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MDM2 Antagonists and p53-Targeting Therapies in Cancer: Clinical Applications, Adverse Effects, and Resistance Mechanisms

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ABSTRACT

Background: Worldwide, cancer is the primary cause of mortality. Research indicates that around half of all cancer types are caused by p53 mutations or downregulation. Alternative or complementary therapy methods are, therefore, desperately needed. The relationship between p53 and the proto-oncoprotein MDM2, a ubiquitin ligase frequently overexpressed in AML that causes the degradation of p53, is an intriguing place to start.

Objective: this review aimed to summarize all research on MDM2 inhibitors and clinical studies, and recorded side effects and resistance profile.

Methods: Review articles compiled from over 100 publications in PubMed, Scopus, and ClinicalTrials.gov using keywords like MDM2 inhibitors.

Results: MDM2 antagonists efficiently stabilize p53, resulting in tumor suppression in malignancies of p53 wild-type individuals. Promising results have been seen in several Phase I and II clinical studies, especially in solid tumors and hematologic malignancies. Adverse effects and medication resistance are still problems, though. P53-targeting medications, on the other hand, may be able to restore P53 function in mutant forms, offering a new treatment option for tumors that have failed previous therapies.

Conclusion: P53 medications and MDM2 antagonists mark a substantial breakthrough in targeted cancer therapy. Although the initial clinical outcomes are promising, further investigation is needed to optimize their application, overcome resistance mechanisms, and integrate them into personalized treatment plans. Future developments in understanding P53-MDM2 interactions are likely to lead to more effective cancer treatments.

KEYWORDS: Complementary Therapies, Hematologic Neoplasms, Ubiquitin's, Leukemia, Myeloid.

INTRODUCTION

Mutation or functional inactivation of the TP53 tumor suppressor gene is a hallmark of approximately half of human cancers. In tumors that retain wild-type p53, the p53 pathway is often silenced by the overexpression of negative regulators, chiefly the MDM2 oncoprotein [1]. MDM2 (murine double minute 2, also known as HDM2 in humans) is an E3 ubiquitin ligase that binds to p53's N-terminal transactivation domain, leading to ubiquitination and proteasomal degradation of p53 [2]. The role of the TP53 mutation in cancer patients is one of the primary causes of cancer [2]. However, dysregulation may result from it. New therapeutic strategies for AML center on antagonists of p53 inhibitors because they inactivate p53 function in cancerous cells [3]. Research has indicated that around half of all cancer types are caused by p53 mutations or downregulation. Alternative or complementary therapy methods are, therefore, desperately needed. The connection between p53 and the proto-oncoprotein MDM2, a ubiquitin ligase that is frequently overexpressed in AML and causes the degradation of p53, is an intriguing place to start with this. The regulatory roles of p53 in the cell cycle and apoptosis are preserved when the connection between p53 and MDM2 is inhibited [4]. A Phase 1 clinical study for the Nutlin family chemical RG7112 has already been completed [6]. However, neither Nutlins nor other p53-MDM2 antagonists have been utilized in the treatment of breast cancer [7]. This medication is now in clinical trials to assess its safety but no one has been approved for the treatment of any cancer, however, this research summarizes the Mechanism of action of MDM2 inhibitors and their role in cancer treatment besides the safety profile of these medications.

MATERIALS AND METHODS

This review was conducted according to the PRISMA Guideline we searched on Google Scholar, PubMed, DOAJ, and Semantic Scholar, by using specific Keywords such as MDM2 inhibitors, Tumor Suppressor Protein p53, Oncogene and we included systemic reviews and articles we excluded case reports and books (to get updated information's), we also exclude the genetically associated protein ether than P53, MDM2 pathways.

We found about 1203 articles related to our keywords. After selecting, deleting repeated articles, and not being able to access about 100 articles from 2020 to 2024, after removing the unreliable journal, the final number is about 64 articles, as shown in Figure 1.

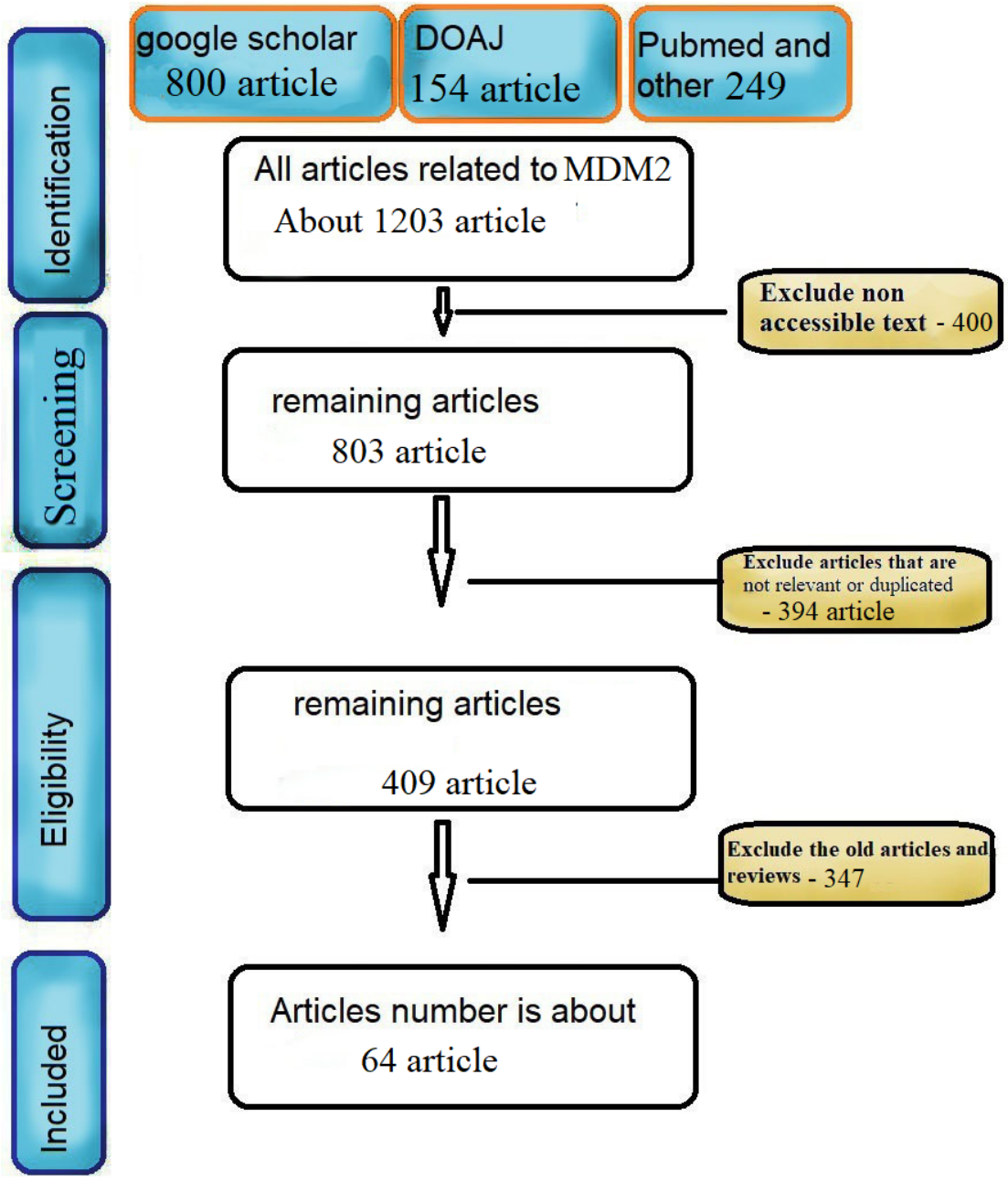

Figure 1: Inclusion and exclusion of the article according to PRISMA flow chart

RESULT

Protein 53 (guardian of the genome)

The p53 protein, sometimes referred to as transformation-related protein 53 (TRP53), phosphoprotein p53, antigen NY-CO-13, cellular tumor antigen p53 (UniProt name), tumor suppressor p53, or DNA-damaging protein with potential oncogenic mutations, prevents the growth of cells in humans [8].

Since the related protein, p53, has a molecular weight of 53 kDa and is associated with the Simian virus 40

(SV40) large T antigen, p53 was first identified in cells transformed by SV40 [9]. The SV40 T antigen's binding to p53 aids in the stability of both components and the cell's transformation during the tumorigenic process [9]. Nonetheless, p53 mutations mediate neoplastic changes [3]. It has been conclusively demonstrated by several later functional investigations that p53 functions as both a transcription factor and a tumor suppressor [3]. Although current estimating techniques reveal that p53 is not 53 kDa, the term "p53" originates from early studies that employed outdated molecular weight measurements of p53, which suggested that it contains 53 kDa. Moreover, alterations (mutations) that inhibit the p53 tumor suppressor system are necessary for the majority of human cancers. Over the past 20 years, research has demonstrated that p53 defends against malignancies, contrary to previous scientific beliefs that it is the cause of tumors. P53 is referred to as the "guardian of the genome" because of this [10].

Regulation of p53 functions

Due to its multiple functions in preserving genome integrity and preventing cell carcinogenesis, the p53 protein is a crucial anticancer protein for the body [3]. p53's primary function is to bind and recognize specific DNA sequences, thereby activating the transcription of a wide range of genes [11].

Commonly, p53 levels are downregulated; however, in the event of DNA damage or mutation, these alterations induce p53 to become activated, increasing its efficacy. Free radicals and ribosomal/oxidative stress can also raise p53 expression. To achieve rapid stability and the subsequent activation of several genes that regulate cellular processes, p53 is post-translationally modified [12]. We can state that p53 plays a critical role in preserving homeostasis by either eradicating or repairing cells that sustain genomic damage [13]. To clarify, the p53 protein triggers the transcription of genes that determine if a cell undergoes apoptosis or fixes its DNA [14]. The tetrameric p53 transcription factor is activated in response to cellular stress through phosphorylation cascades, and the type of stress or stimulus the cell encounters determines whether the activation results in the up- or down-regulation of genes related to cell cycle braking, DNA repair, apoptosis, and senescence (Figure 2).

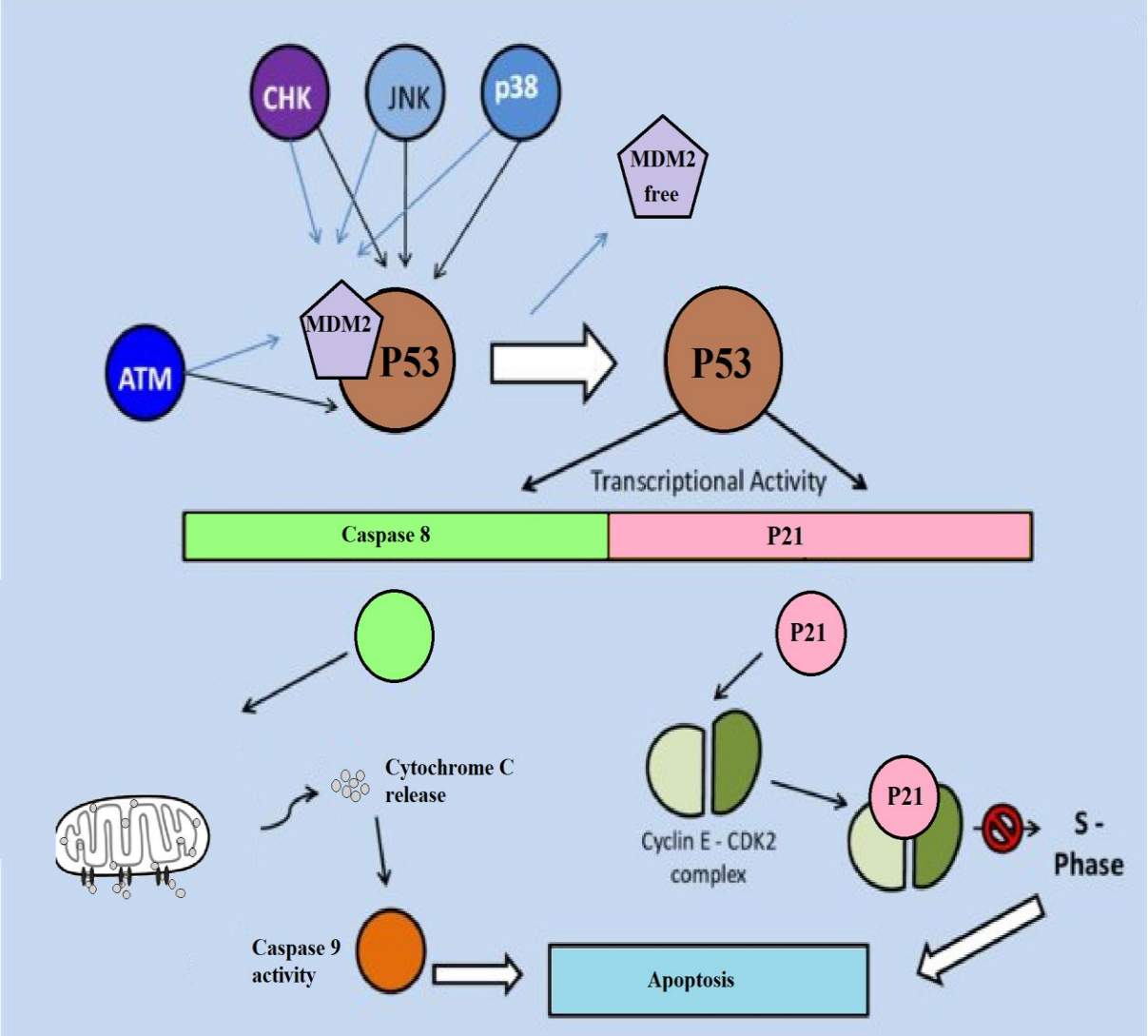

Figure 2 the role of P53 and MDM2 in apoptosis.
ATM: Ataxia Telangiectasia Mutated; CHK: Checkpoint Kinase; JNK: c-Jun N-terminal Kinase; p38: p38 Mitogen-Activated Protein Kinase; MDM2: Mouse Double Minute 2 Homolog; P53: Tumor Protein 53; P21: Cyclin-Dependent Kinase Inhibitor 1A (CDKN1A); CDK2: Cyclin-Dependent Kinase 2; Caspase 8/9: Cysteine-aspartic protease 8/9; S-Phase: Synthesis Phase of the Cell Cycle.

Therefore, we know that p53 may trigger autophagy, a process that results in components being eliminated needlessly or in a disordered intracellular manner when nutrients are few [15]. To stop tissue deterioration and cell damage, this autophagy mechanism lowers p53 levels. Furthermore, p53 can halt or arrest the cell cycle in several ways. One such method involves activating P21 (CDKN1A), a different protein that is essential for senescence and cell cycle arrest [16].

However, studies on senescence have also been conducted using tumor models in mice. For instance, tumor clearance through senescence-specific pathways was achieved when p53 activity was restored in mice that acquired hepatocellular carcinoma and sarcoma in soft tissues where p53 had previously been absent [18].

The wild form of p53 was preserved in models of breast cancer that underwent doxorubicin treatment-induced senescence, but not in those with mutated p53. This suggests the significance of p53 activity in senescence and its role in regulating tumor processes [18]. The activation of p53 is accomplished via a variety of molecular methods and signal cascades. When ionizing radiation causes double-strand breaks in DNA, for example, p53 is maintained by the phosphorylation or acetylation of specific amino acids. This includes the phosphorylation of serine at positions 15, 20, 33, 37, and threonine at position 18 by a variety of protein kinases, including the DNA-dependent protein kinase (DNA-PK), the "Ataxia Telangiectasia Mutated" (ATM) kinase [19], the related "Ataxia Telangiectasia Related" (ATR) kinase (Boatright & Salvesen), the checkpoint kinase Chk 1 and 2 following phosphorylation. By freezing the cell cycle, P53 dissociates from its inhibitor MDM2, which prevents damaged and possibly cancerous cells from proliferating and growing [19]. During this process, phosphorylated amino acids in MDM2's carboxy terminus undergo post-translational changes. These amino acids, when unphosphorylated, facilitate the ubiquitination of p53 and subsequent destruction. Consequently, p53 is stabilized by MDM2 phosphorylation on essential amino acids [6]. Within its C-terminal region, p53 binds to target gene DNA, acting as a transcription factor. It promotes gene transcription, which includes apoptosis induction or the change from the G1-regulate to the S phase [6]. This has a direct bearing on how p53 functions as a tumor suppressor. Abramowitz et al. found 1153 genes that may be controlled by p53 in 2017 [19].

Tumorigenesis due to *TP53* mutations

Since p53 functions as a tumor suppressor, its loss of function signifies a significant stage in tumor development. One of the most often found genetic abnormalities linked to cancer is a mutation in the TP53 gene, which may be brought on by both endogenous and external sources [6]. Twenty-five percent of patients with breast cancer had a TP53 locus mutation. Biological activity and interactions with other proteins can be inferred by mutation analysis. The human gene is located on chromosome 17p [20]. Base substitutions that occur within a 200 bp coding sequence, located within exons 5-8, are often relevant mutations in leukemias. Critical amino acids are required inside this area for p53 action. Faster tumor development and a lower rate of malignant cell death are the outcomes of p53 deficiency [2]. Additionally, tumor cells lacking p53 have a much worse response to chemotherapy, with an average 2.5-month drop in survival time. Furthermore, complex karyotypes and cytogenetic traits are two other equally important prognostic factors that correlate with TP53 mutations [22].

Degradation of p53 by MDM2

Apart from TP53 mutations, MDM2 overexpression also contributes to p53 inactivation. Overexpression of MDM2 is more prevalent than TP53 mutations in breast cancer patients, occurring in over 65% of cases [5]. One of two genes found in amplified DNA in the mouse cell line 3T3DM, the 90 kDa MDM2 protein was first identified as the result of the amplified "murine double minute 2"

(MDM2) in 1987 [7]. Transfected mouse and rat cells that overexpress the MDM2 gene have the potential to become cancerous, indicating that the gene plays a crucial role in regulating cell growth [5]. The 491-amino acid protein MDM2 is a well-studied p53 binding partner that deactivates p53 through ubiquitin-dependent degradation [7]. The ubiquitination of p53 takes place in the cell nucleus (Figure 3).

Three enzyme components, E1–E3, are needed for the ubiquitin system to degrade target proteins. The first stage involves the ubiquitin-activating enzyme (E1) using ATP to bind and activate ubiquitin (Ub) through thioester binding. The ubiquitin-conjugate enzyme E2's SH group receives Ub transfer in the second stage. Together with the substrate-recognizing enzyme E3, this enzyme forms a complex [22]. MDM2 attaches to the p53 C-terminal lysine residues and exhibits p53-specific E3 ubiquitin ligase activity [23]. Following p53's attachment to E3 and MDM2, a complex of ubiquitin (Ub) is transferred to p53. Ultimately, the proteasome poly-ubiquitinates and degrades p53 [23]

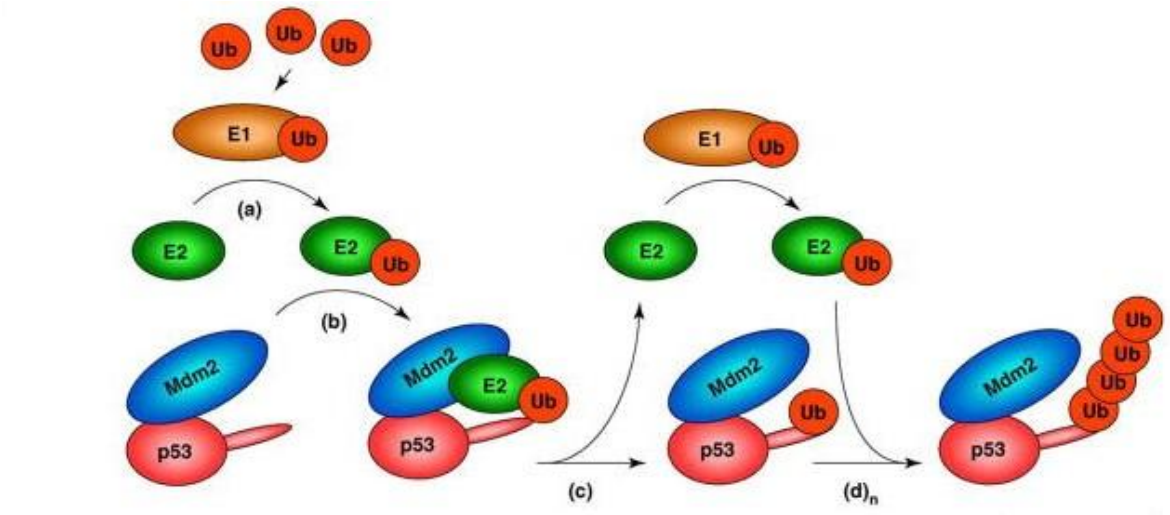

Figure 3 Ubiquitination of p53 by MDM2.

(a) Ubiquitin (Ub) is transferred from E1 to E2. (b) E2 binds to MDM2, which possesses E3 ubiquitin ligase activity and transfers ubiquitin (Ub) to p53 during interaction with MDM2. (c) E2 dissociates from the p53/MDM2 complex to transfer new ubiquitins from E1 to MDM2. (d) This results in the polyubiquitination of p53, leading to its degradation at the proteasome, as described by Sparks et al. [25].

Interaction between p53 and MDM2

MDM2 controls p53's ubiquitination as well as its interaction with other molecules, including p53-dependent promoters, which in turn suppress the expression of target genes (Do Patrocinio et al. [24]). The interaction domain is relatively well characterized by structural and functional research. The crucial amphipathic α helix formed by the amino acids 18 to 26 of p53's N-terminal transactivation domain and the N-terminal amino acids 25 to 109 of MDM2 is necessary for the connection of MDM2

with p53 (Figure 4) [26]. The hydrophobic side of the p53 α helix is inserted into a hydrophobic pocket formed by MDM2, which is composed of amino acids 26 to 109 [27].

The transcription of MDM2 is also downregulated by recognition if the concentration of p53 falls as a result of MDM2-dependent processes. P53 is rendered inactive by mutations that occur in at least 50% of the various forms of Human malignancies [28].

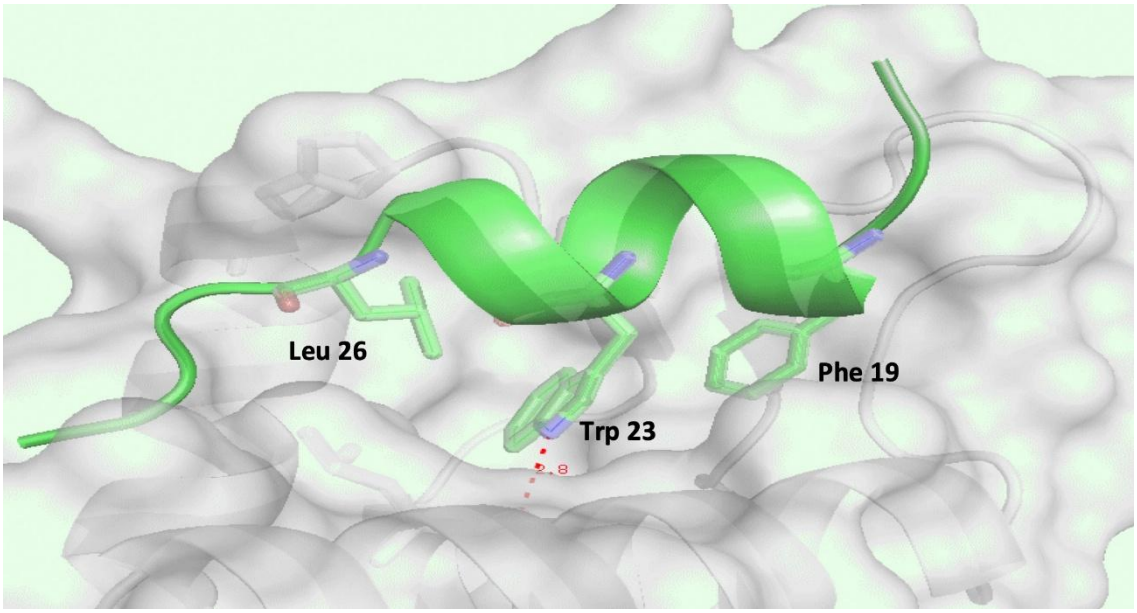

Figure 4: p53 and MDM2 interaction region. The amino acids Leu 26, Trp 23, and Phe 19 link the green p53 α helix to the gray MDM2.

Structural organization of p53

To comprehend the structure of p53, we must first grasp the idea of an intrinsically disordered protein (IDP). Typically, the structure of this type of protein is heterogeneous, consisting of both ordered and poorly defined regions, or an undefined region that extends over the entire protein. Nevertheless, this structural instability provides the IDPs with more flexibility when interacting with other cellular components, enabling them to perform a variety of roles that would otherwise render them ineffective [29]. A region rich in prolines, an intrinsically disordered C-terminal regulatory domain, a tetramerization domain that permits monomer binding, an inherently disordered N-terminal activation domain (TAD), and a DNA-binding domain (DBD) comprise the complex structural structure of p53. As a homotetramer with 393 amino acids per monomer, P53 is active in humans (Figure 5)[30].

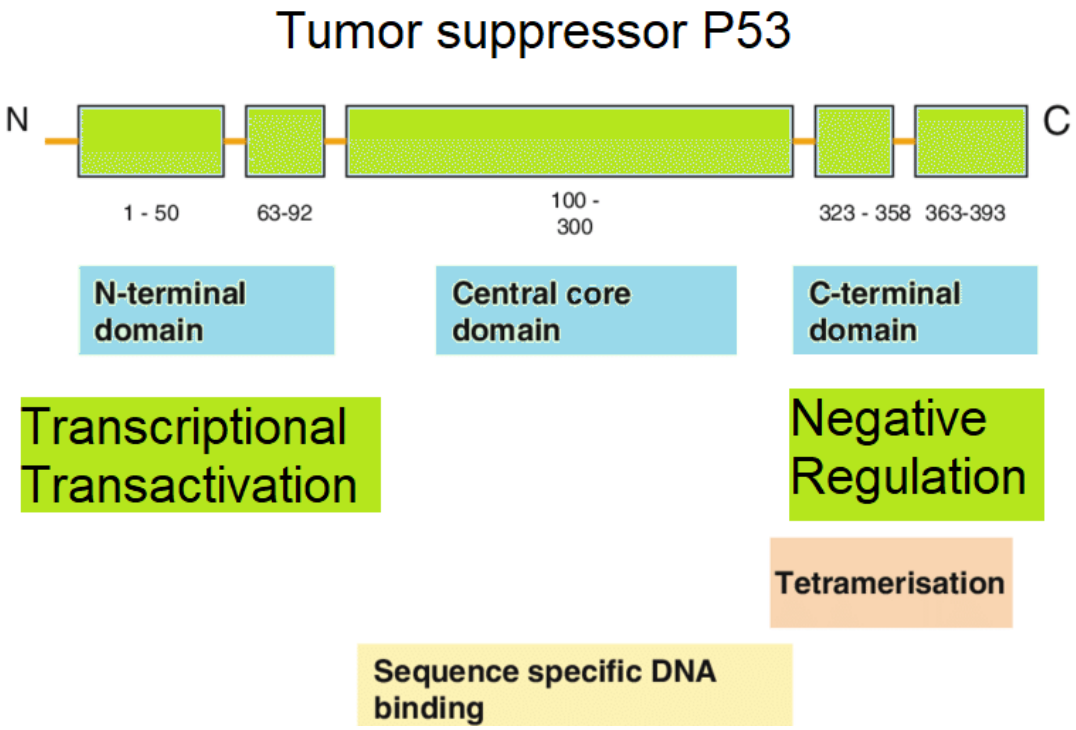

Figure 5 Structural organization of P53.

MDM2 inhibitors

Scientists are attempting to find a chemical compound that is an MDM2 antagonist using automated approaches (Table 1.2). Several research studies were carried out in 2020 in phase III trials[40]. Several compounds, including Nutlin-1, Nutlin-2, Nutlin-3a, MI-773 (SAR405838), NVP-CGM097, Idasanutlin (RG-7388), YH239-EE, and HDM201 (Siremadlin), have demonstrated their efficacy as anticancer agents.
All of these drugs are p53 activators and MDM2 inhibitors; however, not enough research has been done in this area [23].

Nutlin 3: A typical MDM2 treatment reduced the antitumor effects of several medications, including cisplatin (Table 1.1) [31].

Milademetan: An MDM2 antagonist may have oral antitumor effects. Following oral therapy, milademetan interacts with the MDM2 protein and prevents it from attaching to the area of the tumor suppressor protein p53, which is responsible for transcriptional activity. By blocking this MDM2-p53 link, the proteasome-mediated enzymatic degradation of p53 is stopped, and p53's transcriptional activity is restored [32].

YH239: Huang found it in 2014 as a strong anticancer agent that has shown great efficacy as an AML therapy; however, no research has been conducted about its potency (Table 1). [33]. The efficacy of this treatment in raising P53 levels has been the subject of several research. As a result, raising the P53 level may enhance doxorubicin's anticancer effects [34].
According to other research, doxorubicin by itself may raise p53 levels and have an anti-cancer impact. P53 only increases

doxorubicin-induced apoptosis in situations when there is significant DNA damage.

Since 2011, research and studies on MDM2 antagonists have been conducted to find a powerful anticancer medication that targets the MDM2 pathways [5].

Table 1 clinical studies on MDM2 inhibitors and their outcome

Drug or chemical name	phase of clinical trial	dosage form \Participants	Result	References
Milademetan	Phase I	Orally on 107 patients with liposarcoma	Milademetan ≤260 mg markedly improved tolerability	[35]
Milademetan	phase II	Orally on 10 patients with intimal sarcoma.	Milademetan is an effective treatment option for intimal sarcoma.	[36]
Milademetan	Phase III	Orally 86 patients compared with trabectedin-treated patients	PFS was longer for milademetan, and the difference was not significant	[37]
brigimadlin	phase Ia/Ib	Orally - 25 patients with advanced biliary tract cancer	Birimadlin had a tolerable safety profile and good initial effectiveness.	[38]
AMG 232	Phase I	Orally 31 patients for metastatic melanoma in combinational with dabrafenib (D) and trametinib (T)	AMG 232 plus (D) and (T) exhibited a favorable PK profile.	[39]
MK-8242	Phase I	47 patients with Advanced Solid Tumors	MK-8242 activated the p53 pathway with an acceptable safety and tolerability profile.	[40]
DS-3032b	Phase I	38 patients received oral drugs for the treatment of Hematological Malignancies	DS-3032b's disruption of the MDM2-p53 connection seems to be a viable treatment strategy for hematological malignancies.	[41]
RG7112	Phase I	116 patients received RG7112 treatment (96 in Stratum A and 20 in Stratum B).	Clinical efficacy against CLL/sCLL and relapsed/refractory AML was shown by RG7112.	[42]
ALRN-6924 Sulanemadlin	Phase I	71 patients with Solid Tumors and Lymphomas	In addition to having good tolerance, ALRN-6924 showed anticancer activity.	[43]
CGM097	Phase I	Fifty-one patients	Although delayed-onset	[44]

		received oral treatment with CGM097	thrombocytopenia is sometimes reported, CGM097 seems to have a reasonable tolerability profile.	
dasanutlin	Finish phase II	85 patients with advanced cancer	It was shown that isanutlin exhibited schedule- and dose-dependent p53 activation.	[45]
Combinational treatment				
APG-115 Alrizomadlin	Phase II	84 patients with 6 cohorts: melanoma, NSCLC, ATM mutation, liposarcoma, urothelial, and MPNST.	Coupled with pembrolizumab is well tolerated and, based on early anticancer activity in a variety of tumor types,	[46]
RG7112 With doxorubicin	Phase I	23 pts with advanced soft tissue sarcoma	This combination demonstrates apparent potentiation of p53 activation demonstrated by increased MIC-1 levels greater than additive effects of the single agents.	[47]
SAR405838	Phase I	26 patients with advanced solid tumors plus pimasertib	Preliminary antitumor activity was observed.	[48]
HDM201	Phase 1	37 pts with acute leukemia	The side effects expected and manageable, with no dose-limiting GI toxicities	[49]
PFS=Progression-free survival ; PK = pharmacokinetics; pts= Patients				

Resistance Mechanisms

While short-term responses to MDM2 inhibitors can be promising, the durability of these responses is often limited by both intrinsic and acquired resistance mechanisms. Intrinsic resistance refers to cases where a tumor with wild-type TP53 is still not sensitive to p53 reactivation (or responds only with cell cycle arrest, not cell death). Acquired resistance describes the process by which initially sensitive tumor cells adapt under the selective pressure of therapy, leading to regrowth [50].

Intrinsic Resistance Factors:

1. TP53 Mutations or Defects: The most obvious determinant is p53 status itself – any undetected TP53 mutation in a tumor will confer resistance. Tumors often harbor subclonal TP53 mutations. If an MDM2 inhibitor preferentially kills TP53 wild-type cells, a pre-existing TP53-mutant subclone can expand (a form of intrinsic resistance manifesting as early treatment failure) [51-53]. Therefore, accurate sequencing of TP53 is critical in patient selection; some trials required deep NGS to ensure absence of hidden p53 mutations [54].

2. MDMX (MDM4) Overexpression: MDMX can substitute for MDM2 in

binding and inhibiting p53's transactivation, though MDMX cannot degrade p53. Tumors with high MDMX levels (like some melanomas) may not achieve full p53 pathway activation with an MDM2-only inhibitor. As a result, such tumors show blunted transcriptional response and less apoptosis. This intrinsic resistance can potentially be overcome by inhibitors that also target MDMX (e.g., ALRN-6924) . In clinical samples, baseline MDMX expression has correlated inversely with response to Nutlin analogs [55].

3. Anti-Apoptotic Protein Levels: Several studies indicate that the cell's tendency to undergo apoptosis vs. arrest upon p53 activation depends on the balance of BCL-2 family proteins. If BCL-2 or BCL-x_L_ are highly expressed, p53-induced pro-apoptotic factors (PUMA, NOXA) may not sufficiently trigger apoptosis, resulting in a senescence-like arrest instead [56]. Indeed, some nutlin-resistant cell lines were found to have elevated BCL-x_L_ levels [57]. Intrinsically resistant tumors often require combination with a BCL-2 inhibitor to induce apoptosis, as seen clinically (e.g., the need for venetoclax addition in some AML cases).

4. Concurrent Oncogenic Pathways: Activation of certain pathways can buffer the effects of p53. For example, aberrant RAS/MAPK signaling can promote survival and diminish p53-induced apoptosis (through downstream effectors that upregulate anti-apoptotic genes or inactivate pro-apoptotic ones). This is one reason why KRAS-mutant tumors can be less responsive to MDM2 inhibitors [58,59]. High NF-κB activity (which can occur in some leukemias and solid tumors) is another factor that can promote survival independently of p53 and even reduce p53's transcriptional efficacy【7†L1019-L1027】. As noted earlier, FLT3-ITD in AML conferred relative resistance to idasanutlin, likely via MAPK and STAT5 signals that counteract p53 effects; combining FLT3 inhibitors re-sensitized those cells [59].

5. Microenvironment and Cell Cycle State: Quiescent cancer stem cells or cells in protective niches (like bone marrow stroma for leukemic cells) may be less affected by MDM2 inhibitors. P53 activation primarily hits cycling cells (causing arrest/apoptosis). Slow-cycling tumor cell subpopulations might evade initial impact and later repopulate the tumor once drug pressure is gone. Additionally, the tumor microenvironment can secrete factors (e.g., cytokines like IL-6, IL-11) that upregulate MDM2 or activate parallel pathways, creating a protective milieu [60].

6. P53 Polymorphisms: There is a common SNP in TP53 (Arg72Pro) that influences p53's apoptotic potential. Some evidence suggests the Arg72 variant is more potent in inducing apoptosis, whereas Pro72 skews to arrest. Patients/tumors with the Pro/Pro genotype might intrinsically respond less to p53 activation therapy – though clinical data on this are limited.

Research and benefit possibilities

Research on drugs that are thought to be MDM2 inhibitors is still ongoing because some spirulina plant extracts have been shown to have the potential to cure cancer

and increase p53 [60]. Further study has established a noteworthy correlation between elevated levels of MDM2 and some forms of digestive system cancer, suggesting a potential benefit [5]. Gastrointestinal cancer may be treated with drugs that prevent and cure tumors [61], and other studies have discovered elevated p53 concentrations in the neurological system [62, 63]. As a result, MDM2 may be beneficially employed to treat various tumors, in addition to leukemia, as demonstrated by the research presented in the preceding table.

CONCLUSION

P53 medications and MDM2 antagonists greatly enhance targeted cancer therapy. Although the initial clinical outcomes are promising, further investigation is needed to optimize their application, overcome resistance mechanisms, and integrate them into personalized treatment plans. Future developments in understanding P53-MDM2 interactions are likely to lead to more effective cancer treatments.

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Author contribution

Hany A. Al-Hussain, Draft writing, reference collection, proofreading, and Revision; Mohammed A. Jabarah: Supervision support.

Supplementary data

We collect all Clinical and some preclinical studies with the funding agency and the outcome of the research in the supplementary file.

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