP, and ultimately results in apoptosis (programmed cell death) in cancer cells but does not affect non-transformed cells. Additionally, ritonavir inhibits the chaperone function of heat shock protein 90 (Hsp90). As a result, Hsp90 client proteins (for example, Akt) are depleted, and this leads to further destabilization of cancer cell survival signaling.

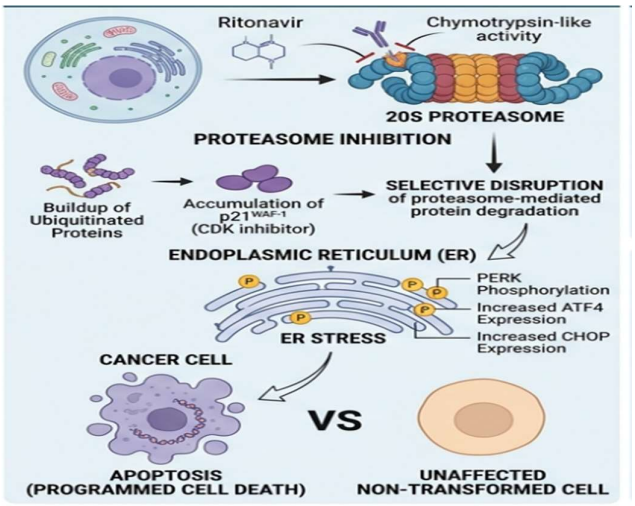

Fig 4 :- *Proteasome inhibition*

- CYP3A4 inhibition (boosts drug levels)

Ritonavir is one of the most powerful known inhibitors of cytochrome P450 3A4 (CYP3A4), which is the primary enzyme that metabolizes many drugs during their first pass through the body (Pereira & Vale, 2024). CYP3A4 expresses itself transcriptionally when prostate cancer xenograft models were treated with docetaxel, however, when this induction occurred within prostate cancer xenograft models, the level of docetaxel intracellularly was significantly increased as well as the effectiveness of docetaxel against prostate cancer at both the cellular and systemic levels when ritonavir was co-administered (Ikezoe et al. 2004). Thus, the pharmacokinetic boosting effect that has been used in HIV therapy to increase levels of other protease inhibitors (which were also co-administered) provides a direct benefit to combination chemotherapy for patients diagnosed with cancer, as it is essential for the effectiveness of combination chemotherapy to have sufficient intratumoral concentration of both agents in order to delay or reverse the development of resistance (Holmstock et al., 2012).

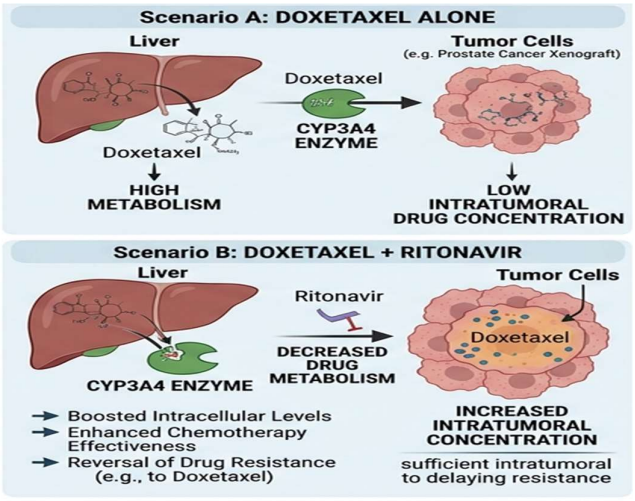

Fig 5 :- *CYP3A4 inhibition*

- Anti-cancer repurposing role

Repurposing the anti-cancer properties of ritonavir has been shown to be beneficial in various types of cancer, including lung cancer, prostate cancer, breast cancer, ovarian cancer, bladder cancer and multiple myeloma (Pereira & Vale, 2024). Anticancer mechanisms of ritonavir include inhibition of the Akt signalling pathway, arresting cell cycle progression, inducing endoplasmic reticulum (ER) stress, and inducing metabolic stress (Pereira & Vale, 2024). Ritonavir has also been shown to reverse chemoresistance to traditional chemotherapeutics, such as gemcitabine and docetaxel (Pereira & Vale, 2024). According to Sato (2015), ritonavir has the potential to inhibit multiple, well-characterized targets (proteasome, Hsp90, and P-glycoprotein) simultaneously, which makes ritonavir a very promising choice for use in combination therapies for the treatment of malignancies that have proven resistant to existing treatment modalities. Ritonavir has also recently been shown to directly inhibit enzymes involved in DNA repair, thus increasing cellular sensitivity to radiation therapy and synergizing with chemotherapeutics in many different cancer models (Pomella et al., 2025).

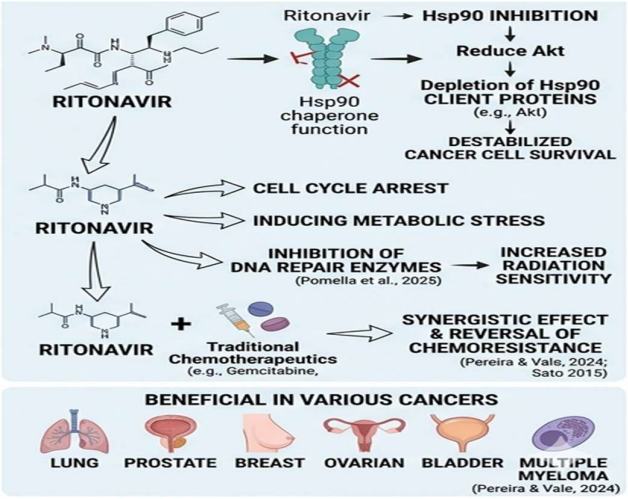

Fig 6:- *Anti-cancer repurposing role*

4.3 Synergistic Mechanisms

Efflux pump inhibition (ritonavir enhances curcumin retention)

Ritonavir is an established efflux pump and P-glycoprotein (P-gp) inhibitor that enhances/benefits retention of co-administered substrates within the cell (Sato, 2015). According to studies by Vadlapatla and colleagues (2014), ritonavir inhibited the overexpression of efflux transporters in cancerous cells and thus increased cellular accumulation of ritonavir when used with co-administered drugs leading to increased apoptosis via caspase activation. As curcumin also inhibits the activity of ABC transporter and competes for the efflux activity of these transporters (Sharma et al., 2009), combining ritonavir with curcumin may have an additive or synergistic effect by further inhibiting efflux transport activities and therefore increasing the amount of curcumin present within resistant tumor cells.

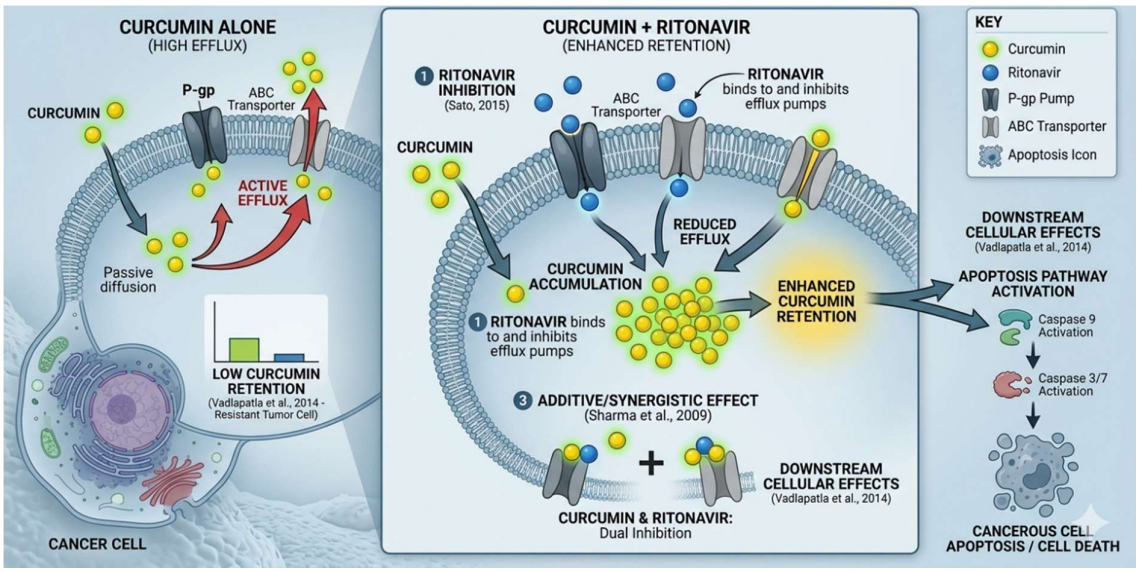

Fig 7:- *Efflux pump inhibition*

Enhanced apoptosis signaling

Increased Apoptosis Signalling Pathways. By converging on several apoptotic pathways simultaneously, the two drugs 'curcumin' (CC) and 'ritonavir' (RTV) work together to help induce cell death in human prostate cancer cells. CC activates both caspase-dependent and caspase-independent apoptotic pathways while decreasing the expression of some anti-apoptotic proteins (Bcl-2 and survivin) by suppressing the transcription factor NF-κB (Mortezaee et al., 2019). In addition, RTV prevents proteasomal degradation of specific protein(s) resulting in increased levels of pro-apoptotic protein(s) (p21 and p53) (Gaedicke et al., 2002) and blocks Akt-mediated survival signalling by inhibiting Hsp90 (Srirangam et al., 2006). Furthermore, when RTV is combined with docetaxel, the ability of RTV helps to induce a significantly greater degree of apoptosis than either drug alone in vitro or in vivo in human prostate cancer xenograft models without causing toxicity in other organs throughout the body (Ikezoe et al., 2004). Therefore, these data support the potential utility of RTV, in combination with other chemotherapeutic agents, for enhanced therapies for the treatment of prostate cancer.

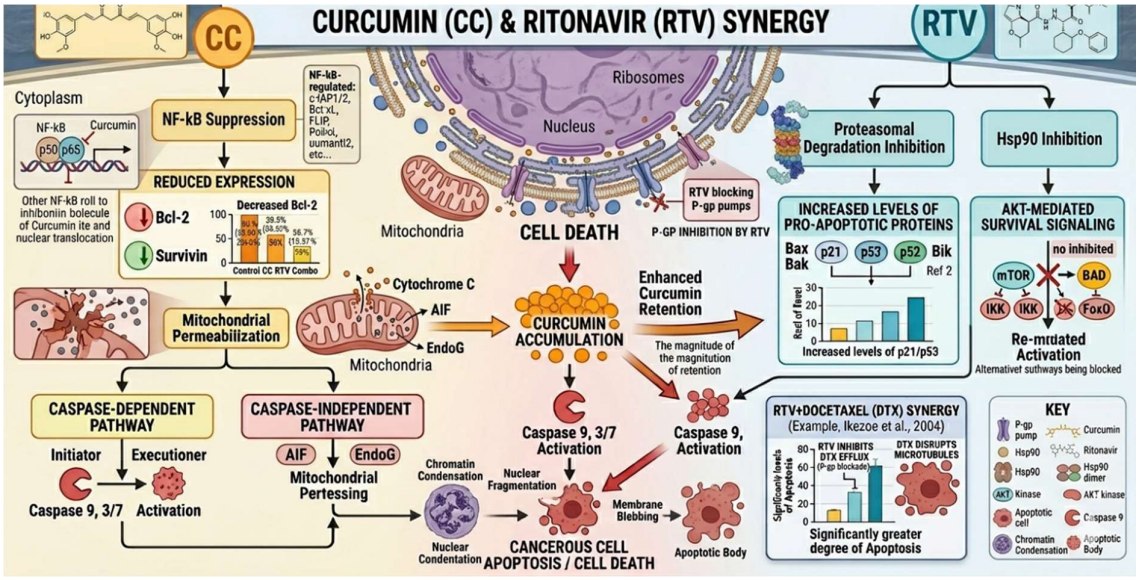

Fig 8:- *Enhanced apoptosis signaling*

ROS-mediated cytotoxicity

Production of cytotoxicity via ROS. In cancer cells, both ritonavir and curcumin are capable independently of stimulating ROS production. Curcumin stimulates apoptosis receptor expression through a process involving redox reactions; and causes alterations in mitochondrial membrane permeability (Mortezaee et al., 2019). Ritonavir creates oxidative stress that can alter the ability of tumor cells to migrate, invade, and maintain DNA integrity (Pomella et al., 2025). It is proposed that the cumulative effects of these ROS-generating mechanisms will exceed the antioxidant capacity of cancer cells, ultimately leading them to a state of uncontrollable apoptosis; yet, there were no direct empirical findings located in my search for experimental support demonstrating a curcumin-ritonavir synergy with respect to their combined effect on ROS production in this way.

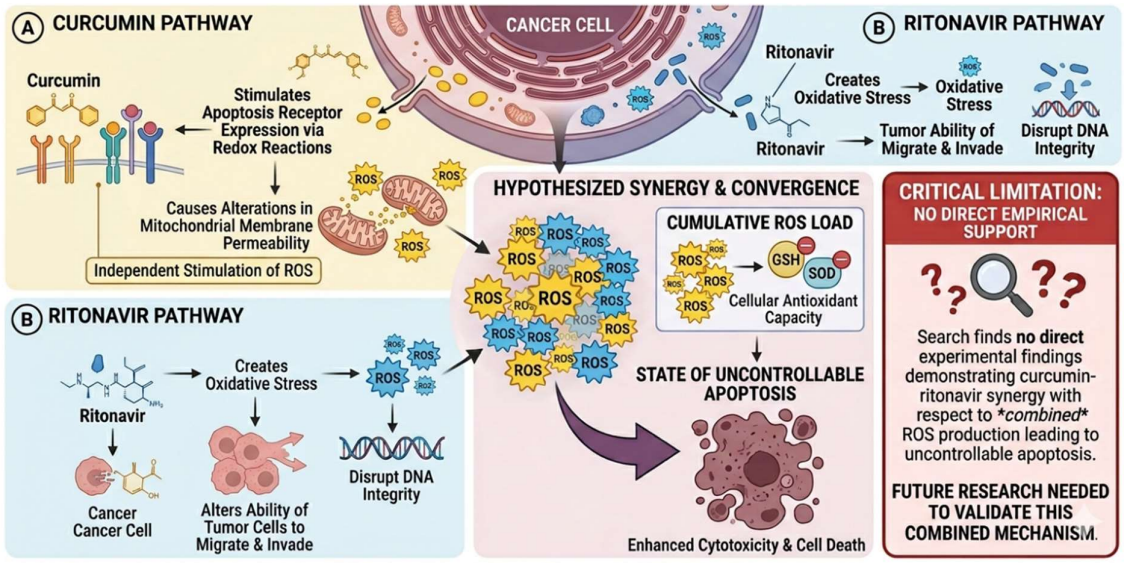

Fig 9:- *ROS-mediated cytotoxicity*

Reversal of MDR

Multidrug resistance (MDR) continues to be a principal barrier to successful cancer treatment. Curcumin and ritonavir have been shown to act on key molecular mechanisms involved in the development of MDR. Curcumin down-regulates the expression of many of the molecular mediators of MDR including MDl, BCRP, and LRP, making it a more effective chemosensitizer when combined with standard chemotherapy agents such as cytarabine (Shah et al., 2015). Curcumin also serves as a P-glycoprotein inhibitor, and therefore diminishes the efflux of drugs and increases drug accumulation within the cells of drug-resistant tumor models (Peng et al., 2018). Ritonavir inhibits P-glycoprotein and CYP3A4 enzymatic activity simultaneously, thereby inhibiting both drug efflux and drug metabolism, leading to dramatically reduced proliferation rates and enhanced apoptosis in drug-resistant breast cancer and prostate cancer cells (Vadlapatla et al., 2014). Taken together, the combination of curcumin and ritonavir's actions of targeting the mechanisms by which drugs are removed from the body, the mechanisms by which drugs are chemically altered by the body and the pathways associated with the development of drug resistance provides a strong rationale for their synergistic ability to reverse MDR in cancer; however, this hypothesis will need to be verified in future experiments with human skin carcinoma models.

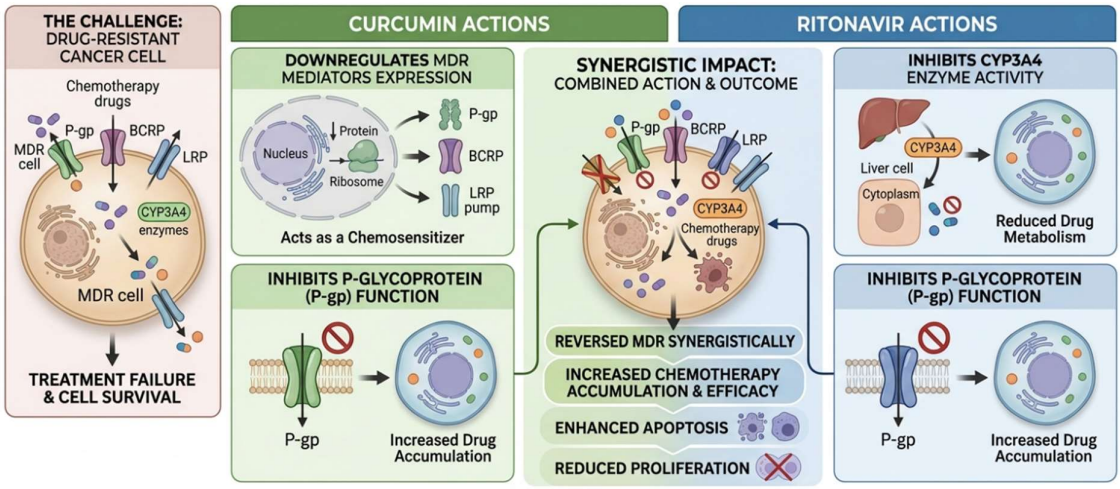

Fig 10 :- *Reversal of MDR*

5. Nanocarriers for Co-Delivery Systems

5.1 Types of Nanocarriers

Liposomes

Liposomes are spherical vesicles composed of phospholipid molecular sheets and hold both a watery and lipid-based core, giving them the ability to encapsulate hydrophilic drugs in their watery core and hydrophobic drugs in their sheet/lipid core (Corte-Real 2024). Corte-Real et al. (2024) evaluated the use of dual-loaded liposomal goods utilizing anti-cancer treatments like doxorubicin, 5-fluorouracil, curcumin and resveratrol, indicating increased anticancer activity, targeted delivery, and fewer side effects than equivalent single-drug products.

PEGylated nanocarriers loaded with curcumin have demonstrated potential for treating skin cancer; Abdel Fadeel et al. (2020) evidenced that PEGylated lipid nano-carriers resulted in double the curcumin body deposition upon the skin compared to free curcumin and demonstrated greater cytotoxic activity against A431 human skin cancer cells compared to the free form when used in photodynamic therapy through blue-light irradiation.

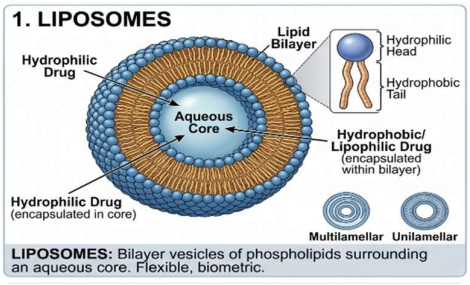

Fig 11:- *Liposomes*

Niosomes

Niosomes are vesicles formed from surfactants that are based on non-ionic surfactants. They are less expensive, more chemically stable, and easier to produce in large quantities than liposomes (Bashkeran et al., 2023). Numerous studies have been completed to examine the use of curcumin-loaded niosomes as a means to provide cancer therapy; Bashkeran et al. (2023) stated that niosomal encapsulation of curcumin improves its absorption into cells and prolongs excretion. Naderinezhad et al. (2017) created a hybrid LipoNiosome system to deliver doxorubicin and curcumin simultaneously with pH-sensitive sustained release, high entrapment efficiency (~80% for each drug), small diameter (~42 nm), and synergistic cytotoxicity that exceeds the 40% increase seen with free drugs when used on cells from cancers. Saharkhiz et al. (2023a) compared the use of co-administration versus co-loading of doxorubicin and curcumin in pH-responsive niosomes and found that co-loaded niosomes produced 79% cancer cell death compared to 39–43% death in the case of either drug alone.

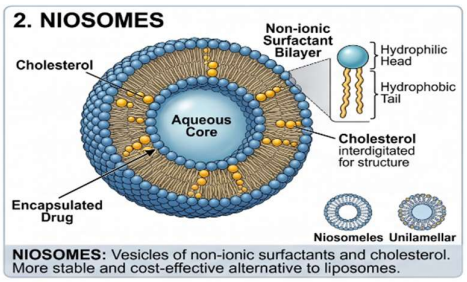

Fig 12:-Niosomes

Polymeric Nanoparticles

Nanoparticle Formulations Using Biodegradable Polymers. Several examples support the use of biodegradable polymers (e.g., PLGA, chitosan, and PEG-PCL) as building blocks for polymeric nanoparticles. These materials provide the ability to produce nanoparticles with altered size, good encapsulation efficiency, and sustained release properties (Miao et al., 2017). For example, nanoparticles made from PEG-b-PCL block copolymers and used for the formulation of ritonavir had a mean particle size of approximately 96 nm and an encapsulation

efficiency of approximately 92% while also enhancing oral bioavailability when compared with non-formulated ritonavir (as reported by Zhang et al. in the Journal of Carcinogenesis in 2025). Sivák and colleagues (2021) created a pH-responsive nanomaterial composed of HPMA copolymeric conjugates of ritonavir, which demonstrated significant anti-tumor efficacy in vivo through (i) pH-sensitive drug release, (ii) proteasome inhibition, and (iii) reduced STAT3 levels; all of these effects resulted in negligible systemic toxicity. Mangalathillam and coworkers (2012) produced chitin-based nanogel formulations (i.e., 70-80 nm sized) that delivered curcumin to high selective toxicity against A375 human melanoma cells and provided a 4-fold increase in the flux of curcumin across the skin when compared to undiluted curcumin solution.

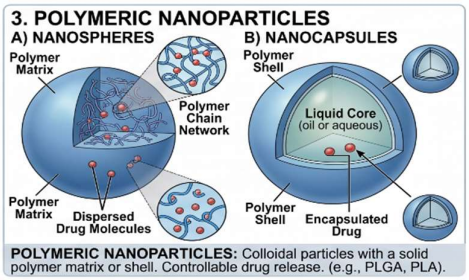

Fig 13:- *Polymeric Nanoparticles*

Solid lipid nanoparticles (SLNs)

Lipid Nanoparticles (LNPs) are composed of solid lipids and are used to combine the benefits of both lipid-based emulsions and polymer materials. LNPs can be produced using more standard manufacturing processes and provide controlled release of drugs, are compatible with biological materials, and can be produced in large quantities (Akanda, 2015). When loaded with ritonavir, LNPs have shown the potential for particle sizes of 270 nm or 3.5 times more than that for free ritonavir suspension, an entrapment efficiency greater than 94%, and a permeability coefficient greater than 3.5 times that of free ritonavir suspension (Guptha et al., 2025). Furthermore, the use of PEGylated LNPs containing ritonavir has also been shown in rat models to provide prolonged systemic circulation and improved pharmacokinetic parameters (Pavan et al., 2019). In addition, the use of curcumin-labeled LNPs prepared from tristearin or stearic acid demonstrated an encapsulation efficiency of 92% to 95% and sustained drug release for more than five days, and resulted in the reduction of LNCaP prostate cancer cell viability at 100 µg/ml to almost zero (Akanda, 2015). Dual LNPs have been investigated as an effective strategy to deliver two different agents in combination for treating prostate cancer, due to the EPR effect and the ability to target specific cells using the binding presence of a specific ligand (discussed in greater detail in an article published in the Journal of Carcinogenesis in 2025).

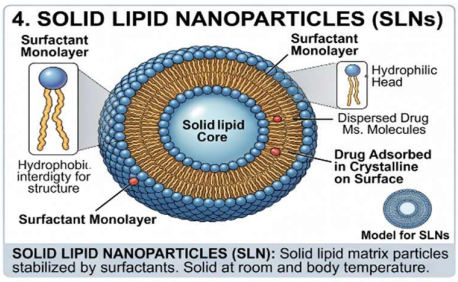

Fig 14:- *Solid Lipid Nanoparticles*

Nano-emulsions

Nano-emulsions are colloidal dispersions with droplet sizes generally smaller than 200 nm that are either thermodynamically stable or kinetically stable and have been found to increase the solubility and skin absorption of lipophilic compounds (Rachmawati et al., 2014). Curcumin with nano-emulsions produced using the process of self-nano-emulsification have been shown to produce droplets with a mean diameter of about 85 nm, increase rates of transdermal permeation, and provide protection from chemical degradation (Rachmawati et al., 2014). Furthermore, Agame-Lagunes et al. (2020) showed in a skin carcinogenesis animal model that nan-emulsified curcumin with modified phosphatidylcholine stabilized produced a 91.8% reduction in the tumorigenesis index and an 89.9% reduction in the tumor areas compared to untreated control groups that were treated with unmodified phosphatidylcholine nan-emulsified curcumin. Additionally, another study showed that curcumin-loaded nanoemulsions with approximately average droplet diameters of about 16 nm had shown to successfully penetrate into the viable layer of the epidermis with little toxicity to cultured human skin Fibroblasts (Saari et al, 2020).

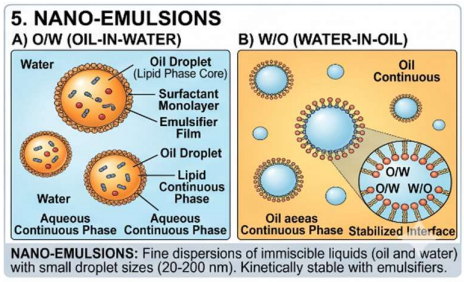

Fig 15:- *Nano-emulsions*

5.2 Advantages of Co-Loading

Improved solubility (both drugs are poorly soluble)

Both drugs are both poorly soluble. Examples include curcumin and ritonavir, both exhibit extremely poor solvents and therefore limited bioavailability and clinical efficacy when given as free drugs (Ratan et al., 2023). The poor water solubility and instability of curcumin and the low absorption through the skin limit its ability to be used as a clinical agent (Ratan et al., 2023). Ritonavir has a low level of bioavailability, indicating that additional delivery systems must be developed to attain pharmacologically relevant blood levels (Guptha et al., 2025). Previous studies demonstrated that an encapsulated nanocarrier system could resolve the water solubility issue. For example, polymeric nanogel systems have been reported to improve the

solubility and oral bioavailability of many hydrophobic drugs (i.e., paclitaxel) using the same strategies for the curcumin-ritonavir combination (Senanayake et al., 2014); therefore, coencapsulation (in a single nanocarrier system) will provide both poorly soluble agents with the opportunity to reach the tumour site at pharmacologically relevant concentrations (Miao et al., 2017).

Controlled release

Controlled release: Sustained and controlled delivery of drug from nanocarrier systems are essential to maintain prolonged therapeutic levels and avoid peak-associated toxicities of drugs (Fumoto and Nishida, 2020). Niosomal formulations that are pH-sensitive have exhibited accelerated release of drug from niosomes at acidic tumor pH (4.5–6.5) compared with physiological pH (7.4) due to their ability to selectively release drug at the tumor site (Saharkhiz et al., 2023b). The release of curcumin-loaded SLN's was sustained over five days (Akanda, 2015), while ritonavir-loaded SLN's produced a controlled release pattern following the Korsmeyer-Peppas model of non-Fickian diffusion (Guptha et al., 2025). Smart dual-stimuli responsive nanoparticles can further refine release profiles through pH-redox, pH-photo and temperature-magnetic triggers, thus allowing for precise spatiotemporal delivery of drug (Wu et al., 2020).

Targeted delivery

Nanocarriers can be developed to selectively target tumours both passively and actively. Passive targeting takes advantage of the enhanced permeability and retention (EPR) effect observed in the blood vessels of tumours, resulting in increased concentrations of nanoparticles at the tumour site (Miao et al., 2017). Active targeting occurs via the conjugation of ligands to the surfaces of nanoparticles, such as transferrin or folic acid; or via specific aptamers that bind to tumour cells (Tavano et al., 2016). Tavano et al. (2016) successfully demonstrated that transcional(fo-2)nanocarriers significantly increased the amount of cellular uptake of both doxorubicin and curcumin when conjugated to transferrin or folic acid, compared to non-conjugated carriers of these drugs, in two different breast cancer cell lines; MCF-7 and MDA-MB-231. In special case, skin tumours have a unique benefit due to their accessibility by topical and transdermal dosage forms composed of nanoemulsions and nanogels of curcumin; which resulted in selective localisation to intact skin epithelium. (Mangalathillam et al., 2012; Paganini et al., 2025).

Reduced systemic toxicity

Co-loaded nanocarrier systems offer a significant benefit in that they can reduce the toxicity seen in the body by administering medications directly to where they are needed, and using less of each drug. Since both medicines are administered via the same nanocarrier, they will simultaneously enter the same tumor cell, providing greater synergy (Sun et al., 2016). Sivák et al. (2021) describe that their polymer-ritonavir nanomedicine did not have any adverse effect on tumor-bearing mice, but provided powerful antitumor effects. Martin et al. (2015) demonstrated that using ritonavir as solid drug nanoparticles provided lower cytotoxicity in hepatic, intestinal and immune cells

compared to utilizing aqueous ritonavir solutions and also provided greater inhibition of CYP3A4 enzyme. Therefore, by reducing the specific amount of drug required to achieve therapeutic results due to the synergistic nature of the combination and targeted delivery of the drugs, co-loaded nanocarriers have the capacity to significantly reduce the side effects caused by traditional systemic chemotherapy (Fumoto & Nishida, 2020).

6. Design Considerations for Co-Loaded Nanocarriers

6.1 Physicochemical Properties

Particle size

Size of the particles is one of not only the most important variables in determination of biodistribution, uptake by the cells and accumulation in tumours of nanoparticle carriers; but also, Öztürk, et. al. demonstrated with extensive and well-supported evidence (2024) that size of the nanoparticles is significantly affected by circulation time, ability to target cells, and ability to be taken up by cells. Generally speaking, nanoparticles that have a size between 10 and 200 nanometres are considered optimal for targeting the Enhanced Permeability and Retention (EPR) effect that is observed when localising to a specific vascular system within a tumor. For the skin cancers specifically, smaller nanoparticle will help penetrate and provide access to the deeper layers of skin. Patel and co-workers (2025) have published reviews as well and determined, again based on optimal particle size in general, that the optimum particle size for anticancer drug delivery is between 10 and 200 nanometres and varies based on the drug formulation itself as well as the characteristics of the target cells and must be determined through systematic optimization and characterization of the specific nanoparticle carrier formulation.

Surface charge

Surface charge. The surface charge of a particle (measured by the zeta potential) influences how stable a nanocarrier is in solution, how well it will be taken up into cells, and how well it will distribute throughout the body. Positively charged nanoparticles generally have a greater chance of being taken up by cells via electrostatic attraction due to their interaction with the negative charge of the cell membrane than do negatively charged nanoparticles, however, positive charged nanoparticles may also interact with blood components and be rapidly cleared (Saadat et al. 2019). In contrast, negatively charged and neutral particles typically exhibit longer circulation times than do positively charged particles are usually have lower rates of cellular internalization (Öztürk et al. 2024). A more sophisticated approach to achieving both prolonged blood residence time and increased uptake at tumor sites is with the design of pH-sensitive nanoparticles that show charge reversal properties where they have an overall negative charge while circulating in the bloodstream and a positively charged when they encounter an acidic tumor microenvironment (Saadat et al. 2019). Values of zeta potential between -30mV to +30mV demonstrate ideal conditions for maintaining a stable colloidal solution of the particles; (Patel et al. 2025).

Encapsulation efficiency

To maximize the drug payload and reduce the wasted materials during the manufacturing phase, you need to have a

high encapsulation efficiency. There is a unique challenge to achieve a high encapsulation efficiency of both drugs when co-loaded because of the two different physicochemical properties of the agents being co-encapsulated (Miao et al 2017). Ghosh et al (Ghosh et al 2022) have systematically investigated important characteristics of co-loaded nanoliposome formulations affecting the encapsulation efficiency to demonstrate that three specific formulation parameters influenced the overall encapsulation efficiency; the concentration of transmembrane gradient, pH of drug loading and lipid to molar ratio; they obtained a total encapsulation efficiency greater than 95% from their optimized doxorubicin – vincristine co-loaded formulation. Another significant variable affecting encapsulation efficiencies is the drug-to-polymer ratio; Holley et al (Holley et al 2018) showed that decreasing the drug-to-PLGA ratio increased encapsulation efficiency without any significant difference in particle size or surface potential.

Drug ratio optimization

Optimizing the Ratio of Co-Medications. The molar ratio of drugs delivered together greatly affects their synergy, addition, or antagonism in combination therapy (Pan et al., 2019). Pan et al. (2019) conducted a literature review of polymer-based co-delivery systems and showed that drug combinations can provide very different clinical results at different molar ratios, indicating a need for systematic optimization. To help solve the historical problem associated with providing drug ratio control, Aryal et al. (2011) created drug-conjugate polymers (DOX-PLA and CPT-PLA) that could be proven capable of being mixed at predetermined ratios prior to encapsulating them into nanoparticles with more than 90% loading efficiency and ensuring that the final drug ratios of the nanoparticles were identical to their initial molar ratios. Additionally, Miao et al. (2014) demonstrated this theoretical principle using PLGA nanoparticles loaded alone with both gemcitabine monophosphate and cisplatin at an optimal ratio of five parts gemcitabine monophosphate to one part cisplatin (mol:mol), resulting in a substantially greater suppression of tumor growth than either drug alone (a standard formulation) when tested on a bladder cancer mouse model.

6.2 Drug Loading Strategies

Co-encapsulation vs. surface conjugation

Methods of loading multiple drugs into nanocarriers include co-encapsulation and surface conjugation to surface of nanocarrier. Co-encapsulation is the act of physically trapping the drug in either the core of the nanocarrier or in the lipid bilayer of the nanocarrier where it protects the drugs from being degraded before released, as well as allows for the controlled and simultaneous release from the nanocarrier (Bhattacharjee, 2022). However, Bhattacharjee (2022) points out that because of the closeness of the co-encapsulated drugs to one another within a confined three-dimensional nanoscale space, unexpected events such as molecular rearrangement, aggregation and denaturation may take place which can negatively affect the therapeutic benefits of the drugs. In comparison, surface conjugation involves the covalent or electrostatic attachment of one drug to the surface of the nanoparticle while the second

drug is encapsulated in the core of the nanoparticle (Saha et al., 2016). A case study of this strategy is provided by Saha et al. (2016) who loaded quercetin into a PLGA nanoparticle and conjugated adriamycin and/or mitoxantrone to either a BSA- or histone-coated surface of the PLGA nanoparticle. This format of delivering two drugs that are chemically separated, and therefore have different release kinetics, results in additional complexity of surface chemistry and may change the biodistribution of the nanocarrier (Tran & Tran, 2019). Another option for loading two drugs into one nanocarrier is a hybrid of drug-polymer conjugation (Aryal et al.,2010).

Sequential vs. simultaneous release

The release of co-load drugs in sequence or simultaneously can have a major impact on drug effectiveness. The delivery of drugs simultaneously allows both drugs to reach the tumour at the same time; this is helpful when both drugs are acting on the same pathway in a synergistic manner, or when one of the drugs makes the tumour cells sensitive to the other (Qi et al., 2017). The use of sequential release strategies has recently become an advanced alternative to simultaneously co-loading drugs and has been suggested as a way to improve sensitivity of cancer cells to a drug that is released subsequently, alter the tumour vascular structure, or overcome particular antibiotic resistance mechanisms (Li et al., 2023). In their review of nano-enabled sequential drug combinations for use in cancer, Shim et al. (2017) proposed that by carefully manipulating the way the dosage is applied through the sequential application of drugs, that the spatiotemporal needs of the drugs would be satisfied and that this approach should produce better anti-tumour effects than simply administering the drugs together. In their discussion of systems of nanomedicine that can be programmed to take advantage of stimuli-responsive release properties for sequential release, Pacardo et al. (2015) concluded that this type of sequential release would produce less drug resistance, lower therapeutic doses, and delivery that is spatiotemporally controlled. In a proof-of-concept study, Kumar et al. (2015) developed multi-layered manganese ferrite magnetic nanoparticles that released tamoxifen from their outer layer when the pH of the tumours decreased and then released diosgenin from within the nanoparticles.

6.3 Stability Considerations

Drug-drug interaction inside carrier

The rise of drug biotechnology has allowed researchers to discover how to create effective combinations of drugs that are then suspended in a single formulation (such as an injectable, oral, or inhalable). Drug delivery systems (nanocarriers) are essential for using multiple medications simultaneously; however, they can also deteriorate co-loaded therapeutics because of possible interactions between the drugs within the carrier space. Bhattacharjee (2022) notes that co-encapsulated therapeutic molecules may have unpredictable fates due to their proximity and, consequently, such intimate relationships among these entities could result in disruption of their molecular structure (e.g., rearrangement of the molecules), aggregation, and denaturation, requiring that the co-encapsulated nanocarrier aims to create an environment where the encapsulated molecules can

harmoniously coexist. Liu et al. (2022) studied drug-drug interactions between daunorubicin and cytarabine within drug-loaded liposomes and proposed that the interaction between drug molecules and metals (copper gluconate) would enhance retention of the drugs and provide for mellifluous release patterns, thus illustrating how drug-drug interactions can be advantageous to the performance of such a carrier even though they may involve both positive and negative outcomes. Bickerton et al. (2012) demonstrated the relationship between the structure of nanocarriers, loading capacity, and the stability of encapsulation, with the increased loading of a therapeutic or combination of therapeutics resulting in decreased stability of encapsulation because of increased interactions among the molecules of the drug inside of the hydrophobic core of the nanocarrier. The co-encapsulated system of curcumin and ritonavir in a hydrophobic compartment might develop vibrational or hydrophobic interactions generated from the two lipophilic drugs co-encapsulated with one another and these interactions could reposition crystals and impact the release kinetics of the co-encapsulated system. Thus, all of these possibilities will require significant study to develop proper formulations for this drug-drug interaction.

Storage stability

The stability of stored products is important to ensure a successful clinical study of the co-loaded nanocarriers. For example, Loo et al. (2023) looked at how stable the curcumin- and quercetin-loaded nanoparticles were over three months when co-stabilized with polyvinylpyrrolidone and stored at 25°C/60% RH vs 40°C/75% RH, finding that higher concentrations of co-stabilizer must be used for maintaining drug content and antioxidant activity. Additionally, Schelker et al. (2025) conducted a systematic study of stabilization methods for co-encapsulated liposomal formulations and found that significant amounts of drug lost occurred at 4°C during storage, leading them to pursue the use of freeze-drying and subsequently develop sucrose at a 10% (w/v) concentration as the best cryoprotectant for preserving liposome sizes that would maximize the EPR effect. Chroni et al. (2023) demonstrated that curcumin-loaded PnBA-b-POEGA nanocarriers exhibited excellent stability after being stored for 210 days, which was due to optimal intermolecular drug-polymer interactions as measured by complete 2-D NMR. Therefore, the selection of storage conditions (temperature, relative humidity, and use of lyophilization with cryoprotectants) represents an important design factor that should be optimized to achieve the intended shelf-life of each co-loaded formulation (Olerile, 2020).

7. Mechanisms of Nanocarrier-Mediated MDR Reversal

Multidrug Resistant cancer (MDR) is one of the greatest barriers to the effective use of chemotherapy; multiple mechanisms play a role in the development and maintenance of MDR, including but not limited to overproduction of ATP-binding cassette (ABC) efflux transporters, malfunctioning apoptotic mechanisms, enhanced intracellular drug detoxification, and modification of drug targets (Kapse-Mistry et al., 2014). Nanocarrier-based drug delivery systems can serve as an effective and versatile approach to overcoming MDR by utilizing multiple mechanisms of action;

both at the tissue and cellular levels, these systems can operate synergistically (Moon et al., 2015).

- **Enhanced intracellular accumulation**

Nanocarriers can help to restore drug sensitivity by increasing the amount of anti-cancer medication inside cancer cells that have developed a resistance to the drugs. In a study, Wang et al. (2011) used doxorubicin (an anti-cancer medication) that was delivered by a gold nanoparticle to demonstrate that it was taken up into the MDR MCF7/ADR cell line at significantly higher levels than free doxorubicin after the drug was delivered to the cells. The treatment was also shown to significantly increase cytotoxicity (by inducing cells to die) and apoptosis (by inducing cells to die) in the drug-resistant cells. Pilapong et al. (2014) demonstrated that doxorubicin-loaded magnetic nanoparticles could be delivered to drug-resistant cancer cells at much higher levels compared to free doxorubicin and that drug release was pH-dependent (favoring drug release in the acidic tumor microenvironment). Wong et al. (2006) demonstrated that polymer-lipid hybrid nanoparticles (PLNs) were effective as delivery vehicles to P-glycoprotein (P-gp) overexpressing drug-resistant breast cancer cells by demonstrating that the nanoparticles produced a significantly greater uptake and retention of doxorubicin than did free doxorubicin following cessation of treatment. The accumulation of drugs via nanoparticles into the cells, however, is through different pathways (endocytosis) compared to free doxorubicin (diffusion across the plasma membrane through efflux pumps; Kirtane et al., 2013).

- **Bypassing efflux pumps**

Evasion of efflux pumps has been shown to occur through two primary strategies with Nanocarriers; these include direct efflux pump inhibition as described by Halder et al. (2021) and physical bypassing of the pump. Direct inhibition of efflux pump function has been extensively studied focussing on P-glycoprotein (P-gp), the most prevalent ABC transporter associated with multidrug resistance (MDR) due to its active transport of chemotherapeutic agents out of cancer cells below therapeutic concentrations (Halder et al. 2021). A well-cited example was demonstrated by Singh & Lamprecht (2015); the incorporation of P-gp inhibitors, verapamil and elacridar, into cationic nanoparticles significantly increased MDR reversal, with the cationic CTAB nanoparticles containing elacridar achieving an overall 193-fold lower IC50 compared to doxorubicin alone in resistant ovarian cancer cells. Liu et al. (2020) created a sequentially responsive nanosystem containing cationic β-cyclodextrin-PEI gatekeepers that decreased P-gp efflux activity via inhibition of ATP production and also provided efficient drug delivery, achieving multi-faceted MDR reversal in vitro and in preclinical tumor models without systemic toxicities. Lipid-based nanoparticles also offer an additional benefit in that excipients often used to prepare lipid-based nanoparticles (e.g. surfactants & amphiphilic copolymers) can independently inhibit P-gp function and provide MDR reversal even in the absence of a chemosensitising agent (Tammam, 2017).

- **Endocytosis-mediated uptake**

Uptake of Nanoparticles via Endocytosis: The Majority of cancer cell uptake of nanoparticles is mediated by energy-dependent pathways such as clathrin-mediated endocytosis, caveolae-dependent endocytosis, or macropinocytosis, as opposed to occurring passively through diffusion through the plasma membrane (Cong et al. 2022). This distinction is important when considering MDR reversal due to the fact that free drug contained within cells via passive diffusion must first pass through the plasma membrane, where it will be recognised and expelled by membrane resident ABC transporters (Shapira et al. 2011). In contrast, when nanoparticles bind specific receptors and enter the cell via receptor-mediated endocytosis, the drug contained within the nanoparticles enters the cell enveloped within endosomal vesicles, thus bypassing first contact with P-gp at the cell surface (Pandhare et al. 2015). Furthermore, Wong et al. (2006) used endocytic inhibition studies to illustrate that phagocytosis is a major pathway by which P-gp-overexpressing cells internalise nanoparticles, suggesting that drugs that are physically associated with nanoparticles can bypass P-gp at the cell surface. Additionally, Singh and Lamprecht (2015) illustrated that nanoparticle uptake was primarily caveolae-dependent for resistant cancer cells compared to non-resistant cancer cells (approximately 20% more), which correlate with differing biophysical membrane compositions of resistant versus non-resistant cancer cells (Peetla et al. 2013). Li et al. (2024) performed a comprehensive review on emerging design strategies focusing on nanoparticle endocytosis and demonstrate that an understanding of the mechanisms that control nanoparticle uptake into cancer cells via endocytotic pathways would provide valuable insights into future effective strategies designed to bypass, or reverse, MDR.

- **Lysosomal escape**

Lysosomal escape is essential to the efficacy of drug delivery to targets within the cell as nanoparticles are generally internalized into a cell via the endocytic pathway and are ultimately routed through the endo-lysosomal pathway where degradation of both the drug carrier and drug occurs due to the acidic environment and presence of a wide range of degrading enzymes (Qiu et al. 2023). Therefore, it is important to devise effective strategies to ensure escape from endosomes and lysosomes occurs to ensure successful delivery of drugs intracellularly and to reverse multidrug resistance (MDR). Qiu et al. (2023) provided a thorough evaluation of various strategies presented in the literature for overcoming endosomal and lysosomal barriers, which include proton sponge effect (PSE) of cationic polymers, fusogenic lipid-mediated destabilization of the endosomal membrane, and photochemical disruption of endosomal membranes. Moreover, Li et al. (2013) performed investigation of lipid/nanoparticle assemblies produced by wrapping a DMAB modified PLGA core with a DPPC shell via lipid raft/caveolae-mediated endocytosis, which resulted in lysosomal escape of the nanoparticles allowing for diffusion of released drug into the nucleus hence effectively reversing MDR. In addition, Smith et al. (2018) demonstrated the proton sponge mechanism by which cationic polymers such as polyethyleneimine (PEI) buffer the

acidifying endosome resulting in osmotic swelling of the endosomes subsequently resulting in membrane disruption and ultimately releasing the nanoparticle payload into the cytosol. Furthermore, Chen et al. (2022) took advantage of the acidified endo/lysosomal compartments characteristic of cancer cells and developed pH-sensitive polymeric nanocarriers with endosomal escape potency that were capable of selectively delivering drug into the cytosol of cells.

- **Tumor-targeted delivery**

Tumor targeting with Nanocarriers: There is passive and active tumortargeting using nanocarrier, each having an important impact on increasing drug levels at the tumor site while reducing drug levels in the rest of the body (Hirsjärvi et al. 2011). Passive targeting uses the enhanced permeability and retention (EPR) phenomenon that occurs with solid tumors (Milane et al. 2011). Tumors have leaky blood vessels and less functioning lymphatics, which provides a unique opportunity for the accumulation of nano-sized carriers to be selective in reach the tumor (Milane et al. 2011). In addition, Milane et al. (2011) suggested that the preferential accumulation of nanocarriers within a tumor by using the EPR phenomenon and the ability of nanocarrier to divert the impact of drug efflux via the ABC-transporter makes nm carriers the most useful treatment option for cancer patients with multidrug resistance (MDR). Tumor targeting with active targeting also increases the selectivity of the nanocarrier based on the use of surface ligands (e.g. antibodies, peptides, aptamers, folic acid or transferrin) to bind the upregulated receptors on tumor cells, which facilitates receptor-mediated endocytosis and ultimately produces a greater cellular uptake of active drugs (Jabr-Milane et al. 2008). Liu et al. (2021) discussed three approaches to MDR reversal using nanomedicine: co-treatment with drugs and ABC transporter inhibitors; circumvention of efflux pumps mediated by nanoparticles through targeting the organelles directly; and the use of multiple therapeutic modalities. Han et al. (2023) provided details of current studies involving dual-targeted (tee) nanomedicine that target two different tumor-specific characteristics, and have demonstrated greater effectiveness than previously described using any other single treatment option.

8. In Vitro and In Vivo Studies

8.1 In Vitro Models

8.1.1 Skin Cancer Cell Lines

Many different types of skin cancer cell lines have been studied extensively as in vitro test systems for the evaluation of curcumin-loaded nanocarriers. However, the two most common skin cancer cell lines used are A375 (human melanoma) and B16-F10 (murine melanoma). The A375 cell line, which was created from a human malignant melanoma, is an appropriate in vitro test system for evaluating the sensitivity of human skin cancers to anti-cancer agents (Michel et al., 2012). The B16-F10 cell line, which is a highly metastatic subclone of B16 and was created from a mouse melanoma, is commonly used as both an in vitro test system for assessing cytotoxicity of an agent and as a source of melanoma cells for subsequent in vivo transplant studies in syngeneic C57BL/6 mice (Mazzarino et al., 2011). In addition, A431 (epidermoid carcinoma) cell lines represent non-melanoma skin cancer and

have also been used to evaluate photodynamically active nanoformulations (Jain et al., 2023). Finally, SKMEL-37 (human melanoma) cells have been used to evaluate magnetic nanoparticles loaded with curcumin (Souza, 2011).

8.1.2 Cytotoxicity Studies

Various nanocarriers with loaded curcumin have shown improved cytotoxicity toward skin cancer cells compared with free curcumin. Wang et al. (2017) created curcumin-loaded MPEG-PLA polymeric micelles, showing these nanocarriers could achieve significantly stronger cytotoxicities to both B16 and A375 human melanoma cell lines than free curcumin in vitro, while determining that these nanocarriers increased the level of apoptosis in these cell lines. Peram et al. (2019) created curcumin-loaded ethosomes by optimizing drug delivery via a factorial design, reporting significantly improved cytotoxicity and cellular uptake in A375 human melanoma cells and using flow cytometry to confirm that cell death from curcumin ethosomes was predominantly due to apoptosis. Paganini et al. (2025) reported that curcumin-loaded TPGS/Kolliphor ELP nanomicelles significantly decreased the viability of A375 cells and resulted in primary apoptotic cell death, not necrosis, indicating a more favorable therapeutic profile and less inflammatory effects and damage to surrounding tissues.

The study conducted by Abobaker et al. (2025) showed that combining iron oxide and curcumin nanoparticles with IFNα loaded in PLGA (poly(lactic-co-glycolic acid)) helps to kill A375 melanoma cells much more powerfully than using either type alone. Also, the combination had little or no effect on NIH-3T3 fibroblasts. The investigators used a combination of curcumin and chrysin encapsulated in PLGA-PEG nanoparticles (very small drug delivery systems). This combination resulted in the most significant inhibition of melanoma tumor growth when tested in B16-F10 cells relative to pure curcumin or pure chrysin (i.e., CurChr NPs >> CurChr > CurNPs > Cur > ChrNPs >> Chr).

Gaedicke et al. (2002) indicated that ritonavir reduced the growth of various tumor cell lines and triggered their apoptosis while at the same time showing lower potency in triggering apoptosis in non-transformed cells than in transformed cells. Further, work by Ikezoe et al. (2004) demonstrated that the anticancer drug docetaxel displayed enhanced apoptosis and inhibition of DU145 (non-hormonal dependent) prostate cancer cell proliferation when CD8+ T lymphocyte cell line M1152 treated with ritonavir was used in vitro. Evidence of apoptosis was shown via activation of caspase 3 and cleavage of poly(ADP-ribose) polymerase. Moreover, work by Vadlapatla et al. (2014) in T47D breast cancer cells and PC-3 prostate cancer cells demonstrated that the combination of ritonavir with anticancer agents, such as doxorubicin, paclitaxel, tamoxifen and vinblastine, significantly inhibited cell migration and proliferation, and increased apoptosis as well as caspase activation in vitro. Finally, Sivák et al. (2021) found that a derivatized form of ritonavir-XHPMA copolymer (RD) showed significant inhibitory effects on six murine and six human cancer cell lines with IC_{50} values ranging from 2.3-17.4 μM for murine, and 4.3-8.7 μM for human cancers and also inhibited cancer cell migration and invasiveness in vitro.

8.1.3 Cellular Uptake Studies

The successful delivery of drugs by way of nanocarriers is dependent on how well they can enter the target cells. Singh et al (2017) showed that curcumin-loaded Au-Lipos Cur nanoparticles had much greater cellular uptake inside B16-F10 melanoma cells than did free curcumin. Peram et al (2019) confirmed that curcumin ethosomes entered A375 cells with much greater efficacy than free curcumin via fluorescence microscopy and that the antiproliferative effects of curcumin ethosomes as measured by the ability of A375 cells to form colonies were significantly greater than those for A375 cells treated with free curcumin suggesting that curcumin ethosomes were able to inhibit the clonogenic ability of A375 cells more effectively. Ghazaeian et al (2020) also found that curcumin-silica nanoparticles had much greater photodynamic effects on A375 cells than free curcumin because of the enhanced cellular uptake from the nanocarrier system. Jain et al (2023) reported that co-delivery of curcumin and chlorin E6 in lipid-based nanoparticles had increased cellular uptake and greater inhibition of tumour growth than free formulations of each drug, as demonstrated in B16-F10 and A431 cell lines. The work of Machová et al (2018) demonstrated that the internalisation of HPMA copolymer-ritonavir conjugates into HeLa cells occurred more efficiently than via either caveolin- or clathrin-mediated endocytosis, as evidenced by co-localisation of the HPMA copolymer-ritonavir conjugate with mitochondria and the resulting significant reduction in ATP production.

8.2 In Vivo Models

8.2.1 Tumor-Bearing Mice

The effectiveness of curcumin nanocarrier products for treating cancer in live (in vivo) experiments has been researched using multiple types of tumor-bearing mice, and the most frequently utilized method has been an implantation procedure to introduce B16-F10 melanoma cells into C57BL/6 (syngeneic) mice (Mazzarino et al., 2011; Deshpande et al., 2022). Wang et al. (2017) utilized both syngeneic C57BL/6 mice with melanoma and the use of curcumin, delivered via MPEG-PLA micelles, and this study demonstrated that the curcumin delivered via the micelle had greater anti-cancer activity than the free curcumin. Mardani et al. (2020) evaluated nanomicellar-curcumin with a C57BL/6 mouse model where B16-F10 cells were injected into the lungs to establish metastases and treated with 20 mg/kg of the treatment intraperitoneally (i.p.) four times weekly for 3 weeks.

Administering ritonavir to mice by mouth inhibited the growth of pre-existing EL4/T cell thymomas (tumors) by approximately 76% to 79% after a week. Combination therapy with ritonavir and docetaxel significantly inhibited the growth of DU145 prostate cancer cell xenografts in BNX nude mice; no abnormalities were seen when histologically examined at a subsequent time point from the liver, spleen, kidneys, bone marrow, skin, and subcutaneous fat pads. HPMA copolymer–ritonavir derivative (P-RD) nanomedicine has shown great activity in inhibiting the growth of both B16/F10 melanoma and CT26 colon carcinoma in mouse models of these two disciplines; this combination shows a synergistic effect with IL-2 based immunotherapy.

8.2.2 Biodistribution

Biodistribution research is important for analyzing the efficiency of target tissue delivery for drugs using nanoparticle (NP) systems. Silvestre et al. (2023) did a systematic review of pharmacokinetics on 11 studies and established that when curcumin was administered as a nanoparticle, it accumulated in a tumor at a much higher level (increased levels) compared to free curcumin and had a better anti-cancer effect. Most curcumin NPs studied to date improved the area under the curve (AUC) 1.3-5 times than free form (Bagheri, 2021). Kianamiri et al. (2025) demonstrated that a mitochondria-targeted curcumin dendrimer nanocarrier (TDC) showed significantly increased accumulation in tumor and liver tissue compared to free curcumin after systemic administration. Jitta et al. (2023) characterized ritonavir-NP lipid carriers (NLCs) and found that animals who received NLCs had more than 2.5 times increased AUC than controls (subjected to the blockade of chylomicron flow), thus exhibiting lymphatic uptake. Biodistribution studies with ritonavir NLCs indicated greater drug levels in lymphoid organs than in all other types of tissues, which indicates that NP formulation could lead to a preferential redirection of the distribution of ritonavir to immunologically active tissues.

8.2.3 Tumor Regression Studies

Tumor regression has been documented in several studies when curcumin is delivered via nanocarriers. Deshpande et al. (2022) found that C57BL/6 mice with B16-F10 melanoma tumors treated with seven alternate doses (40 mg/kg) of ZnO-curcumin nanocomposite had decreased tumor size compared to untreated controls; their data are based on TUNEL assays and Ki-67 staining, indicating a high number of apoptotic cells and low numbers of proliferating cells within the tumors. Mardani et al. (2020) reported that treatment of mice with nanomicellar-curcumin (20 mg/kg) used to induce lung metastases in a melanoma model delayed tumor cell proliferation and improved survival; furthermore, they observed that treatment reduced the infiltration of regulatory T cells into the tumor, angiogenesis in the lung and elevated the expression of IFN-γ and CXCL10. Camargo et al. (2018) demonstrated curcumin-loaded BSA (bovine serum albumin) nanoparticles had greater antitumor activity in a murine melanoma model than free curcumin, even though in vitro free curcumin exhibited greater cytotoxicity; thus, improved pharmacokinetic characteristics and biodistribution are very important for in vivo administration of curcumin.

According to a study performed by Agame-Lagunes et al. (2020), the administration of curcumin (nanoemulsions) in K14E6 transgenic mice resulted in an incredible decrease of 91.81% in the tumorigenesis index and 89.95% reduction in tumor volume when compared to the non-treated group. The histological analysis of the two groups showed that the free curcumin-treated mice developed microinvasive squamous cell carcinoma, while the nanoemulsion treated mice developed slight inflammation. Mazzarino et al. (2011) found significant reductions in tumor volumes after administering curcumin through the use of nanocapsules (6 mg/kg twice weekly for 21 days), in animals with subcutaneous B16-F10 melanoma.

8.3 Key Findings: Enhanced Efficacy of Co-Loaded Systems Versus Single Drugs

The combined preclinical and clinical findings indicate that a co-delivery of two different anticancer agents in one carrier system will produce a greater effect than using either drug alone. For example, Abobaker et al., 2025, scnD that the curcumin and IFNa nanocapsules showed a synergestic ctytoxtc effect in killing A375 melanoma cells compared to the use of either drug given separately. Tavakoli et al., 2018 demonstrated that co-loaded CUR and CHR PLGA-PEG nanoparticles inhibited the growth of B16-F10 melanoma tumours in C57BL/6 mice more than either CUR or CHR nanoparticles, and also reduced the expression of MMP-9, MMP-2, and TERT genes, while increasing the expression of TIMP-1 and TIMP-2. Jain et al., 2023 reported that co-loaded CUR and Chlorin e6 lipidic nanoparticles produced a synergistic effect in terms of 80% skin permeation and marked induction of apoptosis in both B16-F10 and A431 cell lines, when compared with either CUR or Chlorin e6 alone.

Ikezoe et al. (2004) showed that the combination of docetaxel and ritonavir (RTV) significantly inhibited the growth of tumor xenografts when compared to treatment by either docetaxel or ritonavir alone with RTV completely inhibiting the CYP3A4 expression that is induced by docetaxel and also inhibiting the NF-kappaB (NF-κB) DNA binding activity, both of which contribute to resistance to docetaxel. Vadlapatla et al. (2014) supported that the combination of ritonavir and an anticancer drug in cancer cells decreased the expression of efflux transporters (that cause chemosensitivity) and metabolic enzymes (that cause chemosensitivity) which resulted in increased therapeutic exposure for the cancer cells. Sivák et al. (2021) demonstrated that a polymer-bound RTV derivative acted synergistically with IL-2 based immunotherapy in both CT26 and B16-F10 tumor models and showed no toxicity when both were used together.

No research has shown the co-loading of the curcumin and ritonavir in a single nano-system to treat skin cancer. However, the data provided in this paper from similar co-loaded nanocarrier systems and unco-loaded curcumin and ritonavir studies provide both mechanistic and empirical support for the rationale in creating such a vehicle. This data from the demonstrated complementary mechanism for curcumin (i.e. inhibition of NF-κB and pro-apoptotic activity) and ritonavir (i.e. proteasome inhibition, blockade of CYP3A4 and modulation of efflux transporters); together with the preceding data demonstrating enhanced efficacy of the dual-drug nano-systems create a powerful argument for the creation of a co-loaded curcumin/ritonavir nano-system to achieve synergy in anti-cancer activity against drug-resistant skin carcinoma.

9. Topical vs Systemic Delivery Approaches

9.1 Skin Penetration Challenges

The skin forms a very strong barrier to all types of drug delivery, particularly because of the stratum corneum (SC) which lies beneath the surface of the skin. The SC is a dense matrix of lipids and proteins that is approximately 10 to 20 microns thick. The SC serves as a major reason why hydrophilic and lipophilic molecules (including anticancer drugs such as curcumin and ritonavir) do not penetrate

through the SC (Vitorino et al., 2015). Current topical formulations such as creams, gels, and ointments are often only able to stay in the upper epidermal layer and do not allow for deeper penetration for treating skin carcinomas (Lalotra et al., 2020). The efficacy of skin cancer treatments has been limited by poor penetration of drugs into either the SC or the skin lesion(s); low efficacy; and the necessity for high concentrations of active pharmaceutical ingredients to achieve a therapeutic effect (Yadav et al., 2024).

Due to its high anti-cancer, anti-inflammatory and antioxidant capabilities, curcumin suffers from several characteristics which limit its use as a topical agent: low water solubility; poor absorption through the skin; sensitivity to exposure to light; and instability due to its very short half life when stored properly (Waghule et al., 2020). Similarly, ritonavir is also hindered from being delivered via conventional means because of its very high lipophilicity; low water solubility; and poor bioavailability as a result of being delivered through normal routes. The lack of solubility and bioavailability of both curcumin and ritonavir create significant barriers towards their ability to utilize topical delivery systems unless novel delivery carriers are developed.

In addition, when the skin has been damaged or inflamed, or when there is cancerous tissue on your body, this will remove some protection from your skin, allowing nanoparticles through the opening in the barrier (Gupta etal. 2022). However, changes in barrier function due to disease states cannot be relied upon to provide prepared amounts of therapeutic drug for a long period of time.

9.2 Role of Nanocarriers in Topical Delivery

The development of nanocarrier drug delivery systems is changing the way that people can treat skin cancer compared to older forms of topical treatment due to their nanoscale size (10 - 300 nanometers), large surface area to volume ratio, and the ability to modify their surface properties; all of which make it easier for nanocarriers to interact with the stratum corneum (top layer of skin) and penetrate through other layers of skin (Palmer & DeLouise, 2016).

There are multiple groups of nanocarriers that have been studied as topical delivery vehicles for anticancer drug delivery to skin tumors:

1. **Lipid-based nanocarriers**

Nanocarriers made up of lipids like liposomes, niosomes, solid lipid nanoparticles, and nanostructured lipid carriers have a porous structure similar to skin lipids which allows them to penetrate into the stratum corneum at a much higher rate than other forms of drug delivery systems. They provide high drug entrapment, hydration of the skin due to their occlusion properties, greater stability, and an extended period of drug release from specific layers of the skin (Waghule et al., 2020). Curcumin loaded into nanostructured lipid carriers has exhibited an increase of approximately 3.24 times the amount of curcumin that penetrates and retains in the skin compared to a free curcumin gel, with a release period of up to 48 hours (Rapalli et al., 2020). Transfersomes or deformable liposomes are another type of liposomal nanocarrier that have the ability to force themselves through the intercellular lipid channels in the

stratum corneum, providing further penetration of drug into the skin (Punasiya et al., 2010).

2. Polymeric nanocarriers

Polymeric nanocarriers (e.g., chitin nanogels loaded with curcumin) exhibited a four-fold enhancement in steady state transdermal flux (compared to unencapsulated curcumin solution) while exhibiting selective cytotoxicity toward A375 melanoma cells, leaving normal human dermal fibroblasts unaffected (Mangalathillam et al., 2012). The histopathological evaluation found that chitin nanogels were able to disrupt the stratum corneum of the epidermis, allowing for diffusion of nanocarriers through epidermal layers without causing visible signs of inflammation.

3. Vesicular systems

Vesicular systems (e.g., curcumin nanoniosomes) have demonstrated efficiencies of up to 78.32% for encapsulation and particle sizes as small as 91.9 nm when used for topical application to treat the skin carcinogen DMBA (Das & Kumar, 2015). Nanoniosomes demonstrated zero-order and Higuchi kinetics for drug release, while the results from histopathological evaluation revealed that nanoniosome administration significantly decreased the proliferation of abnormally growing skin cells found in DMBA-treated mice (Das & Kumar, 2015). Overall, vesicular drug delivery systems lead to efficient penetration of anticancer agents through the skin, while minimizing skin irritation or degradation of the drug, and reducing systemic toxicity (Kumar et al., 2024).

4. Nano-micelles and hydrogel composites

Implementation of nanomicelles and hydrogel composites showed localized delivery of CUR-embedded nanomicelles (12-25 nm) into thermoreversible hydrogels, depending on tissue viability at depths of 100 as well as 150 µm from the SC. Ultimately, treatment could be administered with greater efficiency from location 100-150 µm to targeted tissue—the basal layer of the epidermis—for patients diagnosed with diseases such as melanoma; this is corroborated through results by paganini and associates (2025). Further, a hybrid strategy polyvalent nanocomposite hydrogel containing both curcumin nanosuspensions (nanosuspensions) and curcumin liposome (liposomes) resulted in liposome transdermal flux of 105.52 ng/cm2/h respectively and much higher cumulative corneometry on the skin than diameters of the same amount; notably, Aye et al. (2025) provided this study.

For co-delivery of curcumin as well as the ritonavir antiviral agent specifically, the combination of co-loaded NLC or layered nanocarrier systems such as polymeric nanoparticles or lipid-polymer hybrids can serve equal weights to eliminate the barriers to co-administer biomarkers necessary for effective treatment purge of tumors. This will also allow a single-system command of co-administering anticancer drugs and their P-gp inhibitors will greatly advance clinical research studies associated with drug-induced chemotherapy and P-gp mediated multi resistance.

9.3 Transdermal Enhancement Technique

In addition to passive nano carrier-mediated delivery of drugs, other methods of enhancing drug penetration through the SC (stratum corneum) have been developed that use active physical methods of enhancement:

Iontophoresis: This uses a low-level electrical current to push charged or polar drug molecules through the skin. Jose et al. (2017) demonstrated that using curcumin-loaded cationic liposomes in conjunction with iontophoresis at a current density of 0.47 mA/cm² resulted in drug penetration up to 160 µm into the skin. Interestingly, iontophoresis when used to deliver curcumin also produced results similar to injection into the tumor in terms of inhibiting tumor growth and suppressing STAT3 protein levels, demonstrating that iontophoresis is an effective alternative to invasive delivery methods if the correct enhancements are used.

Microneedles

Dissolvable and solid microneedles both physically create transient micropores that bypass the stratum corneum (SC). Mice using microneedle pretreatment and cationic doxorubicin-loaded nanoparticles resulted in significant reductions in subcutaneous melanoma tumor size and/or apoptosis compared to either method alone (Yang et al., 2024). CUR-M-DMNs-Gel was another form of microneedle using curcumin-loaded micelles that had enhanced transdermal penetration and collected much of the drug compared with single component formulations (Jin et al., 2025).

Electroporation

Electroporation is a method for enhancing transdermal drug delivery by creating transient aqueous pores in SC lipid bilayers with high-voltage pulses. When used synergistically with nanoparticles as drug carriers, the electroporation can facilitate deeper penetration into the dermis (Zorec et al., 2013).

Chemical penetration enhancers

The use of transdermal delivery systems also utilizes chemical enhancers like ethanol, fatty acids, terpenes, and surfactants to disrupt SC lipid organization and allow macromolecules to more easily penetrate the SC. Chemical enhancers used with nanocarriers work synergistically to protect the physical stability of drugs, while also modifying SC barrier function (Vitorino et al., 2015).

Magnetic field-assisted delivery

Using a magnetic delivery system - Superparamagnetic iron oxide nanoparticles (SPIONs) containing anticancer drugs can be driven into deep skin tissues through an external magnetic field and via follicular pathways, thus avoiding the stratum corneum (SC) (Rao et al., 2015).

These physical enhancement methods work in synergy with nanocarriers, as the nanoparticles, as well as the physical methods, will enhance the absorption of drug molecules through percutaneous routes by totally different mechanisms (Dragičević & Maibach, 2021).

9.4 Comparison of Delivery Routes:

(Table 1 : Comparison of delivery Routes)

Parameter	Topical Delivery	Systemic Delivery
Drug targeting	Localized to skin tumor site; high local drug concentration	Distributed throughout the body; low tumor-site specificity
Systemic side effects	Minimal systemic exposure and toxicity	Significant systemic toxicity (hepatotoxicity, nephrotoxicity, GI effects)
First-pass metabolism	Avoided entirely	Oral route undergoes extensive hepatic first-pass metabolism
Bioavailability at tumor	Enhanced by nanocarriers; SC barrier is the main limitation	Variable; often low at skin tumor site due to dilution
Patient compliance	Non-invasive, easy self-application	Oral or IV routes may cause discomfort and non-compliance
Drug stability	Nanoencapsulation protects curcumin from photodegradation	Curcumin undergoes rapid systemic metabolism and clearance
MDR reversal	Co-localized delivery of curcumin + ritonavir at same site enhances P-gp inhibition synergy	Systemic P-gp inhibition may cause drug–drug interactions
Reservoir effect	Skin acts as drug reservoir for sustained release over days	No reservoir effect; repeated dosing required

Table 1:- Comparative Study of different drug delivery routes

Topical drug delivery represents an alternative method to pharmacological or injectable methods by using the skin as a drug reservoir that allows for prolonged administration (Gupta et al., 2022). Conventional treatment for skin cancer with systemic chemotherapy can have substantial side effects and high rates of infection, while employing topical nanocarrier therapy can decrease both side effects and improve clinical outcomes (Gomes et al., 2024). The benefits of transdermal drug delivery include the elimination of first-pass hepatic metabolism, improvement of pharmacokinetic parameters, reduction of side effects, and increased patient compliance (Zorec et al., 2013).

Despite the existence of topical drug delivery systems, systemic drug delivery will continue to be necessary for deeply invasive or metastatic skin cancers, and intravenously administered nanocarriers will benefit from the enhanced permeability and retention (EPR) effect and the ability to accumulate in solid tumours (Dianzani et al., 2014). The optimal treatment strategy for co-encapsulated curcumin–ritonavir nanocarriers will rely upon utilizing a combination of topical nanocarrier therapy for localized superficial lesions and systemic nanocarrier

intravenous therapy for deeper or disseminated lesions. This multidisciplinary approach will maximize the synergistic effects of MDR reversal and minimize the potential for off-target toxicity.

10. Clinical and Translational Perspectives

10.1 Current Nanoparticle-Based Therapies in Skin Cancer

As much as extensive preclinical studies have been performed, the clinical application of nanoparticle-based therapies for the treatment of skin cancers is still very much in the beginning phases. Skin cancer nanoformulations are also significantly behind other cancers that have had multiple commercialized formulations available (Diaz et al., 2023). For example, Doxil® (pegylated liposomal doxorubicin) was the first nanomedicine to receive FDA approval and is currently used to treat AIDS-related Kaposi sarcoma (Bawa et al., 2016; Longo et al., 2018). Other relevant FDA-approved products include Abraxane® (nab-paclitaxel) and multiple liposomal formulations, however, none were designed specifically as a treatment for primary cutaneous neoplasms (Jadhav & Mandlik, 2024).

There are many types of nanocarrier systems with proven antineoplastic/anti-metastatic activity in skin cancer preclinical models, including: improved drug bioavailability, decreased drug toxicity, increased drug permeability, enhanced permeation and retention (EPR) effect, & inhibition of tumor growth (Diaz et al., 2023). Tumor-targeted formulations using RGD-conjugated TiO_2 nanoparticles, and cetuximab-functionalized liposomes both provide greater than 50% greater rates of tumor regression when compared with traditional therapies in preclinical models (Othman, 2025). Additionally, nanoparticle-loaded microneedle systems present a promising next evolution in delivering sustained and/or stimuli-responsive release of chemotherapeutics, phototherapeutics, and immunotherapeutics; however most existing support for this modality is limited to in vitro and small animal studies (Pareek et al., 2026).

A systematic review of 43 publications on nanoparticle-based approaches for the treatment of skin cancer indicates that although nanoscale systems demonstrate robust antineoplastic activity, relatively little progress has occurred in the translation of these systems from bench to bedside (Diaz et al., 2023). Much research has been conducted to develop nanoparticles for topical drug delivery; however, relatively little progress has been made translating these systems clinically for the treatment of skin cancers specifically (Krishnan & Mitragotri, 2020).

10.2 Status of Curcumin and Ritonavir in Clinical Studies

Curcumin in Clinical Trials

After being tested in widespread studies, there is enough evidence to say that curcumin is not harmful when given orally. For example, Cheng and colleagues (2001) did a landmark study that had 25 patients with high-risk precancerous lesions (such as Bowen's disease) and used curcumin at oral doses of up to 8 g for 3 months. They found no toxicity and an improvement in precancerous skin lesions (e.g., Bowen's disease) occurred in 2 of the 6 patients with Bowen's disease. Therefore, results of this study suggest that curcumin may have a

potential biological effect when used for chemoprevention of skin cancer.

When looking at only Phase I studies, there continues to be no evidence of any type of toxicity when curcumin is given at oral doses of 8 - 12 g/day over a prolonged period of time except for some mild nausea and/or diarrhea (Hsu & Cheng, 2007). Curcumin has a low oral bioavailability; however, topical application appears to create concentrations that could reach therapeutic levels at the site of application (e.g., skin). Additionally, there appears to be no dose-limiting toxicities associated with using high dosages (e.g., up to 10g/day) in human clinical trials (Aggarwal et al., 2003).

An RCT examining the impact of oral curcumin on the severity of radiation dermatitis found that use of the herb reduced the development of moist desquamation (28.6% vs 87.5%; $p = 0.002$) in breast cancer patients receiving radiation treatment. In addition, a follow-up study using nano-curcumin confirmed improved healing of skin reactions compared to placebo and significant reduction in patient-reported pain.

The most substantive clinical trial of curcumin administered with chemotherapy, conducted by Saghatelyan et al. (2020) , examined the response of 150 patients with advanced and metastatic breast cancer following treatment with either curcumin (300 mg IV) or placebo in combination with paclitaxel. Results from the study indicated that curcumin/paclitaxel resulted in significantly greater objective response rate versus paclitaxel plus placebo (51% vs 33%; $p < 0.01$) and no significant safety issues, and potential to reduce fatigue.

However, directly aligned to this review topic, Esmaeli and Dehabadi (2025) recently published a comprehensive narrative review summarizing the literature from 2018-2025, and noted there have not been any human clinical trials of curcumin for use within the treatment of skin cancer, despite promising preclinical evidence.

Orally taking curcumin prevented the development of skin cancer in SKH-1 mice from exposure to UVB light, and when administered through the mouth or on the skin, the tumor count was reduced and the time until a tumor developed was increased (Phillips et al., 2013). The results from this study support pre-clinical studies for both oral and topical routes.

Ritonavir in Cancer Studies

Ritonavir has been investigated as a potential anticancer agent through its use in multiple cancer types including breast, kidney, prostate, lung, and bladder cancers. Its ability to inhibit key signaling pathways of cancer cell growth has been demonstrated through the induction of apoptosis by causing cellular stress (endoplasmic reticulum), metabolic stress, and inducing cell cycle arrest and inhibiting the activity of heat shock protein 90 (Hsp90) and cyclin-dependent kinases (Kumar et al., 2024).

Ikezoe and colleagues (2004) studied how ritonavir could augment the ability of docetaxel to inhibit the growth of androgen-independent prostate cancer cells, both in vitro and in vivo, showing that the combination of the two agents significantly inhibited cancer tumor xenograft growth compared to either agent alone, and no significant histological abnormalities were found in the liver, spleen, kidney, bone marrow, or skin of any animals used for tumor xenograft studies.

Ritonavir causes cancer cells to stop making transporters that let them push out (efflux) drugs and also to stop making proteins that break down (metabolize) drugs. In this way, it makes it more difficult for cancer cells to divide and migrate, and gives rise to caspase-mediated apoptosis when used in combination with anticancer medications such as doxorubicin, paclitaxel, tamoxifen, or vinblastine (Vadlapatla et al., 2014). A study by Srirangam and others (2006) found that ritonavir blocks the growth of breast cancer to some extent through inhibitory activity against Hsp90 substrates, such as Akt, at pharmacologically effective serum concentrations capable of inhibiting intratumoral Akt activity in xenograft models. A polymeric nanomedicine that contains a ritonavir derivative (RD) conjugated to the HPMA copolymer via a pH-sensitive hydrazone linkage exhibited efficacy against CT26 colon cancer, B16F10 melanoma, and FaDu xenograft tumors, and is not toxic. Furthermore, RD was found to be a more potent P-glycoprotein inhibitor than ritonavir (Sivák et al., 2021). Polymer-conjugated ritonavir increased internalization in cancer cells and co-localized with mitochondria, and significantly reduced the production of ATP, which may alter the ability of P-glycoprotein to pump drugs out of multidrug-resistant tumors (Machová et al., 2018).

According to Van der Putten et al. (2022), they have assessed the potential for ritonavir to restore sensitivity to docetaxel and cabazitaxel by inhibiting P-glycoprotein (P-gp), providing conclusive data that ritonavir reverses MDR.

In a study conducted by Dalva-Aydemir et al. (2014), it was demonstrated that the combination of ritonavir (an FDA approved medication) and metformin effectively targets the metabolic plasticity of multiple myeloma cells (including melanoma) through suppressing both AKT and mTORC1 phosphorylation and MCL-1 expression in vitro and in vivo.

To date there have been no clinical trials looking at the combination of curcumin and ritonavir when used together or in co-loaded nanocarriers in skin carcinoma.

10.3 Safety and Toxicity Concerns

Curcumin Nanoparticle Safety

Curcumin nanoparticle safety has been well documented through extensive pre-clinical testing. Dandekar et al. (2010) performed several toxicity tests on curcumin-loaded Eudragit S 100 nanoparticle formulations, including an acute toxicity study, a 28-day chronic toxicity study, and a set of genotoxicity studies: micronucleus, chromosomal aberration, and comet assays. These curcumin-loaded Eudragit S 100 polymeric nanoparticles showed no signs of toxicity even at the highest dose that could mimic therapeutic doses (2,000 mg/kg body weight of curcumin), while no evidence of genotoxicity was found at doses three times greater than therapeutic levels.

Sherin et al. (2017) evaluated the potential toxicity of curcumin-titanium dioxide composite nanoparticles by performing two sets of in vitro tests (cell viability assays with THP1 and H9c2 cell lines) and one set of in vivo tests (Sprague Dawley rat models). In these experiments, there was no evidence of observable toxicity in either the in vitro or in vivo experimental settings at concentrations <200 ng of curcumin. Luss et al. (2023) reported no toxicity with curcumin-loaded amphiphilic poly-N-vinylpyrrolidone nanoparticles to healthy

cells but did report significant cytotoxicity against glioblastoma cells with an average lethal dose of 23 μM in zebrafish.

López-Lázaro (2008) warned there is a possibility that curcumin could be toxic and cause cancerous tumors under certain conditions For Lopez iLazaros's study's sake, he also noted that since curcumin has both antioxidant effects as well as being an oxidative agent it could decrease the effectiveness of radiation and chemotherapy drugs Therefore this points out the need for careful evaluation of the safety of using curcumin in high doses with both radiation and chemotherapy for patients as well as conducting research on curcumin's toxic nature in various doses.

Ritonavir Safety in Nanoparticle Formulations

The biodistribution and toxicity of ritonavir-loaded nanostructured lipid carriers (NLCs) have been documented by Jitta et al. (2023) in Wistar rats. The authors conclude that no significant increase in serum markers of hepatotoxicity attributable to RTV-NLCs occurred and that even though lymphatic uptake was enhanced (implying that it may be possible to reduce the dose of ritonavir in NLCs while still producing a pharmacologically-effective result), consideration should be given to the reduction of noted adverse effects from ritonavir through the use of NLCs for this patient population.

At standard dosages of ritonavir, patients can develop adverse metabolic sequelae, including dyslipidemia, insulin resistance, and gastrointestinal issues. However, because systemic exposure may be minimal following co-loaded topical NLC delivery of ritonavir to treat skin carcinomas, it is likely that these adverse events would virtually disappear.

Nanocarrier-Specific Toxicity Considerations

Nanotoxicology continues to develop as an area of investigation. The distinctive physicochemical characteristics of particles at the nanoscale may cause adverse effects that will need to be considered separately in terms of nanomaterial safety (Beer 2016). Some of the important topics that have been of interest include: (i) the potential for long-term accumulation and undefined biodistribution profiles; (ii) the ability of certain nanomaterials to generate reactive oxygen species (ROS); (iii) the potential for immunogenicity to occur with certain nanomaterials; and (iv) that nanoencapsulated materials could enhance the toxicity of a drug when in at high concentrations. Additional work by Kumar and Jørgensen (2013), who indicate that it is the encapsulant of a PLGA nanoparticle, and not necessarily the PLGA nanoparticle alone (at great dosages), which is implicated with regard to toxicity experiments; therefore, it appears that the safety profile of a drug delivered in nanoform is primarily due to the property of the drug that is being delivered rather than being influenced by the PLGA carrier alone.

10.4 Regulatory Challenges

The challenges of translating nanomedicines into the marketplace include a wide range of issues (including the need to characterize the physicochemical properties and pharmacodynamics and pharmacokinetics) and several specific areas (e.g., biocompatibility and nanotoxicity,

processing and manufacturing, and reproducibility). Each of these challenges needs to be handled carefully and appropriately if successful clinical translation is to occur (Csóka et al., 2021).

Absence of Nano-Specific Regulatory Frameworks

There are currently no dedicated regulatory pathways for nanomedicine established by the FDA or EMA. Instead, existing pharmaceutical regulatory frameworks are used to evaluate nanomedicines; however, these frameworks may not accommodate the unique characteristics of nanocarriers. A key issue affecting many regulatory aspects related to nanomedicines is the continuing controversy regarding what constitutes a formal definition of nanomedicine, which remains a significant issue for regulators, policymakers, drug manufacturers, ethicists, and attorneys (Bawa et al., 2016). If nanodrugs are over-regulated, the possible negative and inhibiting effects could be considerable; therefore, a proper case-by-case balance between the requirements for commercialization and the requirement to mitigate (by reducing) unintentional harm would need to occur (Bawa et al., 2016).

Characterization and Standardization Challenges

In nanomedicine, the main factors affecting the safety and efficacy of a product are its physical characteristics (physical-chemical properties), based on quality control, and the safety of the product based on pharmacokinetics, bio-degradation, accumulation of nanoparticles, and potential toxic effects caused by the nanoparticle (Csóka et al., 2021). The variability between batches in nanomanufacturing is a major barrier to translating technology (Othman, 2025). Therefore, there is an urgent requirement for standardized and reliable methodologies that can be used to assess the critical quality attributes of nanomedicines.

Quality by Design (QbD) Approach

The use of Quality by Design (QbD) for development of nanomedicines is being promoted increasingly by the regulatory authority. Many regulatory authorities will require or highly recommend that QbD-based submissions be used during the drug approval process in order to allow for a more systematic approach to developing, understanding and controlling the manufacturing processes. Consequently, this allows for a smoother transition from the laboratory to clinical studies (Csóka et al. 2021).

Specific Challenges for Curcumin–Ritonavir Co-Loaded Systems

Additional Regulatory Difficulties Related to the Co-Loaded Curcumin-Ritonavir Nanocarriers Under Evaluation are as Follows:

- **Fixed Dose Combinations complexity:** When Co-Loading Two Different Pharmacologically Active Compound Types (A Phytochemical and A Repurposed Antiviral) Into A Single Nanocarrier, Additional Requirements Exist to Demonstrate the Rationale for Combination Use, Synergism Between Compound Types, and Really Good Ratios to Use in the Combination.
- **Classification Uncertainty:** Due to Differences in How Curcumin is

Classified in Different Countries (As A Dietary Supplement, Nutriceutical, or Drug Candidate), There Are Health Regulatory Uncertainties that Exist. Ritonavir is an Approved Drug; However, It Is Being Repurposed for Oncology (So Must Produce New Clinical Evidence for That Indication).

- **Scale-up and manufacturing:** Currently, There Are Many Nanocarrier-Based Treatments in R&D, and Further Studies Still Need to Be Conducted to Optimize the Manufacturing Features of the Carries and the Ability to Duplicate the Properties of the Carries Once Manufactured at the Commercial Scale (Jadhav & Mandlik, 2024). In Addition, Challenges Exist to Be Solved Surrounding Manufacturing Scalability and Biocompatibility (Nisar et al., 2025).
- **Long-term safety data gaps:** At This Time, Gaps Exist in Knowledge About the Long-Term Safety Profile of Topically Applied Nanocarriers, Including Tolerance to Repeated Cutaneous Applications and Long-Term Biodistribution Profile (Pareek et al., 2026).
- **Clinical trial design:** Prior to Conducting Clinical Trials with the Nanocarriers, There Are Several Issues to Address (Optimizing Properties of Nanocarriers, Developing Reliable Characterization Methods, and Evaluating the Safety and Efficacy in Clinical Trials) (di Filippo et al. 2023).

Even with the existing obstacles, the field is progressing rapidly. There is now an increasing amount of information regarding the regulatory landscape for novel nanomedicines and a growing number of guidance documents focused on the generational development of nanomedicines (Gaspar et al was cited in 2014 for this). For the successful transition from preclinical to clinical use of curcumin and ritonavir as co-loaded nanocarriers, there must be sufficient data regarding the quality, safety and efficacy (these also need to adhere to the same, standardized evaluation criteria).

11. Challenges and Limitations

There are still many significant challenges and limitations that will prevent the successful clinical application of curcumin+ritonavir loaded nanocarriers for overcoming multi-drug resistance in skin cancer. Some of these challenges are based on the physical and chemical characteristics of the active ingredients used in their formulations, including but not limited to; formulation stability, a lack of clinical data, scale-up or scalability of manufacturing processes, and batch-to-batch consistency.

11.1 Poor Bioavailability of Curcumin

One of the major limitations of curcumin is the extremely poor systemic bioavailability of curcumin. The aqueous solubility of curcumin can be as low as 11 ng/mL while oral bioavailability is not much (usually 1% in serum) although oral doses of as large as 8 g are administered daily (Drakalska et al., 2015; Fu et al., 2026). The key factors contributing to low bioavailability are low aqueous solubility, poor gastrointestinal absorption, quick phase II metabolism via glucuronidation and sulfation, and quick systemic elimination (Mohanty et al.,

2012). It's been estimated that roughly 60%-70% of oral doses from curcumin are metabolized and eliminated, leading to less than the free amount of pharmacologically active curcumin being delivered at the target sites (Krishnasamy, 2014).

Nanocarrier systems such as liposomes, polymeric nanoparticles, NLC, micelles, and nanoemulsions have been shown to improve the bioavailability of curcumin significantly, with some formulations achieving increases of plasma AUC of more than 178 times (Fu et al., 2026). However, most of these improvements have yet to be confirmed in clinical trials. Curcumin's clinical applicability is severely restricted by the major disadvantages of instabilities, solubility issues, poor bioavailability, and rapid metabolism (Sun et al., 2012). Efficacy of curcumin was limited by poor bioavailability due to insufficient absorption, rapid metabolism, and elimination (Yakubu & Pandey, 2024).

Though there are some obstacles associated with the use of topical medications to treat skin carcinomas, the challenges associated with bioavailability are diminished somewhat by using direct delivery at the location of the disease; however, penetration through the stratum corneum, as well as obtaining adequate dermal concentrations of both curcumin and ritonavir at the same time, is going to be a challenge. Further development of safe, nontoxic, and nonimmunogenic nanocarriers will have a significant impact on the future of delivery systems designed to deliver curcumin and ritonavir simultaneously. (Mohanty et al., 2012).

11.2 Stability Issues

Curcumin is notoriously unstable under a range of conditions, posing significant challenges for formulation development. The stability of curcumin is strongly dependent on pH, light exposure, and temperature.

pH-dependent degradation:

A Study By Wang et al.(1997) Found That Approximately 90% Of Curcumin Decomposed After Incubation In A 0.1M Phosphate Buffer At 37 Degrees Celsius And Ph 7.2 For 30 Minutes. The Decomposing Rate Follows First Order Kinetics, Increasing Drastically From Near-neutral To Alkaline pH Conditions. The Major Products Of Decomposition Were Confirmed As Being Trans-6-(4'-hydroxy-3'-methoxyphenyl)-2,4-dioxo-5-hexenal, Vanillin, Ferulic Acid And Feruloyl Methane (Wang et al., 1997). Kumavat Et Al.(2013) Showcased That Curcumin Is Most Stable At Acidic PH (pH 1.0 - 1.125), With Less Than 1% Decomposition Over 6 Hours Of Illumination At pH 1.125. However, Greater Than 40% Of The Curcumin Will Comprise Of Light. Naksuriya Et Al. (2016) Indicate At pH 8.0, The Degradation Constant For Curcumin Is 280×10^{-3} H^{-1}, Indicating A Half Life Of Only 2.5 Hours, With The Ultimate Decomposition Product Being Dioxygenated Bicyclopentadione.

Photodegradation:

Curcumin has been thoroughly studied for its photochemical stability via photodegradation. According to Tønnesen et al. (1986), photodecomposition of curcumin occurred when curcuminoids were exposed to UV and visible light, which were characterized and helped identify the main degradation by-products and half-lives of curcumin in various solvents and solid form (Tønnesen et al,

1986). Appendino et al. (2021) also showed that curcumin was only photochemically stable in some solvents when exposed to solar radiation, as hydrolysis and subsequent fragmentation of the heptadecadiene group caused to break down in mixed solutions with low pH (Appendino et al, 2022). Only under neutral pH was there a relative amount of stability with curcumin under artificial lighting (Appendino et al, 2020).

Nanoencapsulation as a stabilization strategy:

Curcumin nanoencapsulation is a promising solution for stability challenges associated with curcumin in the aqueous system. Curcumin-loaded polymeric micelles (mPEG-HPMA-Bz) were found to be approximately 300 to 500 times more stable than in aqueous buffer (Naksuriya et al., 2016). The cyclodextrin complexation method can increase curcumin's water solubility by at least 10,000 times at pH = 5 and improve its hydrolytic stability when exposed to an alkaline pH, although photodecomposition rates increased (Tønnesen et al., 2002). Curcumin also has stability challenges during manufacturing and storage due to the inherent nature of the compound, including photosensitivity and limited chemical stability (Obeid et al., 2022). The encapsulation of curcumin within a nanocarrier (core or matrix of lipids or polymers) offers both physical stability and improved chemical stability of the drug (Harwansh et al., 2023).

In contrast, while ritonavir is more chemically stable than curcumin, its formulation challenges stem from its lipophilicity and susceptibility to polymorphic transitions that affect the overall drug loading and release profile from the nanocarrier.

11.3 Lack of Clinical Trials

The lack of clinical trial data for curcumin–ritonavir co-loaded nanocarriers in skin carcinoma highlights one of the largest critical areas within the translational pipeline from discovery to clinical practice; while curcumin has been assessed in more than 200 clinical studies in diverse diseases, and ritonavir has been fully approved by the U.S. Food and Drug Administration (FDA), physiologically-based studies looking at their combination specifically for use in skin cancer do not currently exist. After all, although new formulations of curcumin using nanocarriers are still in their infancy and have not yet received regulatory approval, there remain considerable safety concerns regarding curcumin delivery using nanocarriers (Jacob et al., 2024).

Despite the fact that there is still a substantial gap between the preclinical efficacy shown with nanoformulated curcumin and the clinical use of these formulations, there have already been a handful of Phase I/II clinical trials that suggest that formulations of curcumin such as nanomicelles (Sinacurcumin®) achieve significant modulation of inflammatory cytokines and that the liposomal formulations (Lipocur™) are capable of engaging the target of curcumin in metastatic cancers but will require further dose optimization (Fu et al., 2026). It should be noted that most of the currently known activities of curcumin are based solely upon preclinical studies, and as a consequence, there is still no clinical product resulting from this nano-preparation development of this therapeutic agent (Bodhankar & Chikhle, 2018).

The existing gap in translation is likely due to several factors: Oversimplification of the enhanced permeability and retention (EPR) effect; no correlation of in vivo animal data with their translation to humans; and multiple biological steps that occur during systemic delivery (Nayak et al., 2019). The literature on nanomedicine is nearing consensus that translation of data from animal models to the clinical and commercial use of nanomedicine is extremely challenging (Longo et al; 2018). In the case of curcumin-ritonavir co-delivery, additional barriers to translation include a lack of validated pharmacodynamic biomarkers to demonstrate MDR reversal in skin carcinoma, and an absence of established data for dose-finding of the two drugs in combination.

11.4 Scale-Up Challenges

A major bottleneck in the development of translational nanomedicine is the transition of nanocarrier formulations created at laboratory scale into industrial manufacture. The chemistry, manufacture and controls (CMC) of nanotherapies (nano-CMC) is an essential part of the translational process for nanomedicine in terms of considerations such as raw materials, scale-up synthesis routes, batch sizes, stability checks, analytical methods, and documentation (Liu & Meng, 2021) .

Key scale-up challenges include:

- **Process parameter sensitivity:** Properties include particle size, size distribution (polydispersity), drug load (amount of drug in nanoparticle), encapsulation efficiency (amount of drug successfully encapsulated), surface charge, and kinetics of drug release. These properties will be very sensitive to the process conditions (stirring speed, temperature, solvent ratios, flow rates) under which nanoparticles are produced. On an industrial scale, a small change from the optimum conditions used in the laboratory may produce major differences in the physicochemical properties of the nanoparticles (Sammasagi et al., 2025).

- **Equipment limitations:** Including probe sonication, thin film hydration, and solvent evaporation, present significant challenges to direct scaling of these methods. For example, energy input per unit of volume into the material being mixed and the mixing dynamics with increased batch volume are entirely different (Muthu & Wilson, 2012). No nanoparticle formulation of PLGA nanomedicine is currently commercially available worldwide, primarily due to the inability to effectively transfer the manufacturing process used for production of PLGA nanomedicines from the laboratory to the production level utilized for scale-up with sufficient characterization and quality control measures in place (Operti et al., 2021).

- **Chemical purity at scale:** Industrial-scale production can introduce variability into the chemical characteristics of drug delivery systems based on factors like chemical source Quality. For

example, this may affect reproducibility of the nanoparticles' physical attributes (like hydrodynamic diameter, surface charge, etc.) as well as how they interact with or are toxic to living organisms (Dormont et al. (2019)).

- **Cost considerations:** Production requires scalable manufacturing to increase the throughput quantity and reduce the energy consumed per unit of production (Türeli & Türeli (2020)). Scaling productions require using existing facilities more efficiently than currently being done (e.g., Min & Zhen (2020)), which are suitable for currently used equipment (e.g., Min et al. (2019)).

Examples of possible scalable and cost-effective solutions to produce biopharmaceuticals (the drug product) using continuous production processes include: microfluidic-based continuous production of drug delivery systems; deploying CMC/quality by design approaches (multivariate iterative approach); implementing PAT/AI-Based Real-time Statistical Quality Control (Liu & Meng (2021). In conjunction with Flash NanoPrecipitation (FNP), spray drying can produce solid dosage forms of nanoparticles produced from low-cost materials and have acceptable chemical profiles (Feng et al. (2019)).

11.5 Reproducibility of Nanocarriers

The need for batch-to-batch consistency of pharmaceutical products is a crucial and ongoing challenge in the field of nanomedicine. The major challenges to achieving this include the reproducibility of manufacturing and scale-up methods; the lack of appropriate characterization methods; instability of products once inside the body (in vivo); safety issues; insufficient knowledge regarding the different types of populations that suffer from the same diseases; lack of regulatory guidance; and poor understanding of the biophysical/chemical interactions of nanoformulations (Agrahari & Agrahari, 2018).

Reproducibility challenges in curcumin–ritonavir co-loaded nanocarriers are compounded by several factors:

- **Multi-component complexity:** Loading two drugs with distinct physicochemical characteristics—curcumin (a hydrophobic polyphenol with pH-sensitive stability) and ritonavir (a lipophilic protease inhibitor)—in to one delivery device demands strict control over the drug to lipid/polymer ratios, which is much more difficult to achieve than with single drug-loaded formulations.
- **Characterization gaps:** Identifying Critical Quality Attributes (CQAs) of the drug product (necessary for activity and safety), as well as appropriate analytical methods (physical, chemical, biological) used to characterize them is very challenging and continues to present challenges (Đorđević et al., 2021). Working closely with regulators early in the development process will help ensure an aligned approach and speed acceptance of

future nanomedicines (Đorđević et al., 2021).

- **Raw material variability:** Curcumin is a natural product that has high variability in terms of its composition (the ratio of curcumin, demethoxycurcumin, and bisdemethoxycurcumin),; purity, and even where it comes from; this means that these things can change how well these nanocarriers work. To be able to incorporate these products into routine use, we must have standardized manufacturing processes, complete safety testing, and comprehensive clinical trials (Lalong et al., 2025).
- **Biological variability:** The use of nanomedicines in practice have been significantly limited by the complexity of the interactions of nanoparticles with biological systems, the variability in their ability to get into and remain in the body and the inability to maintain consistent targeted delivery of these particles to a specific location (Liu el al., 2024).

Quality by Design(QbD) has gained much popularity as well as the Design of Experiments(DoE) and the development of Process Analytical Technologies, as tools to improve reproducibility and develop reliable manufacturing processes. However learning opportunities and appropriate regulatory frameworks remain, to ensure that these processes are executed effectively(Agrahari & Agrahari, 2018). Although many companies are researching nanomedicine, only a very small number of them have received FDA approval for clinical use, because there is no rationale or design methodology using intelligent, responsive targeting systems (Abdullah et al.,2025).

12. Emerging Strategies

The rapid development in nanomedicine has opened many new ideas for improving the effectiveness of curcumin and ritonavir combined in nanoparticles for reversing multi-drug resistant (MDR) skin cancers. These include stimulating responsive nanoparticles, ligand based active targeting systems, and working together with immunotherapy, as well as using Artificial Intelligence (AI) to design the formulation.

12.1 Stimuli-Responsive Nanocarriers

The development of stimuli-responsive or “smart” nanocarrier systems creates a new paradigm for how drugs are delivered to cancers and can provide site-specific (i.e. tumor) and on-demand delivery of drugs based on the presence of endogenous or exogenous signals (Bhattacharya et al., 2023); Alsehli 2020). These systems are developed to maintain stability while circulating throughout the body and/or remaining in the topical formulation, and thus will release their drug content only when exposed to certain stimuli found within the specific areas surrounding the tumor microenvironment (TME) or energy sources that have been applied externally (Saravanakumar et al., 2019).

pH-Responsive Systems: Tumor Microenvironment pH: In skin cancer, the tumor microenvironment has a lower extracellular pH of 6.5 to 6.8 compared with normal tissues, which have an extracellular pH of about 7.4. The lysosomal and endosomal compartments of skin cancer have even lower pHs, ranging from approximately 4.5 to 5.5 (Sethuraman

et al., 2021). pH-responsive nanocarriers utilize this pH difference through the use of acid-sensitive (hydrazone bonds, Schiff bases, acetal) linkages or pH-sensitive polymers (e.g. polyhistidine, poly(acrylic acid)) that can change conformations or degrade in acid; this results in rapid release of the drug at the tumor Pharmacokinetics site (Bhattacharya et al, 2023). Hong et al. (2021) showed that curcumin-loaded β-cyclodextrin nanoparticles conjugated with folic acid (FA-Cur NPs) showed a much faster curcumin release at pH 6.4 than at pH 7.4. Therefore, curcumin would accumulate near the tumor site compared to other normal cells. Thus, pH-responsive nano-carriers have potential advantages for localized P-gp inhibition by ritonavir and enhanced cytotoxicity and chemo sensitization of curcumin when used in combination with ritonavir in the acidic microenvironment of skin tumors.

Redox-Responsive Systems: Tumor cells has high levels of intracellular glutathione (~2–10 mM) when compared to the extracellular environment (approximately ~2–20 μM) (Alsehli, 2020). Nanocarriers with disulfide bridges or other types of redox sensitive linkages could use this difference between the two environments to trigger the release of the drug inside the cell. In the case of MDR redox-responsive release will occur at the location of the efflux pumps that contain curcumin and ritonavir, thereby potentially increasing the drug retention in resistant cancer cells.

Light-Responsive and Photothermal Systems: Systems that respond to light and utilize the conversion of Near-infrared (NIR) light to heat have received increasing attention in developing drug-carrier systems, which respond to light due to their ability to deliver drugs to tissues further into the body than traditional carriers without causing harm to healthy tissue because of their ability to release the drug in an accurate, controlled manner, such as with Brachytherapy, where the drug is delivered by a localised source that can be monitored (Saneja et al., 2018). Photothermal therapy and PDT are new ways of treating skin cancers. They involve the use of light to target and destroy the cancer cells by injecting the nanocarrier with the anticancer drug or PDT drug into a cancerous lesion, illuminating it with an appropriate light source to activate an anticancer agent and delivering the light, usually through a device that delivers the appropriate light. The skin is superficially located, making light-triggered delivery systems even more useful in this situation (Singh et al., 2017). Singh et al. (2017) created NIR-responsive gold liposomes loaded with curcumin (Au-Lipos Cur NPs) with an encapculation rate of ~70%, which absorb NIR light (780 nm) due to surface plasmon resonance (conversion of light to heat), destabilising the liposome containing the curcumin. Cytotoxicity against skin cancer cell lines taught with Au-Lipos Cur NPs and laser irradiation was enhanced relative to those treated with laser without Au-Lipos Cur NPs, as evidenced by in vitro studies using Au-Lipos Cur NPs and laser (Singh et al., 2017). In a separate study, Abdel Fadeel et al. (2020) designed curcumin-loaded pegylated liposome nanoparticles for PDT of skin cancer and showed the amount of curcumin extracted from the skin of mice treated with PEGylated liposomes was double than treated with aqueous drug solution, and shown by histopathology that the amount of

curcumin could diffuse deeper within the skin after irradiation.

Multi-Stimuli Responsive Systems: Systems that respond to multiple stimuli (multi-stimuli responsive systems) may be more effective than systems that only respond to one type of stimulus (single-stimuli responsive systems) for the use of drug delivery in the treatment of cancer because they greatly enhance the release and accumulation of a drug at the relevant cancer cells leading to improved tumor cell ablation (Saravanakumar et al., 2019). The review by Abdoh et al. (2025) outlines the use of stimuli-responsive smart nanocarriers for the delivery of drugs to the skin, noting that those which respond to internal stimuli will use the pathological changes that occur in diseased skin, such as changes in pH, oxidative stress, enzymatic activity, or glucose levels, to release the drug specifically at the target location, whereas those that respond to external stimuli will release drugs in response to temperature, light, electric fields, ultrasound, or magnetic fields. On the other hand, the review by Padya et al. (2020) discusses the development of type[s] of stimuli-responsive nanoplatforms or cellular targeted and multimodal therapy for skin cancer by summarizing examples of pH-responsive and temperature-responsive platforms and identifying some ways that may be used to enhance the use of nanoparticles for cancer therapies, such as surface engineering, drug conjugation, and responding to multimodal or stimulus. Additionally, combining multiple stimulus-responsive triggers (e.g., pH + near-infrared light (NIR) or pH + reductive) into one curcumin-ritonavir nanocarrier allows for simultaneous or sequential drug releases to be optimized according to the unique pathology of multi-drug resistant (MDR).

12.2 Targeted Delivery (Ligand-Based Systems)

Active targeting through surface conjugation of ligands to nanocarriers enables selective binding to receptors overexpressed on cancer cells, enhancing cellular uptake via receptor-mediated endocytosis and potentially bypassing P-gp-mediated drug efflux.

Folate Receptor-Targeted Systems: Folate receptors (FR) have excess expression levels in many cancers, including skin cancer, with minimal expression levels in normal cells. As a result, folate can be used as a specific ligand to preferentially target the cancer cell types (Nosrati-Oskouie et al., 2024). In a narrative review conducted by Nosrati-Oskouie et al. (2024) of 38 preclinical studies about curcumin nanoparticle delivery using folate modifications, it was found that in vitro studies reported greater cellular uptake and cytotoxicity, higher cellular inhibition, and anti-proliferation from lower concentrations of curcumin, while in vivo studies indicated greater tumor suppression and lower tumor volumes without showing toxicity. For skin cancer, specifically, curcumin-loaded layer by layer (LB) folic acid and casein coated carboxymethyl cellulose/casein nanogels were created as a method to treat skin cancer by Priya et al. (2017). Priya et al. (2017) demonstrated that by using confocal microscopy, it was shown that the percentage of uptake of the FA-coated nanogels into the MEL-39 melanoma

cancer cell line was higher when compared to pure curcumin. In addition, FA-coated nanogels exhibited a lower IC50 value as well as improved cytotoxicity through folate receptor-mediated endocytosis when compared to pure curcumin (Priya et al., 2017). Additionally, in vitro skin permeation studies revealed dose-dependent mean curcumin concentrations of 3.47 ± 0.03 to 4.15 ± 0.25 µg/mL at stratum corneum, epidermis, and dermis layers (Priya et al., 2017). Folate-targeted nanoparticles with co-loaded docetaxel were demonstrated by Hu et al. (2015).

Transferrin Receptor-Targeted Systems: Which is highly expressed in many tumors, has a critical role in providing iron needed for cell growth; it also helps keep cells alive by transmitting growth signals through multiple signaling pathways (Muddineti et al., 2018). In an attempt to use this receptor as a target for drug delivery, we investigated how effective it would be for transferring targeted vitamin-E/lipid-polymer micelles containing curcumin to tumors. Targeted micelles exhibited significantly greater uptake into the cancer cells and were found to exhibit significantly higher cytotoxicity and greater inhibition of spheroid growth than nontargeted micelles (Muddineti et al., 2018).

Biotin-Targeted Systems: Dezfouli et al. (2022) created biotin-conjugated PEG-PCL nanoparticles that delivered curcumin (CUR-BTN-PEG-PCL) via a targeted system. The use of a targeted nanocarrier resulted in an increased number of cells in the Sub G1 phase of the cell cycle and apoptosis. It was also shown that by improving the bioavailability of curcumin for the specific tumor, the CAM assay (chick chorioallantoic membrane assay) significantly decreased both tumor cell proliferation and angiogenesis.

The co-loading of curcumin and ritonavir within nanoparticles is performed with the aid of a ligand-targeted approach that enhances the accumulation of both agents at the site of action in skin carcinoma cells while simultaneously reducing the likelihood of any off-target activity. Furthermore, the use of both active targeting and P-gp inhibition by ritonavir will help to further enhance their synergistic effects, thereby allowing both the chemosensitizer and the cytotoxic drug to enter the intracellular compartment of the multidrug-resistant tumor cell.

12.3 Combination with Immunotherapy

Nanocarriers combined with ICB therapies (PD-1/PD-L1 mAb) in the treatment of melanoma offer great potential as an innovative area of research. The benefits of ICB in treating melanoma are clear, however the current response rate remains low (Kuang et al., 2022).

Combination Immunotherapy with Nanoparticles in Melanoma: Research in the preclinical phase has shown that the combination of nanoparticle-based therapies and checkpoint inhibitors yields an additive benefit over use of either agent alone when used in tandem with melanoma models. For example, Mi et al. (2018) produced dual immunotherapy nanoparticles (DINP) that delivered antibodies targeting both PD-1 and OX40 (aPD1 & aOX40) by using nanoparticles for precise, spatiotemporal co-delivery, resulting in improved T-cell activation,

superior therapeutic response and increased immunological memory when tested in two tumor models as compared to the use of free antibodies. Similarly, Neek et al. (2020) created different combinations of protein nanoparticle vaccines (CpG-gp-E2) and anti-PD-1 therapy and found that more than half of the experimental animals treated with the combination therapy were free of any visible tumors, whereas all mice treated with either nanoparticle vaccine or anti-PD-1 therapy were 0% and ~5%, respectively. The research conducted by Lucena-Sánchez et al. (2024) with mesoporous silica nanoparticles as carriers for a PD-L1 inhibitor (JQ1) showed that when the PD-L1 inhibitor was capped with siRNA targeting TGF-β, efficient downregulation of PD-L1 and silencing of TGF-β were achieved and that these combinations promote apoptosis in melanoma cells.

Nanoparticle-Mediated Photothermal/Photodynamic Therapy with Immunotherapy: It has been suggested that the combination of immune checkpoint therapy and nanoparticle-based localized heat treatment (hyperthermia) may be an effective way to treat melanoma (Moy & Tunnell, 2017). Photodynamic therapy has the potential to produce an immunogenic cell death (ICD), while a checkpoint blockade could enhance the immunological response produced from this type of therapy (Zhao et al., 2018). Yang et al., (2021) were able to create composite nanoparticles that could simultaneously provide a photosensitizer and an inhibitor of indoleamine 2,3-dioxygenase (IDO), which showed that when the combination of these two treatments was used in the B16F10 melanoma model, tumor suppression was improved and 30% of the animals were able to completely eliminate their primary tumor as well as reject a second tumor inoculation from being accepted.

Relevance to Curcumin–Ritonavir Co-Loaded Systems: Connection Between Curcumin And Ritonavir As Co-Loaded Systems: Curcumin has been shown to have immunomodulatory effects (inhibiting NF-κB signaling, altering cytokine production, and potentially enhancing antitumor immune response) and therefore may be a candidate for passage through a nanocarrier system to provide a quarantined delivery approach (curcumin and ritonavir) when used with a checkpoint inhibitor. Triangulating the attempted modes of action of all three drugs combined through a co-delivery platform could achieve multiple functions, including (1) curcumin and ritonavir providing both cytotoxicity and reversal of multidrug resistance, (2) the checkpoint inhibiters reactivating T-cell-mediated killing by acting to prevent commitment to apoptosis, and (3) curcumin functionally altering the immune system by modulating its action. Furthermore, to enhance co-delivery systems could be developed to add immunoadjuvants or checkpoint inhibitors to the co-delivery of curcumin and ritonavir to create multifunctional systems for a holistic method of destroying tumors. This concept for the curcumin–ritonavir system requires preclinical validation before proceeding further.

12.4 AI-Based Formulation Design

Artificial intelligence (AI) and machine learning (ML) have emerged as transformative tools in nanomedicine, offering data-driven approaches to

accelerate the design, optimization, and characterization of nanoparticulate drug delivery systems (Shen et al., 2025; Chou et al., 2025).

Current Applications of AI in Nano-formulation Development: The Conventional Process of Making Nanoparticles Involves An Extensive Amount Of Trial And Error, Which Can Be Very Costly And Delays Product Availability (Kantesaria & Panda 2026). These Methods Also Produce Many Variable Results And Are Very Time-Constrained To Perform. Machine Learning Can Be Implemented Using Supervised, Unsupervised, And Other Machine Learning (ML) Algorithms To Create Critical Quality Attribute (CQA) Models That Predict Attributes Such As: (I) Particle Size, (II) Encapsulation Efficiency, (III) Drug Loading, (IV) Drug Release Profiles, (V) Surface Charge, (VI) Stability, And Others From The Formulation And Process Parameters Of The Nanoparticles. For Example, Sahu Et Al. 2025 Critically Reviewed Research Showing How ML Algorithms Have Been Used For Supporting The Design Of Nanoparticles, Predicting Drug Release Profiles, And Personalising Patient Specific Therapeutic Regimens.

AI-Driven Formulation Optimization Platforms :- Zhang et al. (2025) developed TuNa-AI, a hybrid keras-machine trained to perform automated liquid handling via ML so as to efficiently explore the nanoparticle formulation space. A total dataset of approximately 1275 unique formulations was created, with composition optimization leading to a success rate of 42.9% in generating nanoparticles based on the composition used in the formulation (Zhang et al., 2025). In an applied example of use, the AI based formulation system reduced the excipient use in a trametinib formulation by 75% while retaining in vitro activity and in vivo pharmacokinetics of the drug after delivery in vivo. As part of the work completed by Shahiwala et al. (2023) in the development of a neural network model to forecast the efficacious entrapment of the drug in the niosomal structure and the particle size, the results indicated that all of the trials resulted in > 97% accuracy of the model predictions. Furthermore, sensitivity analysis demonstrated that the drug/lipid ratio was the most significant variable affecting drug entrapment, while the cholesterol/surfactant ratio was also a key factor affecting the final physical property of the niosomes. In the research published by Silveira et al. (2025), the multi-step machine learning pipeline was used in the development of polymeric nanoparticles via nanoprecipitation, demonstrating that the artificial neural network (ANN) based model consistently performed better than other models. In another study conducted by Hanari et al. (2025) random forest models were utilized to predict drug encapsulation and drug loading of PLGA nanoparticles produced with microfluidic platforms with an R^2 of 0.93 and 0.96 respectively.

Combining AI with Quality by Design (QbD): The combined use of artificial and machine learning within the framework of QbD presents great potential to transform nanopharmaceuticals through the improvement of predictivity, reduction in experimental burden, and establishment of consistent, safe, high-quality products

(Panwar et al. 2026). QbD represents a systematic, risk-based strategy for embedding quality into the development process at the earliest stages of product development by means of establishing Quality Target Product Profiles (QTPPs), identifying Critical Quality Attributes (CQAs) and controlling Critical Material Attributes (CMAs) as well as Critical Process Parameters (CPPs). However, barriers to utilizing AI/ML together with QbD remain that include issues regarding data standardization, model generalizability, and the absence of a definitive regulatory framework as currently there is no guidance issued by the FDA that pertains to the relationship between artificial intelligence (AI) and nanomedicine (Chou et al. 2025). Additionally, Dorsey et al. 2024 described that research conducted in regard to LNP formulations currently consists largely of empirical research and has significant resource demands due to the numerous independent variables affecting LNP formulation development and expression, and described how ML techniques were beginning to be used to improve the productivity of LNP formulation development research by use of in silico models and predictions.

Application of Curcumin-Ritonavir Co-Loaded Nanocarriers: To develop curcumin-ritonavir co-loaded nanocarriers, the use of AI formulation design can solve many significant issues:

- **Drug-excipient ratio optimization:** Machine learning models would be able to estimate the most effective ratios of curcumin to ritonavir and their respective excipients in order to achieve the greatest efficiency of loading when using nanocarriers, and still have stable nanocarriers and the proper release kinetic characteristics.
- **Prediction of skin penetration:** The ability to predict how nanocarriers penetrate through skin via the stratum corneum is possible through artificial intelligence models trained to utilize dermal permeation datasets. AI provides valuable insight into how deep into the skin and how quickly medicine will diffuse across the skin once nanocarriers enter. This information allows researchers to choose the most effective formula parameters when creating topically applied skin cancer treatments.
- **Accelerated screening of stimuli-responsive materials:** AI model can quickly evaluate potential polymers and/or lipid based on their ability to respond to stimuli, such as pH or redox reaction, light intensity), in such a way as to determine if they are compatible with curcumin or ritonavir; this will decrease the number of tests per sample by a great deal.
- **Personalized formulation design:** Advanced AI platforms could potentially integrate patient-specific tumor characteristics (pH, enzyme profiles, receptor expression) to tailor co-loaded nanocarrier formulations for individualized therapy.

Various models such as Multi-Scale Machine-Learned Modelling Infrastructure (MuMMI), Agent-Based Modelling

(ABM), Quantitative Structure Activity Relationship (QSAR), Physiologically Based Pharmacokinetics (PBKK), and Pharmacokinetic/Pharmacodynamics (PKPD) have been developed over time, each improving our ability to predict the physical properties associated with forming NPs, how they interact with living organisms, where they go once in the body, and how toxic they are to living things (Kantesaria & Panda, 2026). These various modelling approaches not only help to create improved nanoparticle structures but also reduce the experimental burden, increase prediction accuracy and enhance translational research activities.

13. Future Directions

Currently, there has been very little research done on using curcumin with ritonavir in combo with nanoparticle based drug delivery in order to find a way to overcome multi-drug resistance in skin cancer. In order to bring this idea into practice, multiple interconnected fields will need to make progress including personalized nanomedicine, development of optimal drug ratios, a structured roadmap for clinical translation of this idea, and linking it with current precision oncology platforms.

13.1 Personalized Nanomedicine

The older model of treatment in general is known as the “one size fits all” which fails to account for the vast differences both within a particular tumor as well as among all of the patients who have been diagnosed with either the same type of tumor or similar types of tumors (Rosenblum and Peer, 2014). Personalized nanomedicines aim to provide individualized therapeutic intervention by utilizing nanoscale drug delivery platforms combined with patient-specific biological data collected through multi-omics profiling, including: genomics, transcriptomics, proteomics, and metabolomics (Rosenblum and Peer, 2014; Herrmann and Rösslein, 2016).

For curcumin–ritonavir co-loaded nanocarriers in skin carcinoma, personalization could operate at multiple levels:

- **Tumor profiling-guided formulation selection:-** Through genomic and transcriptomic profiling of each epidermal malignancy, clinicians can assess how extensively P-glycoprotein over-expression (P-gp/ABCB1) and/or other efflux transporters are expressed within their patients. This information will help them determine which individuals would benefit most from the inhibition of the P-gp efflux pathway by using ritonavir in combination with their administered medication/radiation therapies. The ideal patients for employing the co-loaded formulation within the nanoparticle will be those exhibiting an established multi-drug resistant (MDR) phenotype. Conversely, individuals that exhibit little to no resistance to efflux mediated drug channeling should consider the use of curcumin monotherapy in conjunction with their formulated nanocarriers.
- **Receptor-guided targeting:** You can improve how well nanoparticle carriers enter into the tumors of individual patients with the right receptor binding ligands (such as folate, transferrin, or hyaluronic

acid) by using expression profiling for those specific receptors. Nanotechnology has offered solution(s) to the limitations seen in standard drugs through its ability to deliver medications more effectively to the tumor, thereby allowing greater distributions within the target site and lowering the amount of medication delivered systemically (Yu et al., 2025). Hristova-Panusheva and colleagues (2024) stated that the application of modern nanotechnology is essential for the development of site-specific cancer treatments as well as for developing individualized medicine, and the direction for the continued success of future individualized cancer nanomedicines is dependent upon continued optimization of nanocarrier technology.

- **Screening of theranostic nanoparticles:** The authors (Yaari et al., 2016) used a new way to combine 100 nm liposomes containing different cancer drugs with DNA barcodes, which enabled an assessment of the efficacy of these 100 nm liposomes at a single cell level during the screening process of multiple drugs and an individualized drug treatment plan to be developed for each mouse with triple-negative breast cancer. The adaptation of this tissue barcoded nanoparticle type of screening for skin cancer patients receiving curcumin in combination with ritonavir would provide the ability to quickly develop an optimal drug formulation for each individual patient.
- **Nanomedicine design guided by omics:** Zhang et al. (2025) have used an omics-guided curcumin-based nanomicelle vehicle for the treatment of melanoma, where clinical transcriptome data were mined to find endoplasmic reticulum stress weaknesses and create nanoparticles based on the results. In addition, based on pharmacogenomics data collected, increased expression of the cellular stress biomarker (CHOP) correlates to increased response to many agents; therefore, possible synergistic partners could be evaluated for their potential uses with this delivery system (Zhang et al., 2025). This study highlights how using multiple omics data types can offer a rationale for developing skin cancer-specific nanocarriers.

Nanoinformatics is a new type of research that will allow computational designs for drugs that contain nanoparticles. This means creating ways of designing nanoparticles using computational techniques, and eventually determining how to manufacture nanocarrier-encapsulated drugs that will be safer and work better for each individual patient (Sadan et. al., 2018). By matching what types of nanoparticles can be used for a certain patient's type of cancer with their unique biological characteristics, we can provide patients with a unique type of treatment (Buljan & Wick, 2022).

13.2 Optimized Drug Ratios

The optimization of the drug/drug ratio (i.e. Co-loading) to attain synergistic efficacy is a major missing part of the co-loaded nanocarrier design literature. While some ratios of co-administered drugs may demonstrate a synergistic effect, other ratios of the same co-administered drug may display an antagonistic effect. Therefore, the co-administered drugs that would provide the best possible outcomes would be those that have an optimal ratio of efficacy through either drug at a reduced dosage (Mayer & Janoff, 2007). This paradigm changing idea, that the synergistic window is not the same across all drug combinations, has major ramifications on the design of a curcumin–ritonavir co-loaded system.

The ratiometric delivery paradigm: Ratiometric delivery involves the combined use of multiple different chemotherapeutic agents together as an alternative form of cancer treatment by providing a method for the delivery of many chemotherapeutics in equal quantities at fixed ratios that provide additional benefit in the treatment of cancer via synergies through each of the individual chemotherapeutic agents and significantly reducing systemic side effects and multidrug resistance (Khade et al., 2025). Franco and Oliveira (2017). reviewed the evolution of ratiometric delivery through synergies in vitro, and the ratiometric delivery of chemotherapies in-vivo, with the foundation of developing alternative strategies of ratiometric delivery through the development of nanocarriers, to achieve true synergies through in-vivo delivery of chemotherapeutic agents.

Several technical platforms have been developed to achieve ratiometric control:

- **Polymer-drug conjugate approach:-**Aryal et al. (2011) utilized a polymer-drug conjugate strategy to create polymeric nanoparticles whereby drug loading could be accurately controlled due to their ability to obtain both a specific ratio of drug to polymer (i.e. DOX-PLA, CPT-PLA) and then have these drug-polymer conjugates encapsulated into lipid-encapsulated nanoparticles at >90% efficiency. Controlling the molar ratio of drug-PLA could achieve both a tailored loading yield and improved performance for the dual-drug loaded nanoparticle when compared to cocktail mixtures made from single-drug loaded nanoparticles.
- **PLGA-based ratiometric co-loading:** Miao et al. (2014) constructed nanoparticles made out of PLGA with nearly perfect ratiometric co-loading of the two drugs i.e. gemcitabine monophosphate and cisplatin at an optimal synergistic ratio of five parts gemcitabine monophosphate to one-part cisplatin (5:1 mol:mol). This means that greater than 70% of both of these drugs encapsulated in the nanoparticles will be taken up by the tumor cells, both in vitro and in vivo, and will produce synergies against the cancer (bladder) in a model which contained stroma around the tumor cells.
- **Macrocyclic amphiphile-based systems:** In 2021, Zhang et al. reported self-assembled nanoparticles (called MASNs) that were derived from amphiphilic

macrocycles (pharmaceuticals) through host-guest interactions, which can deliver precise amounts of multiple drugs at predetermined ratios to achieve therapeutic effect by properly combining drug ratio with the known concentrations of the drugs and their characteristics (affinity). Thus, MASNs allow for the rapid determination of the optimal drug ratio in vitro and thus can produce therapeutic benefits in vivo (Zhang et al., 2021).

Application to curcumin–ritonavir co-loaded systems: For the curcumin–ritonavir combination specifically, the optimal ratio remains to be determined. Key considerations include:

- In order for curcumin and ritonavir to be used together there needs to be proper balancing of the amount of curcumin in relation to how much ritonavir is used. If not enough ritonavir is used there may not be adequate P-glycoprotein (P-gp) blockade, and using too much ritonavir may cause CYP3A4 inhibition that may lead to adverse drug interaction.
- Yang et al have recently (2018) described a new approach to use a modular coassembly technique by the coordinated delivery (codelivery) of the two drugs doxorubicin and curcumin. In this model, curcumin acts as a modulator of multidrug resistance (MDR) by being assembled with doxorubicin into a single nanocarrier with acid sensitive linker functionality to create a ratiometric delivery system that produces maximum synergistic activity. A similar method could be developed for curcumin and ritonavir.
- To take advantage of synergistic activity, different release methods could be used employing timed (or sequential) release to first deliver ritonavir in order to inhibit (block) P-gp, followed by curcumin, during this sensitizing period. Baek and Cho (2017) provided an example of this concept using folate conjugated lipid nanoparticles containing both paclitaxel and curcumin where treatment with curcumin is completed rapidly (first) compared to paclitaxel thereby allowing for sufficient P-glycoprotein blockade (inhibition) to allow increasing cellular uptake (accumulation) and cytotoxicity of the paclitaxel.
- Lin et al. (2018) developed a legumain-sensitive nanoparticle based delivery system for the synergistic use of curcumin and doxorubicin through the inhibition of MCF-7/ADR resistance in MCF-7/ADR cancer cells by decreased expression of the multidrug resistance protein (MDRP) and increased nuclear accumulation of doxorubicin. Such systems similar (enzyme-resistant) have great potential use in respect to curcumin and ritonavir.

13.3 Clinical Translation Roadmap

Translating curcumin–ritonavir co-loaded nanocarriers from preclinical concept to clinical application requires a structured, phased approach addressing the multiple barriers identified in the literature. The

nanomedical literature has almost reached a consensus that translating data from preclinical animal models to the clinical and commercial use of nanomedicines is very difficult (Longo et al., 2018).

A proposed clinical translation roadmap encompasses the following sequential stages:-

Phase I — Preclinical optimization (current stage):

- Determining appropriate curcumin:ritonavir molar ratio by comparing CI values using a panel of three different MDR skin carcinoma cell lines (A431, A375, SK-MEL-28) that have been treated so that they develop acquired resistance to ritonavir
- Determining which type of nano carrier will be used (lipid-based NLCs, polymeric PLGA nanomaterials, or hybrid systems) to efficiently deliver both drugs and remain stable while also allowing for transdermal drug delivery
- Conducting efficacy testing in relevant animal models of MDR skin cancer, including studying how the drugs move through the body when dosed
- Conducting comprehensive safety studies, including measuring dermal irritation, hypersensitivity, Mutagenicity, as well as measuring systemic and total exposures.

Phase II — Formulation scale-up and regulatory preparation:

- Scalable manufacturing processes will be developed through novel approaches, like using microfluidics or using high-pressure homogenization, and desire the use of validated analytical methodologies that will be used for simultaneous quantification of curcumin and ritonavir.
- A Quality by Design (QbD) framework will develop critical quality attributes (CQA's), critical material attributes (CMA's), and critical process parameters (CPP's) of the curcumin-altered ritonavir drug product.
- GLP-compliant toxicology studies will be developed in support of the New Drug Application (NDA) for the curcumin-altered ritonavir drug product.
- IND-enabling studies will begin early in the project with the regulatory agency (FDA) in order to get clarification of guidance regarding drug-drug combination product or new drug application.

Phase III — Clinical evaluation:

- Evaluate for safety, efficacy and dermal pharmacokinetics of slow-release form of drug in first-in-human subjects with MDR HCS and cutaneous melanoma for Phase I trial.
- Further evaluate pharmacodynamics of new drug through tumor biopsy analysis for P-gp mRNA, drug concentration within the tumor, and assess overall response rates in a Phase II proof of concept clinical trial.
- Potentially evaluate drug in combination therapy with other positive systemic therapies (immunotherapy and MEK-

inhibitor therapy) in a planned Phase II/III clinical trial.

Before targeted nanoparticles can be translated into clinical settings, several issues still need to be solved. These include property optimization, reliable and accurate characterization, and determining their safety and effectiveness in clinical trials (Di Filippo et al., 2023). Critical steps for translating nanotherapeutics into clinical settings will require significant further interdisciplinary and international collaboration among the entire stakeholder community from the laboratory to patients (Bregoli et al., 2016). Although there has been considerable success in establishing preclinical effectiveness, translating that success into clinics continues to pose challenges, such as poor penetration through the skin, heterogeneity of tumors, immune clearance, and regulatory challenges (Yu et al., 2025).

13.4 Integration with Precision Oncology

The objective of precision oncology is for each patient to receive the most appropriate therapy based on his or her individual tumor's molecular profile. The combination of curcumin and ritonavir delivered via nanocarriers represents a major paradigm shift for the treatment of MDR SKC with respect to precision oncology.

Biomarkers for Patient Selection: Finding and confirming predictive biomarkers will be necessary when determining which patients should be treated with curcumin–ritonavir in nanocarriers. The major potential biomarkers are:

- P-gp (ABCB1) expression in tumor biopsies; patients with high levels of expression will benefit from ritonavir since ritonavir will inhibit the efflux of drugs by P-gp.
- The level of activation in the NFκB Pathway of a patient. Curcumin's anticancer function is thought to occur through the repression of NFκB pathways.
- At the same time that a patient is being assessed for selection for curcumin–ritonavir therapy, a patient's expression of folate receptors and transferrin receptors may also be important when selecting appropriate targeting ligands.
- In addition, after the determination of the appropriate ligands, advanced imaging may be used to generate 3D tumor pH maps in order to assist in obtaining the optimum pH-responsive design for the nanocarrier.

To achieve successful translation of precision nanomedicine, there will need to be a productive partnership between laboratory and clinical investigators so that the appropriate treatment can be matched to each patient and provided at a dose sufficient to enhance the patient's response to treatment (Sharma et al., 2017).

Integration with existing precision oncology workflows in melanoma:

The integration of curcumin–ritonavir nanocarriers into current precision oncology workflows for melanoma includes their use as an adjunctive topical therapy for:

- BRAF V600E mutant melanomas that are resistant to BRAF/MEK inhibitors due to upregulation of P-glycoprotein-mediated multidrug

resistance (the mechanism of action of these drugs)

- BRAF wild-type melanomas that have limited options for targeted therapies and can be resensitized to conventional treatments by using curcumin–ritonavir nanocarriers as an adjunctive topical therapy, which reverses the effects of MDR

In work by Nele et al. (2024), researchers showed that self-assembling nanoparticles could be used to deliver miRNA to treat metastatic melanoma caused by BRAF mutation and prevent drug resistance to the targeted therapies. The miRNA-loaded nanoparticles potentiated the efficacy of the combination of the targeted therapy with the dose-response results of the study. Similarly, curcumin–ritonavir nanocarrier conjugates could potentially be combined with molecularly-targeted therapies.

Monitoring through liquid biopsy: could be a way to monitor treatment responses and detect early resistance to treatment; that is, circulating tumor DNA (ctDNA) and circulating tumor cells (CTCs). Monitoring ABCB1 gene amplification and/or P-gp levels in liquid biopsy samples may help to identify when to start, adjust, or stop treatment with the curcumin–ritonavir nanocarrier treatment.

Immunotherapy used in conjunction with Precision Oncology: Each potential future pathway is quite distinct, e.g., curcumin–ritonavir nanoparticles combined with immune checkpoint inhibitors (Moni et al., 2025). Nanotechnology integrated with advancements in genetics and proteomics can yield scalable, patient-specific therapy in the treatment of melanoma, thus revolutionising the field of melanoma therapy through the introduction of these interdisciplinary technologies into clinical practice to develop safer and more effective treatments for melanoma, as well as improving overall access to treatment. Curcumin's immunomodulatory ability, in conjunction with ritonavir's P-glycoprotein (P-gp) inhibitory effects, and the ability of nanoparticles to provide targeted delivery may provide synergistic effects with immune checkpoint inhibitors to overcome two of the main obstacles to durable responses to treatment in advanced skin cancer — drug resistance and immune evasion.

Digital twin and computational modelling : The concept of having a "digital twin" of a patient is rapidly becoming a reality. Progress is being made in incorporating individual patient-specific data into computational pharmacokinetic/pharmacodynamic (PK/PD) models for the purpose of creating "digital twins" of patients, thus allowing for the optimization of the formulation, drug ratios, dosing schedule, and drug delivery route of nanocarriers, in silico (by computer) prior to clinical administration. This type of approach will also support the broader vision of precision nanomedicine as it relates to a patient-centered therapeutic platform created through the combination of omics data, AI-driven formulation design, and the engineering of nanocarriers.

14. Conclusion

MDR (multidrug resistant) cancer is probably the greatest impediment to successful pharmacological treatment of skin carcinoma primarily due to the

overexpression of ABC (ATP-Dependent Binding Cassette) efflux transporters such as P-glycoprotein (P-gp/ABCB1), which actively transports chemotherapeutic agents out of the tumor cell. Additionally, curcumin and ritonavir co-loaded nano-particle carriers have been examined in this review to provide a comprehensive review of the scientific rationale, and the preclinical evidence, formulation strategies, and outlook for the use of these compounds in reversing MDR for skin carcinoma.

Summary of the Synergy Concept

The combined use of curcumin and ritonavir is a reasonable strategy with regard to the development of an effective treatment regimen for treatment resistant MDR skin cancer. Curcumin is a naturally occurring polyphenol from the plant Curcuma longa that has been shown to exhibit multiple mechanisms of action that exhibit strong anticancer activity in humans. These mechanisms of action include modulation of several oncogenic pathways (e.g., NF- kB, STAT3, PI3K/Akt/mTOR), induction of apoptosis, suppression of angiogenesis, and reversal of multidrug resistance (Rathod & Mishra, 2025). Therefore, while curcumin can act as both a direct cytotoxic anticancer agent and a chemosensitizer of P-glycoprotein, curcumin has also been shown to stimulate drug accumulation in cancer cell lines resistant to chemotherapy by serving as a substrate for P-glycoprotein-mediated drug and playing a direct role in stimulating the activity of the ATP-dependent drug efflux transporter (Poma et al., 2024). Ritonavir is currently FDA approved as an HIV protease inhibitor and acts as a potent inhibitor of P-glycoprotein and CYP3A4 enzymes, which provides both pharmacokinetic enhancement and blockade of direct efflux of drugs from MDR cancer cells. The synergistic activity of curcumin and ritonavir through their respective mechanisms of action against MDR skin cancer will allow for the treatment of MDR skin cancer through multiple mechanisms of action at the same time.

Ritonavir competes with curcumin to block the transport of dissolved anticancer drugs through P-glycoprotein pathways. The ratios between ritonavir and curcumin may lead to synergistic or antagonistic effects on drug delivery. This underscores the importance of determining an effective curcumin-ritonavir ratio in order to achieve maximum therapeutic benefit (Franco & Oliveira, 2017). By co-delivering both ritonavir and curcumin through predetermined ratios that exhibit a synergistic interaction, the concentration of both drugs within the nanocarrier system is maintained from formulation to intracellular release. This principle has been shown to hold true in numerous studies using co-loaded nanocarrier systems (Khade et al., 2025; Mayer & Janoff, 2007).

Importance of Co-Loaded Nanocarriers

To achieve optimal co-delivery of curcumin and ritonavir to a tumor site, the following limitations must be taken into consideration: both compounds exhibit very low aqueous solubility (curcumin) or extreme lipophilicity (ritonavir), rapid breakdown at physiological pH (curcumin), and/or poor bioavailability (curcumin).

Due to these limitations, conventional means of administering either drug cannot adequately achieve therapeutic concentrations over time, let alone achieve the desired anti-tumor effects when co-

administered via the conventional free drug approach.

By utilizing co-loaded nanocarriers (such as an oily lipid or polymeric matrix) to encapsulate both drugs, improve the solubility and stability of both drugs, provide controlled and sustained release of both drugs over long periods of time, and facilitate better penetration through the skin due to the nanocarrier's microenvironment interactions with the stratum corneum barrier, these limitations may be overcome (Borgheti-Cardoso et al., 2020).

A variety of types of nanocarrier systems have been shown to be capable of co-loading two different therapies including nanostructured lipid carriers (NLCs), polymeric nanoparticles (PLGA, chitosan), liposomes, solid lipid nanoparticles (SLNs), nanoemulsions, and hybrid systems. Currently, drug delivery methods increasingly utilize "multi-pronged" drug combinations that deliver multiple types of drugs at the same time using differing routes of action (Jhaveri et al, 2014). In addition, by placing active targeting ligands (e.g., folate, transferrin, hyaluronic acid) on the surface of the nanocarrier pops a method to gain receptor entrance into cancer cells and a method to omit P-glycoprotein (P-gp) evasion via efflux at the membrane of the cell. In addition, folate-conjugated nanoparticles incorporating curcumin have demonstrated greater cellular uptake and cytotoxicity, greater dose-dependent inhibition of cellular proliferation, and greater dose-dependent anti-proliferative impact when delivering lower concentrations of curcumin to cells in preclinical testing (Nosrati-Oskouie et al, 2024). Responsive stimulatory nanocarriers that are capable of utilizing the acidic microenvironment; elevated oxidative potential; or overexpression of a specific enzyme found in neoplasia will add precision to local drug delivery by initiating controlled drug release at the targeted site (Bhattacharya et al, 2023; Saravanakumar et al, 2019).

For topical administration to patients with skin cancers, bioavailability of nanocarriers presents distinct benefits such as increased transdermal absorption and retention, increased follicular penetration, and formation of a long-term drug reservoir in the viable epidermis and dermis (the locations of superficial skin tumors) where optical nanocarrier application may be maximized. Novel therapeutic approaches to improve upon prior methods of drug delivery have been developed using nanofabrication techniques from the field of nanotechnology.

Potential to Overcome MDR in Skin Carcinoma

Based on the previous sections' information, it appears that curcumin and ritonavir co-delivered via nanocarriers may have significant potential to overcome multi-drug resistant (MDR) skin cancer using multiple mechanisms. PEG coated curcumin/doxorubicin nanoparticles inhibited the prominent efflux proteins in drug resistant cancer cells thus improving bioavailability in resistant tumour xenografts and significantly inhibiting tumour growth (Rejinold et al., 2018). In studies by Lin et al. (2018), drug co-delivery of curcumin and doxorubicin through a legumain-sensitive nanocarrier inhibited multi-drug resistance in MCF-7/ADR cells through increased nuclear drug

accumulation and inhibition of MDRP expression. Studies by Baek & Cho (2017), found that the rapid release of curcumin (from folate-conjugated co-loaded lipid nanoparticles) enabled sufficient P-glycoprotein inhibition which led to greater cytotoxicity through increased cellular uptake of the co-loaded chemotherapeutic drug.

While these studies use curcumin with doxorubicin or paclitaxel (instead of ritonavir), they demonstrate proof of concept that nanocarrier-mediated co-delivery of curcumin together with a P-gp modulator or chemotherapeutic agent effectively reverses MDR. By utilizing ritonavir as the P-gp inhibitor, this provides the opportunity for an additional advantage of proven clinical safety, well-known pharmacology and dual CYP 3A4/P-gp inhibitory properties.

Clinical Outlook

The curcumin-ritonavir co-loaded nanocarrier design for treating skin carcinoma has a strong scientific basis but no trial data are available at this time. The current general agreement among researchers is that it is not easy to apply findings from preclinical animal studies to develop nanomedicine for human application (Longo et al., 2018). Four important conditions must be fulfilled before the clinical application will be successful: 1. Performing systematic in vitro synergy studies with Combination Index (CI) for each drug on a population of drug-resistant (MDR) skin carcinoma cells to identify the optimal curcumin:ritonavir molar ratio (CI-optimisation); 2. Validation of their anti-tumour activity in animal models of MDR skin carcinoma and then injury, as well, to ensure clinical application can include both topical and systemic dosing; 3. Complete thorough evaluation of the dermal safety and pharmacokinetic profile of each drug in order to establish the therapeutic window for this combination therapy; and 4. Development of large-scale manufacturing of nanocarriers through the Quality by Design (QbD) concept, where Good Manufacturing Practice (GMP) residual risks can be effectively addressed.

The ability to optimize nanoformulations more rapidly with the use of artificial intelligence (AI) and machine learning (ML) is encouraging as well as the ability to accurately target drug delivery via use of stimuli-responsive and ligand-targeted platforms because of the rapid advancements. Additionally, with advances in multi-omic profiling and understanding of tumor heterogeneity, personalized therapeutic strategies can be developed. By utilizing clinical and molecular biomarkers to create an individualized treatment plan through use of nanotechnology, there will be an opportunity to improve patient prognoses and disease management as well as drug selection and dosing due to the availability of personalized nanomedicine (Rosenblum & Peer, 2014). Moreover, the ability to combine curcumin with ritonavir (labeled) nanocarriers with immune checkpoint inhibitors potentially solves the problems of drug resistance and immune evasion.

the two dominant barriers to durable remission in advanced skin cancer.

In conclusion, nanocarrier co-formulation with curcumin and ritonavir is person-centered, scientifically and mechanistically

based for treating multidrug-resistant skin cancer. The combination of ritonavir's powerful P-gp inhibitors plus curcumin's anti-cancer and chemosensitizing qualities can work synergistically using nanocarrier technology, which has specific applications for skin delivery, targeted release and optimal drug ratio. This successful combination will need sustained collaboration between multiple disciplines and stakeholders throughout this translational process from research to clinical application. There are several milestones that must be achieved in the translational process; therefore, an interdisciplinary and international approach involving all stakeholders across the continuum from bench to bedside is critical here (Bregoli et al., 2016). Although moving from bench to bedside remains lengthy process; the science supporting this work is robust; many enabling technologies exist; and there is a clear clinical need for this research.

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