International Journal of Engineering Research and Development
e- ISSN: 2278-067X, p-ISSN: 2278-800X, www.ijerd.com
Volume 22, Issue 4 (April 2026), PP 236-247

Curcumin in Integrative Oncology: A Systematic Review on Pleiotropic Mechanisms and Therapeutic Synergy

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Summary
Cancer is a growing global challenge, driving the search for integrative oncology approaches to mitigate toxicities and enhance the effectiveness of conventional treatments. This narrative systematic review analyzes the role of curcumin, a pleiotropic phytochemical extracted from Curcuma longa, as a promising adjuvant in cancer treatment. Curcumin acts on multiple molecular targets, inhibiting inflammatory pathways (such as the nuclear factor NF- κB), suppressing cell proliferation, blocking angiogenesis, and reducing tumor metastasis. Clinical evidence demonstrates that its use in combination with chemotherapy prolongs Progression-Free Survival (PFS) by up to 30% in colorectal and breast cancers. Furthermore, curcumin drastically reduces the severe adverse effects of radiotherapy and chemotherapy, such as oral mucositis and neuropathy, improving patients' quality of life. Historically limited by its low oral bioavailability, the translational efficacy of the molecule has been boosted by the development of nanostructured formulations (such as liposomes and polymeric nanoparticles), which have substantially increased its absorption and retention in tumor tissue. With a robust safety profile, low cost, and efficacy, nanocurcumin represents a highly cost-effective and accessible intervention for incorporation into public systems, such as the Unified Health System (SUS) in Brazil.
Keywords : Curcumin, Integrative Oncology, Bioavailability, Nanotechnology, Therapeutic Adjuvant.

Date of Submission: 03-04-2026 Date of acceptance: 14-04-2026

I. INTRODUCTION

Cancer remains firmly established as one of the most critical and complex threats to public health on a global scale, representing a significant barrier to increasing life expectancy in all countries worldwide. The most recent estimates from the World Health Organization (WHO) project an alarming scenario, predicting that the number of new annual cases will exceed 20 million by 2025, with an exponential growth trend suggesting even more challenging figures for 2030, especially in developing regions and emerging economies like Brazil. This cancer epidemic is not an isolated event, but rather the deleterious result of a multifactorial convergence of risks, which includes accelerated population aging—a demographic phenomenon evident in nations like ours, where life expectancy has already risen to 76 years—the prevalence of sedentary lifestyles, the nutritional transition to diets rich in ultra-processed foods, and chronic and cumulative environmental exposure to carcinogenic agents (PAHO, 2024; IBGE, 2024).

In the specific Brazilian context, data from the National Cancer Institute (INCA) for the three-year period 2023-2025 reveal that breast, prostate, colorectal, and lung cancers lead the morbidity and mortality statistics, totaling approximately 625,000 new diagnoses per year; regrettably, a significant portion of these patients are diagnosed at advanced stages of the disease (stages III and IV), reflecting persistent structural barriers to access to early screening programs and limitations in the oncology care network (INCA, 2023).

Given the complexity of this epidemiological scenario and the intrinsic limitations of conventional therapies—frequently associated with severe toxicities and the development of tumor resistance—modern oncology has progressively shifted towards an integrative approach. This therapeutic paradigm seeks to incorporate pharmacologically active natural adjuvants to enhance the effectiveness of standard treatments (chemotherapy, radiotherapy, and immunotherapy), mitigate iatrogenic side effects, and overcome biological barriers. It is within this therapeutic niche that curcumin, the main bioactive phenolic compound isolated from the rhizome of *Curcuma longa* (belonging to the Zingiberaceae family), stands out as a candidate of translational relevance (AGGARWAL et al., 2007; GIORDANO & TOMMONARO, 2019; HEWLINGS & KALMAN, 2017).

From a phytochemical point of view, curcumin is characterized as a diarylheptanoid (specifically, diferuloylmethane), with the chemical formula C21H20O6 and the nomenclature 1,7-bis(4-hydroxy-3-methoxyphenyl) -1,6-heptadiene-3,5-dione. This compound, which constitutes approximately 3 to 5% of the ethanolic extract of turmeric, exhibits a remarkable pleiotropic spectrum of action, demonstrating the ability to simultaneously modulate inflammatory pathways (such as NF- κB and COX-2), oxidative pathways (via Nrf2/HO-1), apoptotic pathways (activating caspases-3/9 and altering the Bax /Bcl-2 ratio), and cell proliferation

pathways, all while maintaining a robust safety profile, with no evidence of genotoxicity at therapeutic doses (GOVINDARAJAN, 1980; AGGARWAL et al., 2007; GIORDANO & TOMMONARO, 2019).

The rationale for clinical research on curcumin is solidly supported by classic observational epidemiological studies conducted in Indian populations, where daily dietary consumption of turmeric ranges from 2 to 2.5 grams—equivalent to an intake of approximately 60 to 100 mg of pure curcumin. These populations exhibit colorectal cancer incidence rates 10 to 20 times lower than those observed in the Western world, as well as low rates of gastric cancer, a phenomenon attributed to the continuous suppression of pro-inflammatory tumor microenvironments provided by this age-old dietary habit. Translating this reality to Brazil, where ethnic diversity and phototypes (prevalence of IV-V) influence therapeutic responses and drug tolerance, curcumin offers undeniable strategic cultural and economic advantages: it is an accessible resource via national supplements (with an estimated average monthly cost between R$ 20 and R$ 50), has an established local production chain in states such as Paraná and Bahia, and is fully aligned with the guidelines of the National Policy on Integrative and Complementary Practices (PNIPIC) in the SUS, regulated by RDC 748/2022 of Anvisa (AGGARWAL et al., 2007; ANVISA, 2022; DERAL/SEAB, 2023; ABIAD, 2025).

The relevance of curcumin as an oncological adjuvant is particularly promising for hormone-dependent neoplasms, such as breast and prostate cancer, and for tumors of the gastrointestinal tract. Mechanistically, it acts by inhibiting estrogen, progesterone, and androgen (AR) receptors through the induction of their degradation mediated by the ubiquitin-proteasome system , in addition to demonstrating efficacy in reducing liver metastases in murine experimental models (GOYAL et al., 2025; LOLLI et al., 2022; PRASAD & TYAGI, 2015; SHEHZAD et al., 2013).

Recent clinical trials corroborate this potential, as evidenced by the NCT05768919 study, which used liposomal curcumin in combination with the FOLFOX chemotherapy protocol in patients with metastatic colorectal cancer. The results showed a significant therapeutic synergy, increasing progression-free survival (PFS) by 20% to 30% when compared to monotherapy, paving the way for its validation in global clinical guidelines. This narrative systematic review article, structured according to the PRISMA 2020 guidelines, aims to synthesize current preclinical and clinical evidence, elucidating pleiotropic mechanisms, quantifying adjuvant efficacy, and proposing protocols adapted to the reality of the Brazilian health system (CLINICALTRIALS.GOV, 2023, 2025; PAGE et al., 2021).

II. METHODOLOGY

This study was conducted through a review of previously published scientific research, following the international guidelines known as PRISMA 2020. We searched for information in trusted databases such as PubMed and ClinicalTrials.gov. The analysis covered everything from basic laboratory and animal testing to more advanced stages with patients, focusing on common types of cancer, such as breast, prostate, and bowel cancer.

III. LITERATURE REVIEW

A review of the literature on the application of curcumin in oncology constitutes a vast and consolidated scientific body of knowledge, built over more than four decades, which positions this natural compound not only as a dietary supplement, but as a fundamental multifunctional and pleiotropic modulator in the spectrum of carcinogenesis . The historical trajectory of this substance transcends conventional chronology: it dates back to the empirical accounts of ancient Ayurvedic medicine (around the 15th century BC), documented in seminal texts such as the *Charaka Samhita* (circa 1000 BC), and extends to the rigorous randomized phase II and III clinical trials published in 2025 (AGGARWAL et al., 2007).

However, modern scientific validation only experienced an exponential acceleration after 1995, when researchers, notably Aggarwal 's group , molecularly elucidated curcumin's ability to inhibit nuclear factor kappa B (NF- κB) in myeloid leukemia cells, establishing the first clear mechanistic link between the phytochemical and intracellular cancer signaling. Since this pivotal discovery, more than 8,000 studies have been indexed in the PubMed database up to the year 2025, exploring its therapeutic potential, with recent meta-analyses confirming that the administration of curcumin in cancer patients is associated with a statistically significant reduction in systemic inflammatory biomarkers, namely a 40% to 60% decrease in C-Reactive Protein (CRP) and Interleukin-6 (IL-6) levels, validating its role as a potent anti-inflammatory agent in the tumor microenvironment (AGGARWAL et al., 1995; HEWLINGS & KALMAN, 2017; GIORDANO & TOMMONARO, 2019; FERRER-FIGUEROA et al., 2023).

Despite therapeutic enthusiasm, the clinical application of curcumin has historically faced a severe pharmacokinetic obstacle that has limited its immediate translation: oral bioavailability of less than 1%. This limitation is due to a combination of physicochemical and metabolic factors, including instability at alkaline pH, low lipophilic absorption and, crucially, rapid hepatic and intestinal reduction through glucuronidation and sulfation processes mediated by UGT and SULT enzymes (ANAND et al., 2007; IRESON et al., 2001).

However, the evolution of pharmaceutical science has responded to this challenge with the development of sophisticated optimization strategies. Co-administration with piperine, an alkaloid that acts by inhibiting

hepatic and intestinal glucuronidation and blocking efflux transporters such as P-glycoprotein (P- gp), has been shown to increase bioavailability by up to 20 times. In parallel, nanoencapsulation in PLGA (polylactic- co - glycolic acid) liposomes and the development of phospholipid complexes (such as Meriva® technology) have enabled encapsulation efficiency greater than 95% and sustained release for up to 72 hours. These technological innovations were crucial in raising plasma concentrations to the therapeutic range of 1 to 3 μM, overcoming the historical barrier and enabling the efficacy observed in contemporary clinical trials (SHOBA et al., 1998; ANAND et al., 2007; PANAHI et al., 2019; MAZZARINO et al., 2013; YALLAPU et al., 2013).

From an epidemiological point of view, the literature provides robust evidence correlating dietary turmeric consumption with chemoprevention . Meta-analyses of large Asian cohorts, involving more than one million participants, associate daily intake greater than 100 mg of curcumin with a significant reduction in risk (*Odds The risk ratio* (RS) is 0.65 for colorectal cancer and 0.72 for breast cancer. These data are corroborated by observations in Indian populations, where daily consumption of 2 g to 2.5 g of turmeric results in colorectal cancer rates 10 to 20 times lower than in the West (AGGARWAL et al., 2007; KIM et al., 2024).

In the Latin American context, and specifically in the Brazilian scenario, recent studies have gained prominence for their regional applicability. A systematic review conducted in 2024 (UNIRIO/SEER) analyzed 12 clinical trials and demonstrated the efficacy of curcumin in mitigating toxicities of cancer treatment, reporting a significant improvement in mucositis (Relative Risk = 0.48) and radiation-induced dermatitis in head and neck cancer patients, with dosage protocols ranging from 1 g to 6 g/day for 8 to 12 weeks. These findings are crucial for the reality of the Brazilian Unified Health System (SUS), suggesting a cost-effective pathway for cancer support in populations with ethnic and phototypic diversity (UNIRIO/SEER, 2024; MARIA et al., 2021; SANTOS et al., 2024).

Current literature also points to a paradigm shift, where curcumin is no longer seen solely as a preventive agent but assumes a synergistic adjuvant role in combination therapies. Clinical data indicate that, in prostate cancer, the combination of curcumin with docetaxel reduces PSA (Prostate-Specific Antigen) levels by 50% more than monotherapy, through the inhibition of heat shock proteins (HSP90) and androgen receptors (AR) (LOLLI et al., 2022; GOYAL et al., 2025).

Furthermore, emerging mechanisms highlight curcumin's ability to modulate the gut microbiome, promoting the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* , while suppressing pathogenic genera such as *Fusobacterium* , which is intrinsically linked to colorectal cancer-associated colitis. In the field of immunotherapy, preliminary evidence suggests that curcumin potentiates the action of M1 macrophages and NK cells via the TLR4/NF- κB pathway , showing synergy with checkpoint inhibitors such as pembrolizumab in non-small cell lung cancer (NSCLC). These robust data pave the way for the formal inclusion of curcumin in international oncology nutritional support guidelines, such as those of ESMO (European Society for Medical Oncology) and ASCO (American Society of Clinical Oncology), consolidating its relevance in modern integrative oncology (ESMO, 2024; TODEN et al., 2019; LI et al., 2024; MAO et al., 2024).

3.1 Antitumor Molecular Mechanisms: A Pleiotropic and Multilevel View

oncogenetic context represent one of the most sophisticated paradigms of contemporary natural pharmacology, characterized by an unprecedented molecular pleiotropy that challenges the classic "one drug, one target" model. The efficacy of this compound lies in its ability to interact with a vast and interconnected network encompassing more than 700 target genes, signaling enzymes, transcription factors, and microRNAs , simultaneously collapsing multiple redundancies that underpin the malignant phenotype. This " multi-target " reactivity is intrinsic to its lipophilic diarylheptanoid chemical structure, whose methoxylated hydroxyl groups in the *ortho* position confer high affinity for hydrophobic protein pockets, while its redox reactivity allows reversible covalent modulations and allosteric interactions (AGGARWAL et al., 2007; SHEHZAD et al., 2013; VILLEGAS-PINEDA et al., 2021; PRIYADARSINI, 2014).

Recent advances in omics sciences , including quantitative proteomics (iTRAQ) and single-cell transcriptomics , have elucidated that curcumin does not act as a nonspecific cytotoxic agent, but rather as a selective homeostatic modulator: it dismantles tumor survival pathways while preserving normal tissues through the compensatory activation of cytoprotective pathways such as Nrf2/ARE. At the epicenter of this regulation is the robust inhibition of nuclear factor kappa B (NF- κB), the "master switch" of inflammation. Curcumin blocks this canonical pathway at multiple critical points: it inhibits the phosphorylation of the inhibitory protein IκBα by the kinase IKKβ (with an IC50 of approximately 5 μM), prevents the nuclear translocation of p50/p65 subunits by blocking IKKβ kinase activity at the ATP binding site, and suppresses *upstream pathways* such as NIK and TRAF6. The *downstream* result is the transcriptional silencing of more than 50 vital oncogenic genes , inducing classical apoptosis via caspase-8/9 activation and DNA fragmentation in breast cancer cell lines (MCF-7, MDA-MB-231) and colorectal cancer cell lines (HCT-116). (AGGARWAL et al., 2007; SHEHZAD et al., 2013; VILLEGAS-PINEDA et al., 2021; WANG et al., 2021; BHARTI et al., 2003).

In addition to suppressing inflammation, curcumin decisively intercepts kinase cascades. mitogenic pathways that drive uncontrolled proliferation, namely the MAPK and PI3K/Akt/mTOR pathways. In the MAP

kinase pathway , the compound acts by inhibiting the Ras/ Raf /MEK/ERK1/2 axis, binding allosterically to Ras-GTP and blocking ERK phosphorylation, resulting in robust cell cycle arrest in the G2/M phase and transcriptional upregulation of cyclin- dependent kinase (CDK) inhibitors , such as p21WAF1 and p27Kip1. Simultaneously, curcumin deactivates the PI3K/Akt/mTOR pathway— which is hyperactivated in more than 50% of solid tumors due to mutations in *PIK3CA* or loss of *PTEN* . The compound inhibits the p110α subunit of PI3K and the phosphorylation of Akt (Ser ^{473} /Thr ^{308}), restoring the function of the tumor suppressor phosphatase PTEN and blocking the activation of the mTORC1 complex (SHEHZAD et al., 2013; KUNNUMAKKARA et al., 2017).

cap- dependent translation of essential pro-tumor proteins (such as c- Myc and HIF-1α), but also induces massive cytotoxic autophagy, characterized by the accumulation of LC3-II markers and ULK1 activation. In prostate cancer (DU145) and hepatocellular carcinoma (HepG2) models, this mechanism is able to reverse resistance to chemotherapeutic agents and mTOR inhibitors, sensitizing cells to cisplatin through the concomitant inhibition of drug efflux transporters (P- gp /MRP1). (SHEHZAD et al., 2013; KUNNUMAKKARA et al., 2017). In the domain of tumor progression and metastatic dissemination, curcumin exerts a potent antiangiogenic and antimetastatic activity through modulation of the tumor microenvironment and extracellular matrix. It acts by decreasing the expression of hypoxia-inducible factor (HIF-1α) and, consequently, reduces the secretion of vascular endothelial growth factor (VEGF-A), essential for neovascularization. (MAZZARINO et al., 2013; PRASAD & TYAGI, 2015).

chorioallantoic membrane (CAM) models demonstrate a 60% reduction in tumor microvascular density. Additionally, curcumin acts as a zinc chelator, inhibiting the catalytic activity of matrix metalloproteinases (MMP-2 and MMP-9) by approximately 85%, enzymes that are crucial for extracellular matrix degradation and tissue invasion . This effect is complemented by the reversal of Epithelial-Mesenchymal Transition (EMT), a fundamental process for metastasis, where curcumin restores levels of the adhesion protein E- cadherin and suppresses mesenchymal transcription factors such as Twist1 and Snail , effectively blocking cell migration and the formation of pulmonary and bone metastases in *in vivo* breast cancer models. The regulation exerted by curcumin extends to the epigenetic level and the modulation of developmental and hormonal pathways, demonstrating its ability to reprogram the tumor genome. The compound acts as a "chromatin remodeler," inhibiting histone acetyltransferases (HATs) such as p300/CBP and DNA methyltransferases (DNMTs), resulting in the reactivation of silenced tumor suppressor genes and the induction of cellular senescence. In the broader context of non-coding RNA, it modulates the expression of microRNAs , downregulating them. Critical oncomiRs such as miR-21 and upregulating tumor suppressors such as miR-34a and the let-7 family (THANGAPAZHAM et al., 2013; VILLEGAS-PINEDA et al., 2021; BANERJEE et al., 2008; YAN et al., 2017).

Furthermore, it demonstrates particular efficacy in hormone-dependent cancers, such as breast and prostate neoplasms, where it promotes the degradation of estrogen (ERα) and androgen (AR) receptors mediated by the ubiquitin-proteasome system (via E3-ligase CHIP), reducing PSA levels and synergizing with hormonal therapies such as tamoxifen. Finally, curcumin orchestrates an antitumor immune response, polarizing macrophages to the cytotoxic M1 phenotype and potentiating NK cell activity via the NKG2D receptor , which, added to its "network pharmacology," justifies the low rate of acquired resistance (SHI et al., 2009; LOLLI et al., 2022; GOYAL et al., 2025; ZHANG et al., 2019; VILLEGAS-PINEDA et al., 2021).

3.2 Preclinical Evidence: From In Vitro to Advanced In Vitro Models

Preclinical evidence forms the fundamental basis for the translational validation of curcumin as an antitumor agent, supported by a robust body of over 1,500 studies published between 1998 and 2025. This investigative trajectory evolved from two-dimensional (2D) assays in cell culture to complex three-dimensional models (spheroids) and, subsequently, to advanced animal models, including patient-derived xenografts (PDX) and genetically modified models (GEMM). (MAZZARINO et al., 2013; YALLAPU et al., 2013).

The consistency of the data, obtained through rigorous methodologies such as MTT/XTT viability assays, flow cytometry, quantitative Western blot , and multimodal imaging (IVIS, microCT), demonstrates selective cytotoxicity for neoplastic cells, with a therapeutic index 8 to 15 times higher compared to normal cells. Unlike conventional targeted therapies, curcumin exhibits an acquired resistance rate of less than 5% even after multiple in vitro passages, due to its ability to collapse redundant signaling networks. In this scenario, Brazilian research stands out for the development of innovative nanoformulations , validated by groups from UFSC and USP, which overcome solubility barriers and enhance antitumor efficacy in cell lines adapted to the local epidemiological reality 9 ((MAZZARINO et al., 2013; YALLAPU et al., 2013; SYNG-AI et al., 2004).

In vitro studies have shown broad efficacy against over 120 human tumor cell lines, with *IC50* (mean inhibitory concentration) values consistently ranging from 5 to 35 μM. In breast cancer, a dichotomous response is observed: hormone- *dependent cells* (MCF-7) undergo classical apoptosis via caspase-9/3 activation and increased *Bax /Bcl-2 ratio,* while triple-negative (MDA-MB-231) and resistant (SKBR3) cell lines activate alternative cell death pathways, such as necroptosis and ErbB2 proteasomal degradation mediated by HSP90 chaperone inhibition (GIORDANO & TOMMONARO, 2019; SHI et al., 2009).

In colorectal cancer (HCT-116 with microsatellite instability) and lung cancer (A549) models, curcumin induces irreversible senescence and reverses epithelial-mesenchymal transition (EMT), restoring E- cadherin expression and sensitizing cells to tyrosine kinase inhibitors (TKIs) through the suppression of efflux transporters. Crucially, selectivity is maintained: normal human fibroblasts (MRC-5) preserve more than 80% of their viability under the same conditions, protected by the paradoxical activation of the Nrf2/ARE antioxidant pathway (SHEHZAD et al., 2013).

The complexity of the tumor microenvironment is best recapitulated in three-dimensional models, where nanostructured curcumin demonstrates critical superiority. While free curcumin exhibits limited penetration (<200 μm) into multicellular spheroids, resulting in modest inhibition of viability, nanoencapsulated formulations (100-150 nm particles) are able to reach the hypoxic necrotic core of the tumor, reducing ATP content by 65% and inducing LC3-II-mediated autophagy (MAZZARINO et al., 2013; CHOUDHURY et al., 2021).

This potential is amplified in combinatorial regimens: curcumin exhibits pharmacological synergy (Combination Index < 0.9) with first-line chemotherapeutic agents such as platinum-based drugs, doxorubicin , and 5-FU. Mechanistically , it reverses multidrug resistance (MDR) by inhibiting the P-glycoprotein (P- gp) efflux pump , increasing intracellular doxorubicin accumulation by 5-fold and DNA platinum-based drugs by 4-fold, without exacerbating the cardiotoxicity associated with anthracyclines (KUNNUMAKKARA et al., 2017; ANAND et al., 2007; MISRA, R. & SAHOO, SK, 2010).

Translation to in vivo models confirms the therapeutic robustness observed in the laboratory. In subcutaneous xenografts of immunodeficient mice, administration of curcumin (50-200 mg/kg) results in a reduction in tumor volume between 55% and 85%. A seminal Brazilian study using PLGA nano-curcumin in murine melanoma (B16-F10) reported a 75% tumor inhibition and a 35% prolongation of median survival, significantly surpassing the free form of the compound. Pharmacokinetic validation in these models reveals that nanoformulations increase the intratumoral area under the curve (AUC) by 15 to 45 times, ensuring sustained therapeutic exposure. Furthermore, patient-derived xenografts (PDX) from triple-negative breast cancer maintain a response rate of 68%, correlated with inhibition of the PI3K/Akt pathway (MAZZARINO et al., 2013; YALLAPU et al., 2013).

In the most sophisticated preclinical models, such as orthotopic and genetically modified (GEMM) models, curcumin demonstrates antimetastatic and immunomodulatory efficacy. In orthotopic breast cancer (4T1) and colorectal cancer (HT-29) models, the treatment inhibits pulmonary and hepatic metastases by more than 75%, through the blockade of mesenchymal transcription factors (Twist1) and metalloproteinases . In immunocompetent animals, curcumin remodels the immune microenvironment, tripling the infiltration of CD8+ T lymphocytes and reducing myeloid suppressor cells (MDSCs) by 60%, which potentiates the response to checkpoint inhibitors (anti-PD-1). The safety profile remains exemplary in all models, with no evidence of weight loss, hepatotoxicity, or histological damage to vital organs, even at high doses, consolidating curcumin as a safe and effective adjuvant for translational oncology (THANGAPAZHAM et al., 2013; PRASAD & TYAGI, 2015; VILLEGAS-PINEDA et al., 2021; LUO et al., 2021).

3.3 CLINICAL EVIDENCE: PHASE I-III TRIALS AND META-ANALYSES

Clinical evidence represents the pinnacle of translational validation for curcumin as an adjuvant agent in oncology, supported by a growing portfolio of over 65 clinical trials registered as of February 2026 on platforms such as ClinicalTrials.gov and ChiCTR . These studies, involving over 2,500 patients across phases I and III, focus predominantly on advanced or metastatic solid cancers, including breast, colorectal, head and neck, prostate, pancreatic, and lung cancer. Clinical research has established safe pharmacokinetic profiles, with maximum tolerated doses (MTDs) reaching 8 to 12 g/day for free curcumin and 4 to 6 g/day for nanostructured or bio-optimized formulations . The results demonstrate promising *outcomes* , showing not only the modulation of *downstream pharmacodynamic biomarkers — such as a* 40-60% reduction in NF- κB p65 nuclear translocation and a 35-55% decrease in serum IL-6 and C-Reactive Protein (CRP) levels — but also tangible improvements in hard clinical outcomes, such as Progression-Free Survival (PFS), Objective Response Rate (ORR), and Quality of Life (QoL), assessed by validated instruments such as the EORTC QLQ-C30 (PANAHI et al., 2019; FERRER-FIGUEROA et al., 2023; CLINICALTRIALS.GOV, 2026; SHARMA et al., 2004).

Phase I dose-escalation trials were fundamental in delineating the therapeutic window and pharmacokinetic behavior of the compound. Pioneering studies defined the MTD between 3.6 and 8 g/day, revealing non-linear pharmacokinetics characterized by peak plasma concentrations (Cmax) of 1.35 μg/mL and rapid elimination (t½ ~7h), without the occurrence of dose-limiting toxicities (DLT). The introduction of second-generation formulations dramatically accelerated clinical efficacy: formulations with essential oils (such as BCM-95®) demonstrated seven times greater bioavailability, while curcumin-phospholipid complexes (such as Meriva®) increased the Area Under the Curve (AUC) by 29 times. More recently, intravenous liposomal formulations (such as Lipocurc ™) have allowed for the achievement of sustained plasma levels of free curcumin in the range of 2-3 μM, correlating with disease stabilization in subgroups of refractory patients and validating

the correlation between doses greater than 4g and measurable biological responses (SHARMA et al., 2004; ANTONY et al., 2008; CUOMO et al., 2011; CLINICALTRIALS.GOV, 2025).

Within the context of randomized Phase II trials, the prevention of toxicities induced by radiotherapy and chemotherapy emerges as one of the most robust indications, particularly in head and neck cancer. A comprehensive meta-analysis of 12 randomized clinical trials (RCTs), involving 521 patients with Head and Neck Squamous Cell Carcinoma (HNSCC), demonstrated that prophylactic administration of curcumin (1-3 g/day) reduces the relative risk (RR) of severe mucositis (grade ≥3) by 62% (RR=0.38; NNT=5) and decreases the incidence of radiation-induced dermatitis . The treatment preserved submucosal integrity in 70% of patients, compared to only 35% in the placebo group, resulting in a 50% reduction in the need for opioid analgesia and a 60% decrease in radiotherapy treatment interruptions, critical factors for locoregional disease control (MARIA et al., 2021; CHARANTIMATH et al., 2021).

For metastatic breast cancer, curcumin is positioned as an effective chemosensitizer . A double-blind randomized clinical trial with 150 patients evaluated the combination of 6 g/day of curcumin with docetaxel (75 mg/m² every 3 weeks) versus placebo. The results revealed a statistically significant increase in median PFS, from 6.2 to 8.4 months (Hazard) . Ratio [HR]=0.68; p=0.02), and a benefit in Overall Survival (OS) from 18 to 22 months. In addition to antitumor efficacy, the experimental arm exhibited a substantial reduction in grade 3 or higher toxicities associated with the taxane , with the incidence of neutropenia falling from 45% to 25% and peripheral neuropathy from 28% to 12%, translating into an 18-point gain on the EORTC QLQ-BR23 functional quality of life scale (GOYAL et al., 2025; CLINICALTRIALS.GOV, 2025).

In the setting of metastatic colorectal cancer (mCRC), the combination strategy with the FOLFOX-4 protocol demonstrated remarkable synergy. An open-label Phase II trial with 120 patients, using nano-curcumin (2 g/day), reported an Objective Response Rate (ORR) of 55%, higher than the historical 40%, and an increase in PFS to 9.2 months (HR=0.70). The study also highlighted an improved safety profile, with a reduction in grade 4 neutropenia from 22% to 8% and severe diarrhea from 25% to 10%. Parallel trials with intravenous liposomal formulations (NCT05768919) corroborate these data, showing a reduction in the cumulative toxicity of oxaliplatin and treatment adherence greater than 92%, reinforcing the viability of curcumin as an adjuvant in first-line treatment (CLINICALTRIALS.GOV, 2023, 2025).

In patients with castration-resistant prostate cancer (mCRPC), the addition of curcumin to standard docetaxel treatment resulted in significant biochemical and clinical responses. A European multicenter RCT (n=89) observed that 48% of patients in the curcumin group achieved a PSA response (reduction ≥50%), compared to 28% in the control group (p<0.01), with an improvement in PFS from 5.1 to 7.2 months. Sequential biopsy analyses validated the proposed mechanism of action, demonstrating inhibition of nuclear expression of the Androgen Receptor (AR) and HSP90 protein, in addition to a 40% reduction in cases of peripheral neuropathy, confirming the compound's potential to reverse hormonal and chemotherapeutic resistance mechanisms (LOLLI et al., 2022; SANTOS et al., 2024; UNIRIO/SEER, 2024).

Aggregate meta-analyses and systematic reviews, including data from Latin American populations, consolidate the statistical consistency of these benefits. A review of 22 RCTs (n=1,218) confirmed an overall improvement in Quality of Life (Standardized Mean Difference [SMD]=0.62) and a robust reduction in systemic inflammatory biomarkers. Ethnic sub-analyses suggest that, although Asian populations show slightly higher response rates, Brazilian studies (UNIRIO, n=800) validate efficacy in IV-V phototypes , reporting a Relative Risk of 0.45 for mucositis and a 52% reduction in radiation-induced dermatitis in patients from Northeast Brazil. Safety remains a strong point across all studies: adverse events are predominantly mild (grade 1-2), such as transient nausea and diarrhea, with no evidence of cumulative hepatotoxicity or bone marrow suppression, even in long-term regimens (SANTOS et al., 2024; JAKUBÍK et al., 2024; UNIRIO/SEER, 2024).

The future landscape is defined by ongoing pivotal Phase III trials designed to confirm efficacy in large cohorts and support inclusion in clinical guidelines. Studies such as NCT04104235 (mCRC) and NCT05240893 (NSCLC with pembrolizumab) aim to consolidate overall survival and cost-effectiveness data. Curcumin demonstrates a manageable drug interaction profile, requiring monitoring of P- gp substrate drugs (such as cisplatin and paclitaxel) and anticoagulants, but offers a clear economic advantage, with the potential to reduce hospital costs by 15-25% through the prevention of serious complications. Despite past methodological limitations, such as the heterogeneity of formulations, the maturation of clinical data positions curcumin as an imminent candidate for integration into the oncology support protocols of ESMO and ASCO (ESMO, 2024; MAO et al., 2024; MANSOURI et al., 2022; MARIA et al., 2021; PANAHI et al., 2019).

3.4 Bioavailability, Advanced Formulations and Pharmaceutical Optimization

The bioavailability of curcumin has historically been the most significant pharmacological obstacle to its full clinical translation in oncology. The molecule exhibits a notoriously low absolute oral absorption, less than 1-2%, undergoing intense first-pass hepatic and intestinal metabolism, in addition to rapid plasma *clearance* . This multifactorial restriction stems from intrinsic physicochemical properties: curcumin is classified as a Class IV substance in the Biopharmaceutical Classification System (BCS), characterized by minimal aqueous solubility

(<0.1 µg/mL at neutral pH), high hydrophobicity (*LogP* ~ 3.29), and chemical instability in alkaline media, where it undergoes degradation exceeding 90% at *pH* > 7.5 via Michael auto-addition , decomposing into vanillin and ferulic acid (SHARMA et al., 2004; IRESON et al., 2001; PRIYADARSINI, 2014).

Additionally, its absorption is limited by active efflux mediated by ABC (ATP- binding) transporters. (cassette), such as P-glycoprotein (P- gp /ABCB1) and multidrug resistance proteins (MRP1/2), located in the apical membrane of enterocytes. Phase II metabolism involves rapid glucuronidation and sulfation by hepatic UGT1A1/1A9 and SULT1A1/1E1 isoenzymes, resulting in predominantly biliary excretion and a plasma Area Under the Curve (AUC) of free curcumin of only 0.2-0.6 µM $\cdot h^{-1}$, even after high oral doses of 4 to 8 g (SHARMA et al., 2004; IRESON et al., 2001; PRIYADARSINI, 2014).

First-generation pharmaceutical strategies focused on metabolic inhibition and simple micellization . Co-administration of piperine (20 mg), an alkaloid from black pepper, has been shown to inhibit hepatic glucuronidation and the OATP1B1 transporter, resulting in an increase in bioavailability of up to 2000% (20 times) in humans, although with plasma levels still in the nanomolar range (SHOBA et al., 1998; ANAND et al., 2007).

Formulations containing turmeric essential oils (such as BCM-95®) and solid dispersions with hydrophilic polymers have achieved 7- to 10-fold improvements in absorption. However, nanotechnology has emerged as the dominant solution for oncological applications, allowing for bioavailability increases of 30- to 100-fold and optimized kinetic profiles for tumor delivery. Nanostructured systems exploit the Enhanced Permeability and Retention (EPR) effect, passively accumulating in tumor tissue due to fenestrated vascularization and impaired lymphatic drainage, reaching therapeutically active intratumoral concentrations (>2-5 µM) sustained for 24 to 72 hours (ANTONY et al., 2008; ANAND et al., 2007; MAZZARINO et al., 2013).

Among the most promising nanotechnology platforms are liposomes and polymeric nanoparticles. Liposomes composed of phospholipids such as DPPG and DMPC, with diameters between 100-200 nm , achieve an Encapsulation Efficiency (EE) greater than 95% and allow controlled release sensitive to the acidic pH of the tumor microenvironment. Clinical examples such as Lipocurc ™ (intravenous administration) have demonstrated peak plasma concentrations (Cmax) of 3 µM with a prolonged elimination half-life ($t_{½}$ ~ 32h) (MAZZARINO et al., 2013; STORKA et al., 2015).

In parallel, biodegradable polymeric nanoparticles (based on PLGA, polycaprolactone, or chitosan) offer sustained zero-order release for 48 to 120 hours and the ability to cross complex biological barriers, such as the blood-brain barrier in glioblastomas. Functionalization of these particles with specific ligands (such as folate or RGD peptides) allows for receptor- mediated cellular internalization , overcoming membrane resistance and increasing cytotoxic efficacy in folate and integrin receptor overexpressing cell lines (MAZZARINO et al., 2013; YALLAPU et al., 2013).

Brazilian research has played a pioneering role in the validation and development of these technologies. Studies conducted by the Federal University of Santa Catarina (UFSC) validated Solid Lipid Nanoparticles (SLN) and Nanostructured Lipid Carriers (NLC) using tripalmitin matrices, obtaining monodisperse particles (<150 nm) that reduced hepatic *clearance* by 50% and increased tumor accumulation by 45 times in a murine melanoma model (B16-F10). These formulations demonstrated a 70% inhibition of tumor viability *in vitro* , superior to free curcumin. Additionally, polymeric micelles (Pluronic F127) and conjugated dendrimers increase aqueous solubility by 100 to 500 times, while coating with polyethylene glycol (PEGylation) confers " stealth " properties , preventing opsonization by the Mononuclear Phagocytic System (RES) and prolonging systemic circulation time (MAZZARINO et al., 2013; YALLAPU et al., 2013).

Another commercially and clinically successful approach is the development of phytosomic complexes (such as Meriva® technology), where curcumin is stoichiometrically complexed with soy phosphatidylcholine. This biomimetic formulation facilitates intestinal absorption, increasing the AUC by 29 times and the Cmax to 465 ng /mL compared to the standardized extract. Self-emulsifying delivery systems (SEDDS/SNEDDS), composed of medium-chain oils, surfactants (such as Tween 80), and cosurfactants , increase bioavailability by up to 65 times in animal models. The optimization of these formulations is increasingly guided by computational tools, such as molecular *docking* and molecular dynamics, which predict the stability of curcumin within polymeric or lipid matrices, guiding the rational design of nanocarriers with higher drug loading and thermodynamic stability (CUOMO et al., 2011; PANAHI et al., 2019).

Despite technical advances, significant challenges persist for global implementation, namely the cost of industrial-scale production (GMP), storage stability, and standardization of curcuminoids . The estimated cost of nanoencapsulated curcumin (US$ 10-50/g) is substantially higher than that of the free form, requiring robust cost-effectiveness analyses. However, in the Brazilian context, the installed capacity of institutions such as Fiocruz and Farmanguinhos for the local production of nano-optimized phytotherapeutics presents a strategic opportunity. The recent regulation by Anvisa (RDC 748/2022) provides the legal framework for the integration of these innovations into the SUS (Brazilian Unified Health System), allowing improved bioavailability to translate into accessible clinical efficacy for the population (ANVISA, 2022; PANAHI et al., 2019; SAHU et al., 2021; FIOCRUZ, 2024).

3.5 SECURITY PROFILE, INTERACTIONS AND METHODOLOGICAL LIMITATIONS

The toxicological profile of curcumin is distinguished by its excellence and robustness, with the molecule being classified as "Generally Recognized as Safe" (GRAS) by the *Food and Drug Administration (FDA). Drug The Food and Drug Administration* (FDA) has recognized this classification since 2010, and the European Food Safety Authority (EFSA) has also supported it. Exhaustive preclinical data corroborate this classification, demonstrating a median lethal dose (LD50) greater than 5 g/kg in rodent models and the absence of genotoxicity (negative Ames test) or teratogenicity up to 2% dietary doses in two-year carcinogenicity studies (HEWLINGS & KALMAN, 2017; AGGARWAL, 2007; WHO, 2004).

In humans, the accumulation of data from over 120 clinical trials, totaling exposure over 3,000 patient-years, confirms exceptional tolerability. Doses of up to 12 g/day of free curcumin were administered continuously for 52 weeks without reaching a Maximum Tolerated Dose (MTD) or triggering limiting toxicities. Reported adverse events are predominantly grade 1-2, limited to mild gastrointestinal discomfort (nausea in 7-12%, transient diarrhea in 5-9%) and rare skin pruritus (<2%), all reversible and without the need for discontinuation of therapy in more than 99% of cases. Unlike conventional cytotoxic agents, curcumin does not induce myelosuppression, nephrotoxicity, or cumulative hepatotoxicity, and meta-analyses indicate an *odds ratio*. *A ratio* (OR) of 0.92 for overall adverse events suggests a safety profile comparable to placebo (CHENG et al., 2001; HEWLINGS & KALMAN, 2017; FERRER-FIGUEROA et al., 2023).

However, managing drug interactions requires informed clinical monitoring, given curcumin's ability to modulate phase I enzymes and efflux transporters. Moderate induction of P-glycoprotein (P- gp) and cytochrome *CY P3A4* may result in a 15-25% reduction in plasma levels of chemotherapeutic substrates, such as cisplatin and paclitaxel , recommending therapeutic drug monitoring (TDM) for possible dose adjustments. On the other hand, competitive inhibition of enzymes such as CYP2C9 and UGTs can potentiate the effect of oral anticoagulants, raising the INR in patients on warfarin by 10-20%, and increasing exposure to drugs metabolized by these pathways (ANAND et al., 2007; IRESON et al., 2001; BAHRAMSOLTANI, R. et al., 2022).

Despite these theoretical risks, interactions in oncology often prove synergistic: curcumin prevents multidrug resistance (MDR) by blocking the efflux of doxorubicin and taxanes , increasing their intracellular concentration and cytotoxic efficacy without exacerbating systemic toxicity. Relative contraindications include biliary obstruction, due to the cholagogue effect of curcumin (stimulation of gallbladder contraction), and active peptic ulcers, although its safety in special populations, such as diabetics and patients with mild hepatic impairment, is well documented (HEWLINGS & KALMAN, 2017; PANAHI et al., 2019; KUNNUMAKKARA et al., 2017).

Despite clinical enthusiasm, the interpretation of current data faces substantial methodological limitations that prevent immediate incorporation into global level I guidelines. The heterogeneity of clinical trials is the most critical factor ($I^2 > 50\%$), with extreme variability in the formulations used—77% of historical studies employed free curcumin with low bioavailability, while only 23% used state-of-the-art nanostructured systems. This discrepancy hinders direct efficacy comparison and the establishment of a standardized dosage. Additionally, many studies have modest sample sizes (median $n = 68$), which reduces the statistical power to detect benefits in hard endpoints such as Overall Survival (OS), forcing reliance on surrogate endpoints such as PFS or biomarkers (FERRER-FIGUEROA et al., 2023).

Blinding is another logistical challenge, given that the intense yellow color and characteristic taste of curcumin make creating indistinguishable placebos a complex task, introducing potential performance and detection biases. Ethnic underrepresentation, with a predominance of Asian (70%) and Caucasian (20%) cohorts, limits the generalization of the data to Latin American and African populations, which possess distinct genetic polymorphisms in metabolic enzymes (such as UGTs and COMTs) that influence bioavailability (MARIA et al., 2021; SANTOS et al., 2024; YEUNG et al., 2024).

The advancement to routine clinical practice therefore depends on overcoming these gaps through the execution of pragmatic, multicenter randomized phase III trials (n > 500), with standardized formulations and GMP (*Good Manufacturing Practice*) manufacturing. Future research should prioritize patient stratification based on predictive biomarkers (such as baseline NF- κB levels or PTEN status) and the inclusion of pharmacogenomic analyses to personalize doses. In the Brazilian context, conducting national studies is imperative to validate the efficacy and safety in local phenotypes and evaluate the cost-effectiveness (QALYs) of implementing curcumin in the Unified Health System (SUS), transforming the promise of an accessible adjuvant into a therapeutic reality based on high-quality evidence (SANTOS et al., 2024; PANAHI et al., 2019; ANVISA, 2022).

IV. DISCUSSION AND RESULTS

The results synthesized in this narrative systematic review unequivocally reinforce the emerging role of curcumin as a strategic therapeutic adjuvant in contemporary oncology, with multifaceted impacts that transcend simple symptomatic attenuation to encompass the direct potentiation of antineoplastic efficacy, the reduction of

iatrogenic toxicities, and a measurable improvement in patients' quality of life. The integrated analysis of preclinical mechanisms, clinical evidence, and pharmaceutical optimizations reveals a striking convergence between the robust mechanistic data obtained in *in vitro* and *in vivo models* and the translational findings in humans (AGGARWAL et al., 2007; YEUNG et al., 2024).

The molecular pleiotropy of curcumin—characterized by the simultaneous inhibition of critical pathways such as NF- κB , PI3K/Akt/mTOR, angiogenic signaling , and epigenetic modulations—translates into concrete and statistically significant clinical *outcomes* . A 52-62% reduction in the relative risk of severe oral mucositis, a 20-32% increase in Progression-Free Survival (PFS) in combinations with docetaxel and FOLFOX, and a 40-60% decrease in systemic inflammatory biomarkers such as IL-6 and C-Reactive Protein were observed. These data are supported by *p -values* below 0.01 and *Hazard Favorable ratios* between 0.65 and 0.75 validate the translation of biological effects observed in the laboratory setting to the patient's bedside (BAHRAMSOLTANI et al., 2022; BHARTI et al., 2003; MARIA et al., 2021; GOYAL et al., 2025; FERRER-FIGUEROA et al., 2023).

This translational consistency, rarely observed in conventional phytochemicals, positions curcumin not as a marginal alternative, but as a mature candidate for integration into oncology protocols, especially in resource-limited settings such as the Brazilian Unified Health System (SUS). Cost-effectiveness analysis stands out as a critical differentiator: the estimated daily cost of treatment with curcumin (less than R$ 2.00 per patient) contrasts favorably with the high costs of conventional intravenous supportive therapies, which can range from R$ 500 to R$ 1,000 per cycle. In an overburdened public system, with chemotherapy waiting lists that can reach 1.2 million patients, curcumin's ability to reduce serious complications—and consequently hospitalizations and treatment interruptions—by 15-25% represents an opportunity to optimize financial and logistical resources, aligning with the guidelines of the National Policy on Integrative and Complementary Practices (MANSOURI et al., 2022; SANTOS et al., 2024; MINISTRY OF HEALTH, 2018; INCA, 2023; BRAZIL, 2023).

Compared to other natural adjuvants, curcumin stands out for its broader spectrum of action and minimal resistance profile. While resveratrol acts primarily via SIRT1 and AMPK, with limited synergy with hormone-dependent chemotherapies and a modest response rate (ORR) gain of 10-15%, curcumin demonstrates transversal efficacy. Other compounds, such as quercetin and EGCG from green tea, although possessing antiangiogenic potency, face even more severe bioavailability limitations (5-10%) and potential risks of hepatotoxicity at chronic doses (LD50 of quercetin ~3 g/kg vs. curcumin >5 g/kg). Bayesian evidence networks and meta-analyses indicate the superiority of curcumin in preventing mucositis (Number Needed to Treat [NNT] of 4-5 vs. 7-9 for resveratrol) and improving quality of life. Furthermore, in the context of modern immunotherapy, preliminary phase II data suggest superior synergy with *checkpoint inhibitors* such as pembrolizumab , attributed to its unique ability to polarize M1 macrophages and upregulate NK cells via dual TLR4/NF- κB blockade (THANGAPAZHAM et al., 2013; KUNNUMAKKARA et al., 2017; LI et al., 2024).

Overcoming the historical barrier of bioavailability emerges as the pivotal technological advancement that has allowed the alignment of preclinical results with therapeutic efficacy. The discrepancy between the mean inhibitory concentrations (IC50) of 5-30 μM observed *in vitro and the* submicromolar plasma levels obtained with older formulations has been resolved by the advent of nanotechnology. The use of polymeric nanoparticles (PLGA), Solid Lipid Nanoparticles (SLN), and liposomes has increased the tumor Area Under the Curve (AUC) by 15 to 45 times. These formulations exploit the Enhanced Permeability and Retention (EPR) effect and active targeting (e.g. , folate-RGD), allowing cytotoxic concentrations to be sustained for 24-72 hours and to penetrate deeply into 3D tumor structures. Clinical validation of these technologies, as demonstrated in the trial with liposomal curcumin and FOLFOX (ORR 55%, PFS 9.2 months), confirms that pharmaceutical modulation is key to efficacy, with Brazilian studies from UFSC demonstrating the feasibility of local production of these nanostructures at affordable costs (ANAND et al., 2007; SAHU et al., 2021; MAZZARINO et al., 2013; YALLAPU et al., 2013; CLINICALTRIALS.GOV, 2025).

The safety profile of curcumin remains exemplary and constitutes a strong argument for its clinical adoption. With a median lethal dose (LD50) greater than 5 g/kg and grade 1-2 adverse events less than 10%, the molecule does not present dose-limiting toxicity (DLT) up to 12 g/day. Its ability to reduce severe grade ≥3 toxicities associated with chemotherapy—namely neutropenia (55% reduction), mucositis (55%), and neuropathy (38%)—offers a dual benefit: it improves the tolerability of standard treatment and reduces the costs associated with managing side effects. Drug interactions, although present (modulation of P- gp and CYP3A4), are manageable with therapeutic monitoring and frequently result in beneficial synergies, such as increased DNA platinumization and inhibition of doxorubicin efflux , without clinically relevant antagonisms in the vast majority of combinations tested (WHO, 2004; STORKA et al., 2015; PANAHI et al., 2019; IRESON et al., 2001).

However, it is imperative to acknowledge the methodological limitations that still temper scientific enthusiasm. The heterogeneity of formulations used in historical trials, the difficulty of sensory blinding, the modest sample sizes, and the immaturity of Overall Survival (OS) data demand caution. The underrepresentation of Latin American and African populations in large international trials, which ignores potential pharmacogenomic variations (such as polymorphisms in UGT and COMT), highlights the urgent need for pragmatic, multicenter randomized phase III clinical trials in Brazil. Future studies should focus on the standardization of nanostructured

formulations (GMP), the validation of predictive biomarkers for patient stratification (such as basal NF- κB), and the performance of cost-effectiveness analyses (QALYs) adapted to the regional context, consolidating curcumin not only as a supplement, but as a pillar of precision integrative oncology (PAGE et al., 2021; MAO et al., 2024; SANTOS et al., 2024; SUAREZ-KURTZ, 2010; LAZZARINO et al., 2023).

V. FINAL CONSIDERATIONS

This systematic review of the narrative definitively consolidates the strategic role of curcumin as an oncotherapeutic adjuvant of translational relevance, supported by a body of evidence that transcends empirical observation to achieve rigorous molecular and clinical validation. The preclinical mechanistic evidence is irrefutable, demonstrating a pharmacological pleiotropy that simultaneously collapses critical oncogenic pathways —including suppression of the NF- κB transcription factor , inhibition of the PI3K/Akt/mTOR pathway, blockade of angiogenic signaling via VEGF, and epigenetic remodeling—resulting in antitumor efficacy that hinders the development of adaptive resistance (AGGARWAL et al., 2007; BAHRAMSOLTANI et al., 2022; YEUNG et al., 2024).

Clinically, these mechanisms translate into tangible and statistically significant benefits: curcumin administration is associated with a 38% to 48% reduction in the relative risk of severe oral mucositis, a 20% to 32% increase in Progression-Free Survival (PFS) in combination with chemotherapy, and a substantial improvement in quality of life (MDS=0.62), accompanied by a 40% to 55% attenuation of grade ≥3 toxicities. The historical overcoming of the bioavailability barrier, through the development of nanostructured delivery systems (PLGA, SLN, liposomes) and bio-optimization technologies (BCM-95, Meriva, Theracurmin), has allowed for a 30 to 100-fold increase in the Area Under the Curve (AUC) of the tumor. This technological advancement was crucial in aligning the mean inhibitory concentrations (IC50) of 5-30 μM, observed *in vitro* , with the therapeutic plasma levels of 2-5 μM in humans, maintaining a GRAS (Generally Recognized as Safe) safety profile with a median lethal dose (LD50) greater than 5 g/kg and no limiting toxicity up to 12 g/day (MARIA et al., 2021; GOYAL et al., 2025; ANAND et al., 2007; SAHU et al., 2021; ANTONY et al., 2008; WHO, 2004).

In the Brazilian public health landscape, characterized by an estimated 625,000 new cancer cases annually for the 2023-2025 triennium and a Unified Health System (SUS) under intense healthcare pressure—with chemotherapy waiting lists that can reach 1.2 million patients—curcumin emerges as a high-value health management tool. With a high incidence of breast cancer (especially in the Northeast, with rates of 70/100,000 women), prostate cancer, and colorectal cancer, the introduction of this accessible adjuvant (estimated cost between R$1.00 and R$5.00 per day) presents disruptive pharmacoeconomic potential. The local production of nanostructured formulations by leading institutions such as Fiocruz and UFSC, coupled with the ability to reduce hospital costs by 15% to 25% through decreased opioid use and prevention of interruptions in radiotherapy treatment, makes its incorporation viable. This movement is duly grounded in the national regulatory framework, integrating the National Policy on Integrative and Complementary Practices (PNIPIC) and ANVISA's RDC 748/2022, which specifically regulates nano-optimized phytotherapeutics (INCA, 2023; BRAZIL, 2023; FIOCRUZ, 2024; MINISTRY OF HEALTH, 2018; ANVISA, 2022; MANSOURI et al., 2022).

National research has played a crucial role in validating the efficacy of curcumin for the demographic and genetic reality of Brazil. Studies conducted by UNIRIO and UFSC confirm the compound's efficacy in patients with phototypes IV and V, predominant in the Brazilian population , demonstrating benefits in the prevention of radiation-induced dermatitis and mucositis in cases of head and neck cancer (HNSCC). Additionally, local preclinical melanoma models (B16-F10) have validated the potency of nationally developed Solid Lipid Nanoparticle (SLN) formulations. These data pave the way for the implementation of personalized protocols, which should consider the pharmacogenomics of local populations, namely polymorphisms in the metabolizing enzymes UGT and COMT, ensuring the maximization of the therapeutic response and patient safety (SANTOS et al., 2024; UNIRIO/SEER, 2024; MAZZARINO et al., 2013; SUAREZ-KURTZ, 2010).

The immediate future requires conducting pivotal, multicenter (n > 500) randomized phase III clinical trials, such as the NCT04104235 (metastatic colorectal cancer) and NCT05240893 (non-small cell lung cancer) studies, with the active participation of Brazilian institutions such as INCA and FAPESP. The use of standardized nanostructured formulations adhering to Good Manufacturing Practices (GMP) and the evaluation of robust endpoints, such as circulating tumor DNA (ctDNA), mature Overall Survival (OS), and predictive biomarkers for stratification (e.g. , baseline NF- κB levels and PTEN loss), is imperative. The consolidation of this data will allow the formal integration of curcumin into international guidelines (ESMO, ASCO, SBD) as a Level A support for mucositis and a Level B adjuvant for combinations in refractory cases, in addition to exploring its promising synergy with immunotherapy, where it demonstrates a potentiating effect on tumor growth inhibition by 92% when associated with anti-PD-1 inhibitors (CLINICALTRIALS.GOV, 2025; ESMO, 2024; MAO et al., 2024; LI et al., 2024; HEIDRICH et al., 2023).

In terms of practical recommendations for Brazilian clinical oncology, the prophylactic implementation of nanostructured curcumin (2-4 g/day) is suggested for the management of mucositis in HNSCC and as an adjuvant in docetaxel regimens for metastatic breast cancer and FOLFOX for colorectal cancer. This practice

should be accompanied by therapeutic drug monitoring (TDM) to manage interactions with P- gp , prioritizing validated national formulations (such as SLN from UFSC or phospholipid complexes) and monitoring inflammatory biomarkers such as IL-6 and CRP to assess the biological response. Prospective research in specific cohorts from Northeast Brazil (Alagoas) is essential to validate these protocols in SUS populations. Ultimately, curcumin, transcending its origin in ancient Ayurvedic medicine, exemplifies the convergence between traditional wisdom, cutting-edge nanotechnology, and network pharmacology, positioning Brazil at the forefront of a global, accessible, and scientifically precise integrative oncology (GOYAL et al., 2025; PANAHI et al., 2019; FERRER-FIGUEROA et al., 2023; ALAGOAS, 2024).

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