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# Targeting the P53–Mdm2 Axis In Breast Cancer: Integrating Artificial Intelligence, Multi-Omics, and Natural Compounds to Overcome Therapeutic Resistance

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**ABSTRACT**

Breast cancer management is complicated by therapeutic resistance and molecular heterogeneity, including abnormalities in the p53–MDM2 pathway. Artificial intelligence [AI], multi-omics profiling, and bioactive natural compounds offer complementary approaches for clarifying resistance mechanisms and advancing individualized treatment. This systematic review examined the involvement of the p53-MDM2 axis in breast cancer progression and therapeutic resistance and explored integrating AI, multi-omics, and natural compounds for response prediction and therapeutic discovery. The review followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines. PubMed/MEDLINE, Scopus, and Web of Science were searched from inception to March 2026 using terms related to breast cancer, p53/TP53, MDM2, treatment resistance, AI, machine learning, multi-omics, and natural compounds. Of 1,550 records, 1,530 remained after duplicate removal. Screening resulted in full-text assessment of 130 articles, with 67 studies included in the qualitative synthesis. Observational, experimental, computational, and modeling studies were eligible. The methodological robustness of the included studies was evaluated with the Newcastle–Ottawa Scale (NOS). Disruption of the regulatory interaction between p53 and MDM2 can contribute to cancer progression and treatment resistance by limiting programmed cell death and enabling malignant cells to persist and proliferate. AI and machine learning support treatment-response prediction and patient stratification, whereas multi-omics identifies molecular features linked to resistance. Natural compounds show preclinical potential to modulate p53–MDM2 signaling and restore p53 activity. However, clinical translation is limited by validation requirements, tumor heterogeneity, TP53 status, toxicity, poor bioavailability, and limited clinical evidence. Integrating AI, multi-omics, and natural-product discovery may strengthen precision strategies against p53–MDM2-associated therapeutic resistance. Further prospective research and clinical trials are required to establish clinical utility.

*Keywords:* p53-MDM2 network, Breast cancer, natural anticancer compounds, Breast cancer incidence, Tumor response prediction

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## Introduction

The increasing incidence of breast cancer among middle-aged and younger individuals worldwide has become a major global health concern, with over two million new cases diagnosed annually and more than 500,000 related deaths. Both incidence and mortality rates are projected to rise by up to 40% in the coming years. However, in economically stable countries with well-structured healthcare systems and comprehensive treatment programs, breast cancer-related mortality has been significantly reduced.[1] Preoperative systemic therapy is increasingly used to treat early-stage breast cancer before surgery. Although this approach is becoming more common, few studies have thoroughly examined the surgical implications of such treatment. Identifying patients who respond well to therapy is crucial, as they may require less extensive surgery or radiation.

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This information can guide shared decision-making between patients and healthcare providers.[2] Identifying patients who are likely to respond to preoperative treatments enables clinicians to plan less extensive surgical interventions, reducing side effects, promoting faster post-surgical recovery, and improving quality of life. This approach also allows for more efficient use of healthcare resources. Recent research has focused on developing biomarkers and imaging tools to predict tumor responses to therapy.[3] A better understanding of these tumor behaviors enables clinicians to personalize treatment strategies, giving each patient the best chance for a successful long-term outcome.

Cancer cells possess several protective mechanisms that enable them to survive and proliferate despite advanced therapeutic interventions. Among these, the p53–MDM2 regulatory network plays a critical role. Normally, p53 acts as a "guardian" of the cell, preventing damaged cells from multiplying or inducing their self-destruction. However, MDM2 inhibits p53, thereby enabling cancer cells to survive, proliferate, and evade apoptosis.[4] In solid tumors such as breast cancer, dysregulation of the p53–MDM2 network strongly promotes cancer progression and is associated with reduced effectiveness of therapy.[5] Targeting the interaction between MDM2 and p53 represent a promising strategy to restore the tumor-suppressing functions of p53, which include halting the replication of damaged cells and inducing their programmed cell death. Such approaches have the potential to enhance therapeutic efficacy and promote tumor regression.[6] Recent studies indicate that certain natural compounds, including bioactive phytochemicals, can inhibit MDM2 and restore p53 activity. By reactivating p53, these compounds can halt the growth of damaged cancer cells and increase their sensitivity to therapy.[7]

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Although therapeutic inhibition of the p53–MDM2 interaction is supported by strong mechanistic and preclinical evidence, its advancement into routine clinical practice has been impeded by substantial limitations, including dose-limiting hematologic adverse effects, transient therapeutic responses, reliance on intact TP53 status, and the development of adaptive resistance pathways that compromise long-term efficacy.[8] Several modified drugs designed to inhibit the MDM2 protein have been tested in clinical trials. Although some showed promising results, they were associated with serious side effects when the dose was increased to effective therapeutic levels. This means that doctors cannot safely administer high enough doses to achieve optimal treatment outcomes. Over time, cancer cells also develop resistance mechanisms against these drugs, reducing their effectiveness. As a result, researchers are now exploring therapies that target multiple pathways simultaneously rather than focusing only on MDM2.[9] Naturally occurring bioactive phytochemicals, particularly polyphenolic and flavonoid derivatives, have increasingly gained scientific interest owing to their multifaceted anticancer mechanisms.[10] These plant-derived molecules exhibit diverse biological activities, including oxidative stress attenuation, induction of programmed cell death, inhibition of malignant cell proliferation, and modulation of host immune responses. Emerging evidence suggests that such compounds may function through bidirectional molecular regulation by downregulating aberrant MDM2 expression while simultaneously promoting p53 stabilization, thereby reactivating tumor suppressor signaling pathways and potentially improving cellular sensitivity to conventional anticancer therapies.[11]
This review seeks to characterize the contribution of the p53–MDM2 signaling network to breast-cancer progression and the emergence of treatment resistance. It further examines how genomic, transcriptomic, proteomic, metabolomic, and other multi-omics strategies can be used to uncover molecular changes associated with this regulatory network. In addition, the review assesses the application of artificial intelligence and machine-learning techniques for interpreting complex biological data, predicting therapeutic responses, identifying resistance-associated patterns, and improving patient stratification. The review also evaluates naturally derived compounds that have demonstrated potential to alter p53-MDM2 signaling and considers their prospects as therapeutic candidates. Finally, it explores how computational approaches, multi-omics profiling, and natural-product research could be brought together into an integrated precision-oncology strategy aimed at understanding and overcoming therapeutic resistance in breast cancer.

## Materials and Methods

*Study Design*

This study was conducted as a systematic review to synthesize evidence on the relationship between p53-MDM2 network, Breast cancer, natural anticancer compounds, Breast cancer incidence, and Tumor response prediction, and was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA] guidelines to ensure methodological rigor, transparency, and reproducibility. A total of 1,550 records were identified through database searching, of which 1,530 remained after duplicate removal. Following title and abstract screening, 1,400 records were excluded, and the full texts of 130 articles were assessed for eligibility. Of these, 62 studies were excluded due to being out of scope [n = 21], lacking sufficient methodological or outcome detail [n = 24], or demonstrating limited methodological rigor [n = 17]. The study selection process is presented in Figure 1

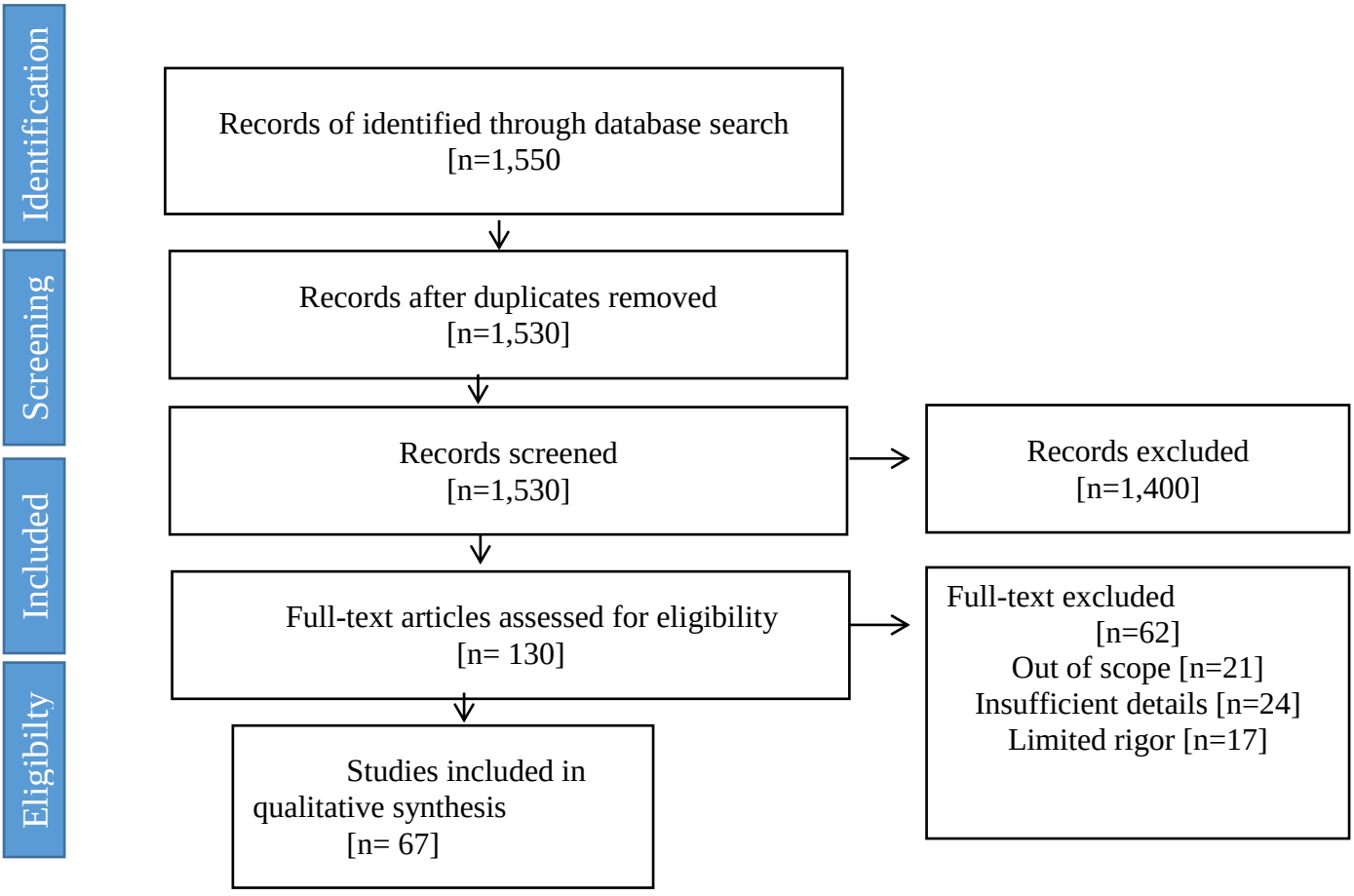


**Figure 1:** PRISMA 2020 flow diagram illustrating the study selection process.

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*Inclusion and Exclusion Criteria*

Studies were included in this systematic review if they investigated p53-MDM2 network, Breast cancer, natural anticancer compounds, Breast cancer incidence, and Tumor response prediction. Eligible studies employed observational designs [such as cross-sectional or cohort studies], interventional approaches, or modeling methodologies, and reported quantitative epidemiological measures including incidence rates [IR], odds ratios [OR], risk ratios [RR], incidence rate ratios [IRR], or prevalence ratios [PR]. Studies were included if they provided data from single-country or multi-country settings. Studies were excluded if they did not examine Breast cancer, did not, were conference abstracts, editorials, or letters, lacked sufficient methodological detail or full-text availability, or were published in languages other than English.

*Search Strategy*

A systematic search of the published literature was performed in PubMed/MEDLINE, Scopus, and Web of Science to retrieve studies pertinent to the objectives of this review. The search encompassed records indexed in the databases from their respective inceptions through March 2026. For each database, an appropriately tailored search strategy was developed using both free-text keywords and controlled indexing terms, including MeSH terminology where applicable. Boolean operators [AND and OR] were applied to combine the major search concepts. The search incorporated terms related to breast cancer, p53/TP53, MDM2, therapeutic or drug resistance, artificial intelligence and machine learning, multi-omics approaches, and naturally derived compounds. Specifically, combinations of terms such as “breast cancer,” “breast carcinoma,” “p53,” “TP53,” “MDM2,” “therapeutic resistance,” “artificial intelligence,” “machine learning,” “multi-omics,” “genomics,” “transcriptomics,” “proteomics,” “metabolomics,” “natural compounds,” “phytochemicals,” and “natural products” were used to retrieve potentially relevant publications. The reference lists of relevant and eligible articles were additionally examined to identify studies that may have been missed during the electronic database search. Eligibility was restricted to peer-reviewed articles published in English, while studies were not excluded on the basis of design and could include observational, experimental, computational, and modeling investigations.

*Study Selection*

To reduce the likelihood of bias and strengthen methodological consistency, all identified records were initially transferred to Zotero for organized reference management, during which duplicate records were detected and deleted. The resulting deduplicated records were subsequently uploaded to Rayyan, facilitating independent and blinded study screening. Two reviewers independently examined the titles and abstracts of all identified studies. After completion of this initial assessment, blinding was removed, and differences in judgment were addressed through discussion and mutual agreement; unresolved disagreements were referred to a third reviewer for final determination. Full-text versions of studies considered potentially eligible were then obtained and independently examined by the same reviewers under blinded conditions. After full-text assessment, outstanding disagreements were settled through consensus or, where necessary, consultation with a third reviewer. As presented in Figure 1, the risk of bias in the included studies was evaluated and graphically presented using the Robvis tool, thereby improving clarity and transparency in the reporting process. The review team subsequently reached agreement on the final set of studies included in the review.

*Data Extraction*

Data were systematically extracted from all included studies using a standardized approach, capturing key study characteristics such as year of publication, study design, study population, methodological characteristics, and primary findings related to p53-MDM2 dysregulation and therapeutic resistance in breast cancer. Additional relevant variables, including molecular alterations, therapeutic resistance mechanisms, artificial intelligence applications, multi-omics approaches, natural compounds, treatment-response patterns, and reported translational implications, were also extracted where applicable. To ensure consistency and facilitate meaningful comparison across studies, the extracted information was organized into structured summary tables according to the major themes and objectives of the review.

*Quality Assessment [Risk of Bias]*

The quality of the studies included in the review was evaluated using the Newcastle-Ottawa Scale [NOS], with the resulting assessments presented using the Risk-of-bias Visualization [robvis] tool [Figure 2]. The assessment followed a domain-oriented approach appropriate to the methodological characteristics of the included studies. The principal domains considered were study selection, including the representativeness of the study population; comparability, particularly the extent to which potential confounding factors were addressed; and outcome assessment, including the validity and reliability of the measurement methods. Based on the evidence within these domains, studies were classified according to the applicable risk-of-bias categories. Two reviewers independently performed the quality assessments. Differences in judgment were discussed and resolved by consensus, with a third reviewer consulted when consensus could not be reached. The completed assessments were subsequently generated in robvis to provide a clear and consistent visual representation of the methodological quality of the included studies.

*Data Synthesis*

Due to substantial heterogeneity in study designs, methodologies, and statistical approaches, a meta-analysis was not undertaken and pooled effect estimates were not calculated. Instead, a qualitative comparative synthesis was performed to systematically summarize and interpret findings across studies, with a focus on the magnitude and direction of reported outcomes related to immunization gaps, vaccine hesitancy, and associated epidemiological patterns.

## Results and Discussion

*The p53-MDM2 Regulatory Network*

p53 is a major tumor suppressor protein that functions as a sequence-specific transcriptional regulator, orchestrating the expression of a broad network of target genes involved in apoptosis [table 1], cell cycle checkpoint control, DNA repair mechanisms, cellular metabolism, and cellular senescence. [12, 13] Under normal conditions, intracellular p53 levels are maintained at low concentrations due to continuous proteasomal degradation [Table 1]. However, upon DNA damage induced by radiation or other genotoxic stressors, the DNA damage response [DDR] pathway is activated, leading to p53 stabilization and accumulation.[14]

MDM2 is widely recognized as the principal negative regulator of the tumor suppressor p53, functioning as a critical modulator of cellular homeostasis.[15] Through its multidomain architecture comprising an N-terminal p53-binding domain, a central acidic region, a zinc finger motif, and a C-terminal RING E3 ubiquitin ligase domain, MDM2 orchestrates the binding, transcriptional repression, ubiquitination, and proteasomal degradation of p53.[4] This coordinated regulation not only controls p53 protein stability but also fine-tunes stress-responsive pathways governing cell cycle arrest, apoptosis, and genomic integrity. Dysregulation of this axis is a hallmark of numerous malignancie.[15] The C-terminal RING domain of MDM2 mediates homodimerization and/or heterodimerization with MDMX, forming a structural platform that engages E2 ubiquitin-conjugating enzymes and facilitates efficient ubiquitin transfer to substrates such as p53, as shown in Table 1.[16]

Table 1

The tumor suppressor TP53 regulates MDM2 expression, forming a negative feedback loop. p53 induces MDM2 transcription, and MDM2 promotes p53 ubiquitination and proteasomal degradation. This mechanism maintains cellular homeostasis by preventing excessive

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p53 activity and apoptosis in unstressed cells.[17] The p53-MDM2 regulatory axis operates as a negative feedback mechanism that maintains low basal p53 activity under physiological conditions to preserve cellular homeostasis.[4] In response to genotoxic stress, inhibition of p53 is attenuated, enabling its stabilization and accumulation, which subsequently activates downstream signaling pathways that induce cell cycle arrest or apoptosis to safeguard genomic integrity.[18] Overexpression of MDM2 suppresses p53 activity through enhanced ubiquitination and proteasomal degradation, thereby impairing its tumor-suppressive function.[19] This disruption weakens genomic surveillance, allowing damaged cells to undergo uncontrolled proliferation and accumulate additional mutations that promote tumorigenesis. Clinically, cancers characterized by elevated MDM2 expression are often more aggressive, demonstrate therapeutic resistance, and are associated with poor patient prognosis and reduced survival outcomes.[20] Consequently, pharmacological disruption of the MDM2-p53 interaction has become a major focus in oncology research, with several emerging therapeutic strategies designed to prevent MDM2-mediated p53 degradation and thereby reactivate p53 tumor-suppressive functions in malignancies retaining wild-type TP53.[21]

Dysregulation of the p53–MDM2 Network in Cancer Progression

Alterations in the p53–MDM2 regulatory network play an important role in determining tumor responses to therapy, with increasing evidence indicating that disturbances within this pathway substantially promote the emergence of resistance to anticancer treatment.[28] MDM2 functions as a principal negative regulator of p53, which is widely recognized as an essential tumor-suppressor protein.[29] Mechanistically, MDM2 acts as an E3 ubiquitin ligase and induces several post-translational modifications of p53, including polyubiquitination and monoubiquitination.[6] Through these ubiquitination processes, MDM2 influences p53 stability by facilitating its degradation and also controls its intracellular distribution by promoting its export from the nucleus.[30] Abnormal activation of the p53-MDM2 axis, particularly through increased MDM2 expression or gene amplification, can continuously suppress p53-dependent transcriptional responses. This persistent inhibition may promote genomic instability, uncontrolled tumor-cell proliferation, and reduced sensitivity to both chemotherapy and radiotherapy.[31]

Fig 2

**Table 1:** Biological relevance of p53 protein in Cellular Regulation

| P53 Functions | Target Genes | Cellular Outcome | Role in Tumorigenesis | References |
|---|---|---|---|---|
| G1/S-G2/M checkpoint arrest | p21 [CDKN1A], GADD45 | It allow DNA repair by halting progression through the cell cycle. | Keeping Genomic stability by halting division of damaged cells. | (32) (56) |
| Regulated elimination of damaged cells | P53-regulated intrinsic programmed cell death mediator [BAX, PUMA, NOXA] | Induces controlled cellular self-destruction | Gets rid of cancerous cells | (57) (54) |
| Genomic integrity maintenance | DNA repair sensor [DDB2, XPC] | Induce transcription of DNA repair genes | Maintains genomic integrity | (58) |
| Stress-induced proliferative arrest | Cyclin-depedent kinase inhibitors and senescence stabilizer [p21, PAI-1] | Induces permanent growth arrest | Avoids tumor development | [22] |

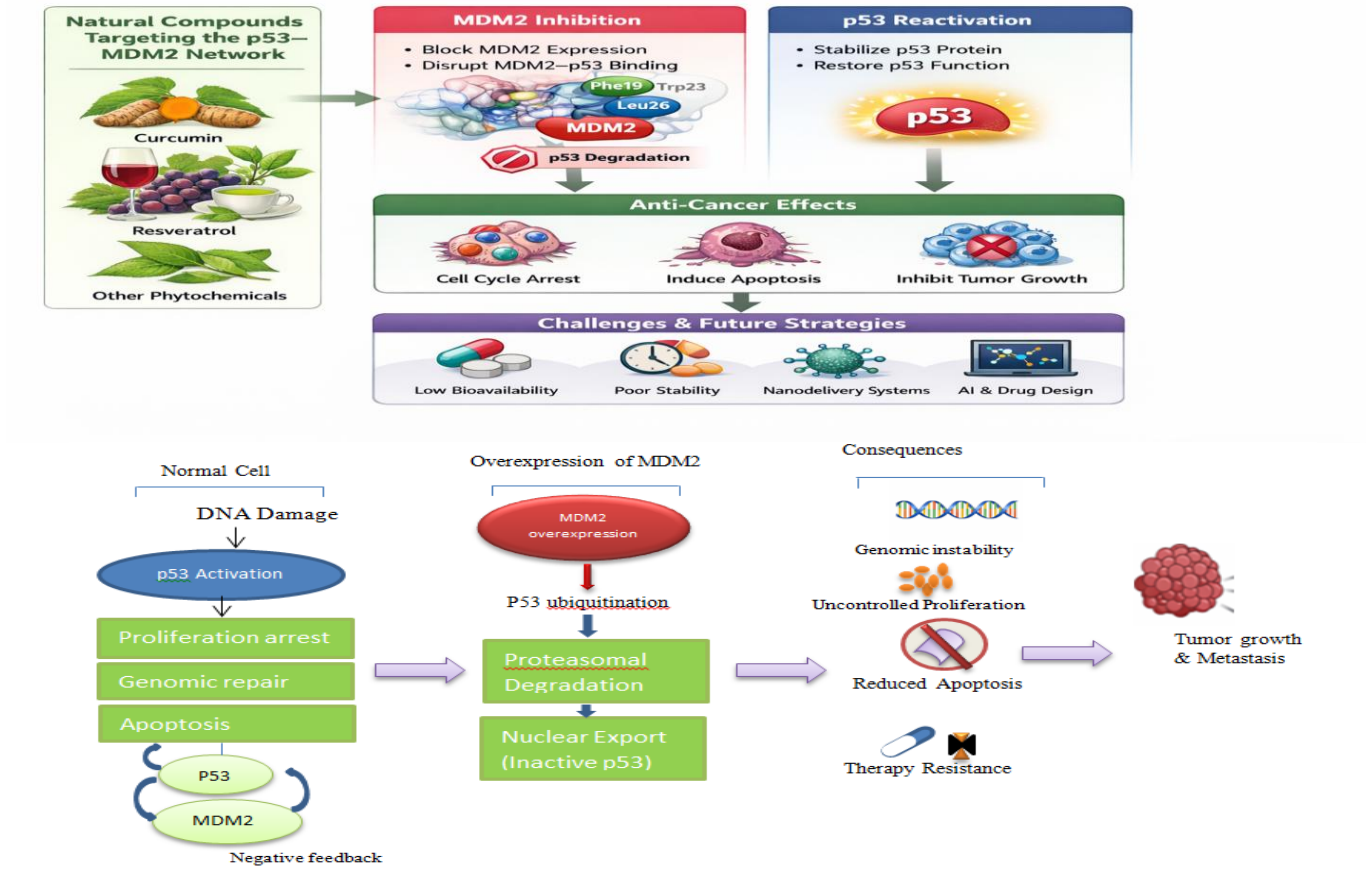


**Figure 2:** Mechanistic overview of natural compounds targeting the p53–MDM2 signaling axis and their anticancer effects

Figure 2 illustrates the molecular mechanisms associated with breast cancer progression, emphasizing the p53–MDM2 regulatory axis and its involvement in controlling p53 stability, ubiquitination, and subsequent tumor-suppressive activities.[32,15] Under normal physiological conditions, cellular stress caused by DNA damage activates p53, enabling this tumor suppressor to regulate transcriptional responses responsible for halting cell-cycle progression, facilitating DNA repair, and initiating apoptosis, thereby maintaining genomic stability.[16] However, disruption of this regulatory pathway, particularly through excessive MDM2 expression, can weaken p53-mediated tumor suppression by increasing p53 ubiquitination and promoting its degradation through the proteasome system. Fig. 1. [33] Consequently, p53 becomes functionally inactive, compromising essential cellular defense mechanisms.[31] Cells with damaged DNA may therefore escape programmed cell death, accumulate additional genetic alterations, and continue proliferating without normal regulatory control. With continued progression, these molecular abnormalities can facilitate tumor formation, disease advancement, metastatic spread, and diminished responsiveness to anticancer treatment.[12,20,34]

*Role of the p53-MDM2 Axis in Therapeutic Resistance: Predicting Resistance via Ai Models*

The treatment of breast cancer encompasses a range of therapeutic modalities, including HER2-targeted agents, chemotherapy, endocrine therapy, targeted therapies, immunotherapy, and PARP inhibitors, each characterized by specific limitations, resistance mechanisms, and potential adverse effects.[22, 23] As shown in Figure 2, despite considerable advancements in clinical research and therapeutic development, treatment resistance persists as a significant barrier to achieving optimal clinical outcomes as shown in table 2. [24] The emergence of therapeutic resistance is influenced by diverse molecular mechanisms, including the activation of alternative signaling networks, genomic instability and mutations, enhanced DNA repair capacity, elevated drug efflux activity, and immune evasion strategies.[25] In particular, impairment of the p53-MDM2 regulatory axis significantly contributes to therapeutic resistance through inhibition of apoptotic pathways and enhancement of tumor cell survival.[26] Accordingly, the identification and targeted modulation of these resistance-driving mechanisms hold significant promise for mitigating therapeutic resistance and improving the efficacy of cancer treatment, table 2. [23]

**Table 2:** Role of the p53-MDM2 Axis in Therapeutic Resistance and AI-Based Prediction in Breast Cancer

| Therapeutic modality | Key resistance mechanism | Role of p53-MDM2 axis | AI contribution [ML/DL/XAI/multi-omics] | Clinical implication | references |
|---|---|---|---|---|---|
| Chemotherapy | DNA damage tolerance, apoptosis evasion | Loss-of-function of the tumor suppressor p53 tumor suppressor pathway enables evasion of apoptosis and drives unchecked cellular proliferation; MDM2 suppresses p53 activity | Apoptosis resistance is predicted through integrative analysis of genomic alterations and transcriptomic expression signatures | Early detection of therapeutic resistance enables timely identification of emerging treatment failure driven by tumor adaptive or intrinsic resistance mechanisms. | [49] [47] |
| Human epidermal growth factor receptor 2 | Pathway resurgence; compensatory signaling. | Dysfunction of the p53 tumor suppressor pathway promotes uncontrolled cellular proliferation, sustains pro-survival signaling, and drives chromosomal instability. | Deep learning identifies HER2 escape pathways | Treatment adaptation and combination synergy | [31] [44] |
| Hormone suppressor | ER pathway alteration. Mutation | Loss of p53 enhances survival under hormone deprivation | Multi-omics AI identifies interaction patterns between Estrogen receptor signaling pathway and p53 tumor suppressor pathway | Prediction of endocrine therapy resistance. | [47] [41] |
| Inhibition of PARP enzymes impairs DNA repair and induces synthetic lethality in tumor cells. | Homologous recombination reactivation | p53 mutation alters DNA repair balance, reducing drug sensitivity | AI models predict DNA repair pathway reactivation | Improved patient stratification | [46] [48] |
| biotherapy | Immune evasion, low ability of tumor to induce immune responses. | p53 disruption alters tumor immune microenvironment | AI integrates spatial + immune profiling data | Identification of immunotherapy responders | [23] [50] |
| Targeted therapy [general / MDM2 inhibitors] | Alternative pathway activation | MDM2 amplification inhibits tumor suppressor function | Explainable AI models feedback loop dysregulation in p53–MDM2 axis | Supports development of MDM2 inhibitors and precision therapy | [51] [6] |

Previously, breast cancer treatment relied on relatively uniform approaches across tumor subtypes, often limiting effectiveness and patient outcomes.[24] However, precision oncology and targeted therapy now enable detailed molecular characterization of tumors, identifying specific genetic and proteomic drivers of disease.[27] This has led to the use of tailored therapies that selectively target these abnormalities, improving treatment specificity and clinical outcomes.[25] Advanced cancer management now employs sophisticated technologies, including genomic sequencing, transcriptomics, proteomics, and spatial analysis, to comprehensively characterize tumors. These approaches examine tumor DNA, gene expression, protein profiles, and cellular organization, while liquid biopsies enable non-invasive monitoring of tumor evolution.[28] Collectively, these tools allow oncologists to identify actionable mutations, understand tumor vulnerabilities, and make more informed, targeted treatment decisions.[29] these scientific advancements have improved cancer care by enabling therapies that inhibit key signaling pathways driving tumor growth, deliver cytotoxic agents directly to cancer cells, and enhance immune-mediated tumor elimination.[30] They have also advanced diagnostics through circulating tumor DNA [ctDNA],

facilitating early detection and non-invasive monitoring of disease progression.[31] However, these treatments are not universally effective, as only a subset of patients achieve durable responses. Over time, many tumors develop resistance due to evolution, intratumoral heterogeneity, and activation of alternative pathways that bypass therapeutic effects.[32] Additionally, scientists can now study the molecular details of cancer and identify various genetic alterations within tumor cells. However, despite these discoveries, effective drugs are not yet available for many of these targets.[33] Most cancer-driving factors remain difficult to inhibit, meaning that although their existence is known, they cannot be effectively targeted for long-term treatment. Only recently have a few previously 'undruggable' targets, such as RAS mutations, begun to become therapeutically actionable.

Current research demonstrates that artificial intelligence, including deep learning, explainable AI, and multi-omics integration, enhances the understanding of molecular mechanisms underlying therapeutic resistance in breast cancer.[34] These approaches enable the analysis of complex biological data to identify patterns and molecular alterations that are not easily detectable by conventional methods. Consequently, AI supports the prediction of treatment response and facilitates the development of more precise and personalized therapeutic strategies.[35] Artificial intelligence enables the simultaneous analysis of multiple biological datasets, in contrast to conventional approaches that typically examine individual datasets sequentially and are often time intensive.[36] This integrative, multi-layered approach facilitates the identification of complex non-linear molecular relationships and pathway-level alterations that underlie therapeutic resistance phenotypes.[37] To enable the characterization of tumor subclones that may contribute to therapeutic failure and to monitor dynamic changes in cancer cell populations, artificial intelligence facilitates high-resolution single-cell analysis.[39] The p53 tumor suppressor pathway plays a critical role in preventing malignant transformation by inducing cell cycle arrest in damaged cells; however, its activity can be inhibited by overexpression of the MDM2 oncogenic regulator, thereby promoting tumor progression.[4] AI-based computational models enhance the understanding of dysregulation within the p53-MDM2 regulatory axis, including associated feedback loop disruptions, and support the identification and prioritization of therapeutic strategies aimed at restoring p53 tumor suppressor function.

*Natural Compounds Targeting The P53-Mdm2 Network*

Natural product-derived compounds represent a prominent class of therapeutic agents with the capacity to modulate the p53-MDM2 regulatory axis, a critical pathway governing tumor suppression and cancer progression.[39] By influencing this interaction, these compounds can restore p53 activity and thereby inhibit the proliferation and survival of malignant cells.[40] The p53 protein is a key transcription factor that maintains genomic stability by inducing cell cycle arrest, DNA repair, and apoptosis in response to cellular stress. In contrast, MDM2 negatively regulates p53 by inhibiting its activity and promoting its ubiquitin-mediated degradation, thereby controlling its cellular levels.[41,42] In many cancers, including breast cancer, overexpression of MDM2 results in the functional inactivation of p53 through enhanced ubiquitin-mediated degradation and suppression of its transcriptional activity. The loss of p53 tumor suppressor function permits uncontrolled cellular proliferation, evasion of apoptosis, and accumulation of genomic instability, thereby promoting tumor progression and contributing to therapeutic resistance.[43,44] Consequently, restoration of p53 activity through pharmacological inhibition of the p53-MDM2 interaction has emerged as a promising strategy in precision oncology, as it enables reactivation of tumor suppressor function and selective suppression of cancer cell proliferation as shown in figure 3. Consequently, restoring p53 activity through inhibition of the p53-MDM2 interaction has become a promising strategy in precision oncology.[7]

A growing body of recent research has identified several plant-derived and naturally occurring compounds, including polyphenols and alkaloids, that can disrupt the p53-MDM2 interaction, thereby stabilizing p53 and restoring its tumor suppressor activity in cancer cells.[45] Plant-derived compounds such as polyphenols, flavonoids, alkaloids, and terpenoids can reactivate p53 signaling by inhibiting MDM2 expression and or stabilizing p53 protein, thereby restoring its tumor suppressor function in cancer cells.[46] As shown in figure 3 curcumin, resveratrol, and epigallocatechin gallate [EGCG] have demonstrated anticancer activity in preclinical breast cancer models by inducing apoptosis and inhibiting tumor cell proliferation through modulation of key apoptotic signaling pathways.[47,48] These natural agents often exert multi-target effects, influencing not only the p53-MDM2 axis but also other oncogenic signaling pathways involved in cell survival and metastasis.[44]

Despite demonstrating strong anticancer potential in preclinical studies, the clinical translation of natural compounds targeting the p53-MDM2 axis is limited by poor bioavailability, inadequate pharmacokinetic stability, and insufficient target specificity.[40,44] Recent advances in nanotechnology-based delivery systems have begun to address these limitations by enhancing compound stability and improving tumor-targeted delivery. Concurrently, computational approaches, including molecular docking and artificial intelligence driven drug discovery, are accelerating the identification and optimization of potent natural inhibitors.[37,49] Collectively, these developments underscore the growing potential of natural compounds as lead structures or adjunct therapeutic agents for restoring p53 function and overcoming MDM2-mediated therapeutic resistance in breast cancer.[40]

Fig 2

*Translational Challenges and Limitations*

Although considerable research has been undertaken to clarify the molecular mechanisms underlying the interaction between p53 and MDM2, important knowledge gaps persist, creating obstacles to successful clinical translation and limiting potential improvements in patient outcomes.[41,8] The biological significance of these proteins remains considerable because both are fundamental regulators of tumor initiation, development, and progression, as summarized in Table 3.[42] One major challenge is the inconsistent relationship between promising preclinical findings and outcomes observed in clinical trials, as presented in Table 3.[43] Existing experimental models may partly explain this disparity because they often fail to reproduce the biological complexity of human tumors and the dynamic interactions within their surrounding microenvironment, potentially leading to an overestimation of therapeutic efficacy.[45] A further concern identified in Table 3 is the emergence of dose-limiting toxicities, especially hematological adverse events reported with MDM2 inhibitors.[46] Such toxic effects can prevent administration of therapeutically optimal doses, consequently compromising treatment efficacy in clinical practice. Moreover, as outlined in Table 3, the requirement for functional wild-type TP53 substantially narrows the therapeutic population, particularly because TP53 alterations occur frequently among patients with breast cancer.[47]

Tumor heterogeneity and adaptive resistance mechanisms, also outlined in table 3, further complicate therapeutic outcomes.[50] Variability between and within tumors leads to inconsistent responses, while activation of compensatory signaling pathways contributes to treatment resistance and disease progression. Consequently, single-target strategies, such as isolated MDM2 inhibition, often fail to achieve sustained clinical benefits.[51] In the case of natural compounds, table 3, emphasizes key pharmacokinetic challenges, including poor bioavailability, rapid metabolism, and limited systemic distribution, all of which hinder effective drug delivery to tumor sites.[40] Furthermore, issues related to target specificity, as presented in table 3, increase the likelihood of off-target effects and complicate dose standardization.

Clinical translation is also affected by limitations in trial design and validation, as detailed in table 3, including small sample sizes and heterogeneous study populations, which weaken the strength of clinical evidence.[34] Although artificial intelligence offers promising solutions for predicting therapeutic responses, its application remains constrained by data quality and validation challenges.[34,37,38] Overall, the challenges outlined in table underscore the need for integrated and multidisciplinary approaches, including combination therapies,

improved drug delivery systems, and robust clinical validation strategies, to enhance the successful translation of p53-MDM2-targeted therapies into routine clinical practice.[31,52]
Table 3

**Table 3:** Key Translational Challenges Limiting Clinical Application of p53–MDM2–Targeted Therapies in Breast Cancer

| Challenge Category | Specific Limitation | Underlying Cause/Mechanism | Clinical Impact | Potential Mitigation Strategy | References |
|---|---|---|---|---|---|
| Pharmacotoxicity | Hematologic dose toxicity | Off-target MDM2 inhibitory effects | Constrains safe dosing and compromises therapeutic efficacy | Dose optimization, combination therapy | [64] [63] |
| Genomic dependency | Therapeutic efficacy is contingent upon wild-type TP53 gene status | Mutant TP53 gene is refractory to reactivation | Restricted patient eligibility | Patient stratification | [67] [64] |
| Intratumoral and intertumoral biological variability | Variable tumor biology | Intratumoral and interpatient variability | Inconsistent treatment response | Precision medicine approaches | [65] [68] |
| Therapeutic resistance to pharmacological intervention | Adaptive resistance mechanisms | Reactivation of alternative signaling cascades | Diminished sustained treatment effectiveness | Combination therapies | [38] [39] |
| Quantitative analysis of drug disposition in biological systems | Suboptimal oral bioavailability of phytochemicals | Rapid metabolism, low absorption | Low therapeutic concentration | Nanoparticle delivery systems | [31] [53] |
| Target specificity | Off-target effects | Multi-pathway interactions | Increased side effects | Structural optimization | [20] |
| Preclinical limitations | Poor clinical translation | Inadequate human tumor modeling | Overestimated efficacy | Advanced translational models | [64] |
| Clinical validation | Limited large-scale trials | Small/heterogeneous populations | Weak clinical evidence | Larger controlled trials | [68] |
| AI integration | Data limitations and bias | Limited datasets, lack of validation | Reduced predictive accuracy | Data standardization, validation | [47] [44] |

**Table 4:** Comparative characteristics of artificial intelligence, multi-omics and natural-product approaches targeting therapeutic resistance in breast cancer

| Dimension | Artificial intelligence [AI] | Multi-omics approaches | Natural compounds | references |
|---|---|---|---|---|
| Principal function | Uses computational algorithms to integrate complex information and generate predictions of treatment response or resistance. | Combines complementary molecular datasets to provide a multidimensional view of tumor biology. | Explores bioactive molecules as potential agents for altering disease-associated molecular pathways. | [50,64] |
| Evidence/data base | Clinical records, molecular profiles, imaging information, and other high-dimensional datasets. | Genomic, transcriptomic, proteomic, metabolomic, and related molecular datasets. | Experimental, cellular, biochemical, and preclinical pharmacological evidence. | [52,62,64] |
| Relevance to p53–MDM2 | Can identify computational patterns associated with p53–MDM2 dysregulation and predict resistance or treatment-response phenotypes. | Enables detection of molecular alterations and regulatory signatures associated with the p53–MDM2 network. | Provides candidate molecules capable of influencing p53–MDM2 signaling, including approaches aimed at restoring p53 activity. | [26,49] |
| Key strength | Rapid integration of large and heterogeneous datasets, facilitating predictive modeling and patient stratification. | Provides a broader molecular representation of tumor heterogeneity and resistance-associated alterations. | Offers structurally diverse molecules with the potential to influence multiple biological targets simultaneously. | [22,51] |
| Principal limitation | Performance may be affected by dataset quality, algorithmic bias, inadequate external validation, and limited generalizability across populations. | Requires substantial data generation, computational infrastructure, analytical expertise, and careful interpretation of complex datasets. | Therapeutic development is constrained by poor bioavailability, pharmacokinetic variability, target specificity, and limited clinical evidence. | [44,47,48] |
| Complementary role within an integrated framework | Can combine clinical and multi-omics information to identify patterns, predict outcomes, and prioritize potential therapeutic targets. | Supplies molecular signatures and biological features that can serve as inputs for computational prediction and mechanistic interpretation. | Candidate compounds can be prioritized according to molecular targets and resistance signatures identified through omics and AI analyses | [1,55,56] |

*Future Directions and Clinical Perspectives*

Future developments in breast cancer management should focus on comprehensive, multi-target therapeutic approaches capable of addressing the limitations associated with therapies directed at individual molecular pathways, particularly interventions involving the p53-MDM2 axis.[53] Despite encouraging preclinical evidence

supporting MDM2 inhibition, its translation into clinical practice remains constrained by treatment-related toxicity, the emergence of resistance, and the requirement for functional wild-type TP53.[44,53] Future therapeutic strategies should therefore investigate rational combination regimens that concurrently interfere with complementary signaling networks, with the aim of limiting adaptive resistance and achieving more sustained treatment responses.[54] Developments in precision oncology, incorporating genomic, transcriptomic, and proteomic characterization together with liquid biopsy approaches, are expected to improve patient selection and facilitate continuous assessment of tumor evolution during treatment.[55] Furthermore, the integration of multiple omics datasets through artificial intelligence may strengthen the prediction of treatment sensitivity and resistance, thereby facilitating individualized therapeutic decision-making.[56] Natural compounds capable of modulating the p53-MDM2 interaction also warrant further investigation as potential complementary treatments; however, their clinical application will require advances in bioavailability and targeted delivery, including nanotechnology-enabled systems.[57] Ultimately, translating these emerging strategies into standard clinical care will require rigorous validation in adequately powered clinical trials, supported by sustained collaboration among researchers and healthcare professionals. [58]
Current breast cancer treatment modalities including chemotherapy, HER2-targeted therapy, endocrine therapy, PARP inhibitors, immunotherapy, targeted therapies, and natural compounds exhibit distinct mechanisms of action but share common limitations related to therapeutic resistance and tumor heterogeneity.[50,59] Chemotherapy and endocrine therapies remain widely used but are often limited by systemic toxicity and resistance driven by p53 dysfunction.[60] HER2-targeted therapies and PARP inhibitors offer greater specificity but are susceptible to pathway reactivation and restoration of DNA repair mechanisms, respectively. Immunotherapy provides durable responses in a subset of patients but is constrained by immune evasion and variability in tumor immunogenicity.[54] Targeted therapies, particularly MDM2 inhibitors, offer mechanistic precision but are hindered by toxicity, compensatory signaling pathways, and limited applicability to patients with intact TP53. Natural compounds provide a multi-targeted, lower-toxicity alternative, yet their effectiveness is restricted by poor pharmacokinetics and insufficient clinical validation.[55] Collectively, these limitations highlight the need for combination-based, precision-guided approaches that integrate molecular profiling, AI-driven prediction, and advanced drug delivery systems to achieve more effective and sustained therapeutic outcomes.[61]

## Conclusion

The review shows that the p53–MDM2 pathway is closely involved in breast cancer progression and resistance to treatment (25, 28). Studies included in the review also show that artificial intelligence, multi-omics analysis, and natural compounds may complement one another in identifying molecular changes linked to resistance, predicting treatment response, and identifying possible therapeutic options (34, 38, 40, 51). However, the use of these approaches in clinical practice is still limited by tumor heterogeneity, TP53 alterations, treatment-related toxicity, poor bioavailability of some natural compounds, limited target specificity, and inadequate clinical evidence (40, 51). Further studies should examine how molecular profiling, computational methods, and improved drug-delivery systems can be combined to guide treatment. Large, well-designed clinical studies are also needed to confirm the safety and effectiveness of these approaches in breast cancer management.

## Conflict of Interests

The authors declare no conflict of interest.

## Authors' Declaration

The authors hereby declare that the work presented in this article are original and that any liability for claims relating to the content of this article will be borne by them.

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## References

1. Burstein HJ, Curigliano G, Gnant M, Loibl S, Regan MM, Loi S, Denkert C, Poortmans P, Cameron D, Thurlimann B. Tailoring treatment to cancer risk and patient preference: the 2025 St Gallen International Breast Cancer Consensus Statement on individualizing therapy for patients with early breast cancer. Ann Oncol. 2025 36(12):1433–46. doi:10.1016/j.annonc.2025.09.007
2. Kramer G, José Volders, Den Haring F, Opperman R, Spronk P, Petrousjka Van Den T. National Breast Cancer Surgery Snapshot Study: Breast Cancer Surgery after Neoadjuvant Systemic Therapy in Primary Breast Cancer (MANS Study). Clin Breast Cancer. 2026 26(1):64–72. doi:10.1016/j.clbc.2025.10.019
3. Li M, Zhou S, Lv H, Cai M, Shui R, Yang W. Neoadjuvant chemotherapy response in androgen receptor-positive triple-negative breast cancer: potential predictive biomarkers and genetic alterations. Breast Cancer Res. 2025 27(1):41. doi:10.1186/s13058-025-01994-y
4. Russano F, Sturlese M, Dall'Olmo L, Callegarin F, Brugnolo D, Del Fiore P, Patti V, Purpura A, Moro S, Rastrelli M, Mocellin S. MDM2 in Tumor Biology and Cancer Therapy: A Review of Current Clinical Trials. Int J Mol Sci. 2025 27(1):99. doi:10.3390/ijms27010099
5. Yousuf A, Khan NU. Targeting MDM2-p53 interaction for breast cancer therapy. Oncol Res. 2025 ;33(4):851–61. doi:10.32604/or.2025.058956
6. Yao Y, Zhang Q, Li Z, Zhang H. MDM2: current research status and prospects of tumor treatment. Cancer Cell Int. 2024 24(1):170. doi:10.1186/s12935-024-03356-8
7. Ramli I, Cheriet T, Posadino AM, Giordo R, Fenu G, Chukwuemeka Nwachukwu K, Adebayo Oyewole O, Oluwaseun Adetunji C, Calina D, Sharifi-Rad J, Pintus G. Modulating the p53-MDM2 pathway: The therapeutic potential of natural compounds in cancer treatment. EXCLI J 23Doc1397 ISSN 1611-2156. 2024. doi:10.17179/EXCLI2024-7791
8. Zhao J, Chen H, Liang C. Dual functionality of MDM2 in PROTACs expands the horizons of targeted protein degradation. Biomark Res. 2025 13(1):111. doi:10.1186/s40364-025-00826-7
9. You W, Feng J, Guo L, Yan J, Yan S. Selenium nanoparticle-delivered MDM2 inhibitor reactivates p53 and reprograms tumor immune microenvironment in colorectal cancer. Front Immunol. 2025. 16:1684611. doi:10.3389/fimmu.2025.1684611
10. Cheriyan BV, Pandi K, Murali D, Boobalan N, Harikrishnan J, Kannan D, Jebaraj LPC, Munuswamy S, Manaksha SH. Polyphenols Target Apoptosis and Cell Cycle Regulation in Various Cancer Models: Emphasis on Flavonoid Subclasses. Biomed Pharmacol J. 2025;4(18):2515. doi:10.13005/bpj/3274
11. Karmakar S, Sen A, Majumdar S, Singh B, Pramanik A, Mondal S. In-silico approaches to unravel the efficacy of naturally occurring C–C and C–O–C type biflavonoids towards the inhibition of MDM2–p53 interactions. Discov Chem. 2025 ;2(1):91. doi:10.1007/s44371-025-00167-2
12. Kalathiya U, Marek-Trzonkowska N, Padariya M. Characterizing p53 structural insights of variants in vertebrates that interfere its regulatory interaction with Mdm2. Dev Comp Immunol. 2026;176:105554. doi:10.1016/j.dci.2026.105554
13. Liu B, Peng Z, Zhang H, Zhang N, Liu Z, Xia Z, Huang S, Luo P, Cheng Q. Regulation of cellular senescence in tumor progression and therapeutic targeting: mechanisms and pathways. Mol Cancer. 2025;24(1):106. doi:10.1186/s12943-025-02284-z
14. Suarez OJ, Vega CJ, Sanchez EN, González-Santiago AE, Rodríguez-Jorge O, Alanis AY, Chen G, Hernandez-Vargas EA. Pinning Control for the p53-Mdm2 Network Dynamics

Regulated by p14ARF. Front Physiol. 2020. 11:976. doi:10.3389/fphys.2020.00976
15. Di Grazia G, Conti C, Nucera S, Stella S, Massimino M, Giuliano M, Schettini F, Vigneri P, Martorana F. Bridging the Gap: the role of MDM2 inhibition in overcoming treatment resistance in breast cancer. Crit Rev Oncol Hematol. 2025. 14:104834. doi:10.1016/j.critrevonc.2025.104834
16. Cooke SF, Wright TA, Lappin G, Kyurkchieva E, Sin YY, Ling J, Zorn A, O'Gorman B, Banyard W, Chang CJ, Wheadon H, Huang DT, Baillie GS, Blair CM. Targeting MDM2 homodimer and heterodimer disruption with DRx-098D in TP53 wild-type and mutant cancer cells [Internet]. Cancer Biology; 2025. Available from: http://biorxiv.org/lookup/doi/10.1101/2025.01.10.632324 doi:10.1101/2025.01.10.632324
17. Yi H, Han Y, Wang X, Li Q, Xiong L, Li S. Novel antagonist APG-115 targets MDM2-p53 to induce p53-mediated apoptosis and radiosensitization in colorectal cancer. Clin Exp Med. 2026. 26(1):128. doi:10.1007/s10238-026-02049-y
18. Huang Y, Li W, Zhou Y, Bai J, Li N, Su Z, Cheng X. Strategies for p53 Activation and Targeted Inhibitors of the p53-Mdm2/MdmX Interaction. Cells. 2025. 14(8):583. doi:10.3390/cells14080583
19. Brown AL, Lian X, Wang Q. The Structure, Pathogenesis, and Inhibition of the p53-MDM2 Pathway. Cancers. 2026. 18(4):546. doi:10.3390/cancers18040546
20. Sun D, Qian H, Li J, Xing P. Targeting MDM2 in malignancies is a promising strategy for overcoming resistance to anticancer immunotherapy. J Biomed Sci. 2024. 31(1):17. doi:10.1186/s12929-024-01004-x
21. Castillo Tarazona MY, Miscione GP. Enhancing structure-based virtual screening of MDM2–p53 inhibitors: a benchmark of machine learning vs. traditional docking scoring functions. Front Drug Discov. 2026. 5:1731262. doi:10.3389/fddsv.2025.1731262
22. Ismaili N. A Systematic Review of Major Advances in Breast Cancer Therapeutics in 2025: Synthesis of Conference and Published Evidence. Int J Mol Sci. 2026. 27(4):1971. doi:10.3390/ijms27041971
23. Xiang J, Li J, Guo Z, Wu J, Ma D, Xu H, Shang T, Pu P, Cong L, Zhou R, Wang X, Yu Y, Liu J. Clinical application of PARP inhibitors and emerging strategies to overcome resistance: a pan-cancer perspective. Biomark Res. 2026. doi:10.1186/s40364-026-00908-0
24. Wang X, Luo X, Xiao R, Liu X, Zhou F, Jiang D, Bai J, Cui M, You L, Zhao Y. Targeting metabolic-epigenetic-immune axis in cancer: molecular mechanisms and therapeutic implications. Signal Transduct Target Ther. 2026. 11(1):28. doi:10.1038/s41392-025-02334-4
25. Li J, Hu J, Yang Y, Zhang H, Liu Y, Fang Y, Qu L, Lin A, Luo P, Jiang A, Wang L. Drug resistance in cancer: molecular mechanisms and emerging treatment strategies. Mol Biomed. 2025. 6(1):111. doi:10.1186/s43556-025-00352-w
26. Zou Y, Guo Z, Rong R, Zhang H, Han S. Exploration of atractylenolide III targeting MDM2/p53 axis in breast cancer cell progression based on network pharmacology, molecular docking and ubiquitination analysis. Curr Proteomics. 2025. 22(2):100016. doi:10.1016/j.curpro.2025.100016
27. Qiao D, Wang RC, Wang Z. Precision Oncology: Current Landscape, Emerging Trends, Challenges, and Future Perspectives. Cells. 2025. 14(22):1804. doi:10.3390/cells14221804
28. Lee Y, Lee YY, Park J, Maksakova A, Seo D, Kim J, Yeom JE, Kim Y, Kim CH, Ryoo R, Kim SN, Park J, Park W, Kim TH, Choy YB, Park CG, Kim KH, Lee W. Illudin S inhibits p53-Mdm2 interaction for anticancer efficacy in colorectal cancer. Biomed Pharmacother. 2025. 182:117795. doi:10.1016/j.biopha.2024.117795
29. Yousuf A, Khan NU. Targeting MDM2-p53 interaction for breast cancer therapy. Oncol Res. 2025;33(4):851–61. doi:10.32604/or.2025.058956
30. Schaberl-Moser R. ASCO 2025: metastatic colorectal cancer—focus on precision oncology. Memo - Mag Eur Med Oncol. 2025. 18(4):316–9. doi:10.1007/s12254-025-01075-y
31. Young NA, Prosperi JR, Freud AG, Yee NS, Petricoin EF. Editorial: Clinical implementation of precision oncology data to direct individualized and immunotherapy-based treatment strategies. Front Immunol. 2025 ;16:1631591. doi:10.3389/fimmu.2025.1631591
32. Prabhu KS, Therachiyil L, Masoodi T, Bhat AA, Uddin S. GADD45: a crucial component of the DNA damage response and a potential cancer therapeutic target. Expert Opin Ther Targets. 2025;29(10):743–56. doi:10.1080/14728222.2025.2589807
33. Guruvaiah P, Gupta R. IκBα kinase inhibitor BAY 11-7082 promotes anti-tumor effect in RAS-driven cancers. J Transl Med. 2024 ;22(1):642. doi:10.1186/s12967-024-05384-4
34. Ran D, Li J, Zhao M, Du L, Zhang Y, Zhu J. Artificial intelligence integrates multi-omics data for precision stratification and drug resistance prediction in breast cancer. Front Oncol. 2025 ;15:1612474. doi:10.3389/fonc.2025.1612474
35. Frascarelli C, Venetis K, Marra A, Concardi A, D'Ercole M, Mangione E, Negrelli M, Porta FM, Keswani S, Curigliano G, Guerini-Rocco E, Fusco N. Computational pathology in breast cancer: optimizing molecular prediction through task-oriented AI models. Npj Breast Cancer. 2025 ;11(1):141. doi:10.1038/s41523-025-00857-1
36. Kumar D, Choudhary N, Kaur S, Kondaveeti SB. Breast cancer frontiers: mapping molecular signals, intelligent diagnostics, and adaptive therapies. Discov Oncol. 2026 . doi:10.1007/s12672-026-04453-y
37. Chua BN, Thng DKH, Toh TB, Ho D. Artificial intelligence for breast cancer management. Commun Med. 2026 ;6(1):79. doi:10.1038/s43856-025-01342-3
38. El Ouardani S, Chibani H, El Ouardani F, Brahmi SA, Afqir S. Artificial Intelligence in the Management of Breast Cancer: A Comprehensive Review. Cureus. 2026. 10. doi:10.7759/cureus.106764
39. Yao Y, Zhang Q, Li Z, Zhang H. MDM2: current research status and prospects of tumor treatment. Cancer Cell Int. 2024 ;24(1):170. doi:10.1186/s12935-024-03356-8
40. Tsukamoto S. Natural products that target p53 for cancer therapy. J Nat Med. 2025 ;79(4):725–37. doi:10.1007/s11418-025-01906-6
41. Liu J, Duan Y, Xiao Q, Deng S, Li A, Wu D, Wu J, Liu C, Yi H, Wang M, Shu G, Yin G. Ubiquitination of MEIS1 by MDM2 serves as a switch for p53 stabilization and DNA damage response activation. Cell Death Differ. 2026. 14. doi:10.1038/s41418-026-01714-9
42. Liu Y, Su Z, Tavana O, Gu W. Understanding the complexity of p53 in a new era of tumor suppression. Cancer Cell. 2024 ;42(6):946–67. doi:10.1016/j.ccell.2024.04.009
43. Wang W, Alley A, Sun N, Tadesse M, Wang X, Zhang R. Targeting MDM2, RAS, and PCNA for cancer targeted therapy: pan-cancer approaches vs. cancer-specific strategies. Front Pharmacol. 2025 ;16:1663766. doi:10.3389/fphar.2025.1663766
44. Niazi S, Kavana CP, Aishwarya HK, Dharmashekar C, Jain A, Wani TA, Shivamallu C, Purohit MN, Kollur SP. Synthesis, characterization, and anti-cancer potential of novel p53-mediated Mdm2 and Pirh2 modulators: an integrated In silico and In vitro approach. Front Chem. 2024 ;12:1366370. doi:10.3389/fchem.2024.1366370
45. Hu Q yong, Li L, Li Y huang, Zhang H bo, Deng T, Liu Y, Li F tian, Xiao Z xiong, Cao Y. A structure-based virtual screening identifies a novel MDM2 antagonist in the activation of the p53 signaling and inhibition of tumor growth. Acta Pharmacol Sin. 2025 ;46(3):740–50. doi:10.1038/s41401-024-01394-6
46. Zeng F, Chen C, Fu Z, Huang H, Cui W, Zhou Y, Kong Y, Liu X, Xu Z, Wang S, Xiao T, Xia H. A novel β-carboline alkaloid derivative targeting MDM2-p53 pathway suppresses colorectal cancer progression. Cell Oncol. 2025 ;48(6):1821–36. doi:10.1007/s13402-025-01111-3

47. Asiri A, Bokahri BT, Sadaf, Eisa AA, Aljohani HM, Nofal W, Kausar T, Najm MZ. Curcumin, EGCG and apigenin in cervical cancer: mechanistic insights and therapeutic potential. Front Pharmacol. 2025 ;16:1592395. doi:10.3389/fphar.2025.1592395
48. Bahadar N, Bahadar S, Sajid A, Wahid M, Ali G, Alghamdi A, Zada H, Khan T, Ullah S, Sun Q. Epigallocatechin gallate and curcumin inhibit Bcl-2: a pharmacophore and docking based approach against cancer. Breast Cancer Res. 2024;26(1):114. doi:10.1186/s13058-024-01868-9
49. Xu B, Maimaitijiang A, Nuerbiyamu D, Su Z, Li W. The Multifaceted Role of p53 in Cancer Molecular Biology: Insights for Precision Diagnosis and Therapeutic Breakthroughs. Biomolecules. 2025 ;15(8):1088. doi:10.3390/biom15081088
50. Vichi G. Tumor Heterogeneity: Challenges and Opportunities in Precision Medicine. Vol. 9. 9(2).
51. Alaseem AM. Advancements in MDM2 inhibition: Clinical and pre-clinical investigations of combination therapeutic regimens. Saudi Pharm J. 2023 ;31(10):101790. doi:10.1016/j.jsps.2023.101790
52. Yousuf A, Khan NU. Targeting MDM2-p53 interaction for breast cancer therapy. Oncol Res. 2025;33(4):851–61. doi:10.32604/or.2025.058956
53. Pei HZ, Guo Y, Zhao Y, Zhang D, Chang Z, Zhou J, Baek SH, Zhao ZJ, Chen C, Chen Y. FLT3 inhibitors induce p53 instability, driven by STAT5/MDM2/p53 competitive interactions in acute myeloid leukemia. Cancer Lett. 2025 ;611:217446. doi:10.1016/j.canlet.2025.217446
54. Mustafa M, Ahmad R, Tantry IQ, Ahmad W, Siddiqui S, Alam M, Abbas K, Moinuddin, Hassan MdI, Habib S, Islam S. Apoptosis: A Comprehensive Overview of Signaling Pathways, Morphological Changes, and Physiological Significance and Therapeutic Implications. Cells. 2024 ;13(22):1838. doi:10.3390/cells13221838
55. Tornesello M. TP53 mutations in cancer: Molecular features and therapeutic opportunities (Review). Int J Mol Med. 2024 ;55(1):7. doi:10.3892/ijmm.2024.5448
56. Ticli G, Cazzalini O, Stivala LA, Prosperi E. Revisiting the Function of p21CDKN1A in DNA Repair: The Influence of Protein Interactions and Stability. Int J Mol Sci. 2022 ;23(13):7058. doi:10.3390/ijms23137058
57. Valverde-Lopez JA, Li-Bao L, Sierra R, Santos E, Giovinazzo G, Díaz-Díaz C, Torres M. P53 and BCL-2 family proteins PUMA and NOXA define competitive fitness in pluripotent cell competition. Sasaki H, editor. PLOS Genet. 2024 ;20(3):e1011193. doi:10.1371/journal.pgen.1011193
58. Barham SY, Omotade D, Yılmaz S, Akdeniz FT, Goralı BÇ, Attar R, İsbir T. Investigation of Polymorphisms in Global Genome Repair Genes in Patients With Ovarian Cancer in the Turkish Population. Cancer Control. 2024 ;31:10732748241270597. doi:10.1177/10732748241270597
59. Yan J, Chen S, Yi Z, Zhao R, Zhu J, Ding S, Wu J. The role of p21 in cellular senescence and aging-related diseases. Mol Cells. 2024 ;47(11):100113. doi:10.1016/j.mocell.2024.100113
60. Hiwase K, Verma P, Zade N, Kumar P, Weerarathna IN, Gundewar S. A Review on the Applications and Implications of Artificial Intelligence and Machine Learning in Oncology. Int J Comput Intell Syst. 2026 ;19(1):59. doi:10.1007/s44196-026-01164-8
61. Li J, Zhang L, Yu Z, Bao Z, Li D, Wang L. The impact of AI on modern oncology from early detection to personalized cancer treatment. Npj Precis Oncol. 2026 ;10(1):69. doi:10.1038/s41698-026-01276-6
62. Yamamoto N, Tolcher A, Hafez N, Lugowska I, Ramlau R, Macarulla T, Geng J, Li J, Teufel M, Märten A, LoRusso P. Efficacy and Safety of the MDM2–p53 Antagonist Brigimadlin (BI 907828) in Patients with Advanced Biliary Tract Cancer: A Case Series. OncoTargets Ther. 2024 ;Volume 17:267–80. doi:10.2147/OTT.S440979
63. Ramesh RPG, Yasmin H, Ponnachan P, Al-Ramadi B, Kishore U, Joseph AM. Phenotypic heterogeneity and tumor immune microenvironment directed therapeutic strategies in pancreatic ductal adenocarcinoma. Front Immunol. 2025 ;16:1573522. doi:10.3389/fimmu.2025.1573522