


REVIEW

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Targeting mutant p53: a key player in breast cancer pathogenesis and beyond

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Abstract

The p53 mutation is the most common genetic mutation associated with human neoplasia. TP53 missense mutations, which frequently arise early in breast cancer, are present in over thirty percent of breast tumors. In breast cancer, p53 mutations are linked to a more aggressive course of the disease and worse overall survival rates. TP53 mutations are mostly seen in triple-negative breast cancer, a very diverse kind of the disease. The majority of TP53 mutations originate in the replacement of individual amino acids within the p53 protein's core domain, giving rise to a variety of variations referred to as "mutant p53s." In addition to gaining carcinogenic qualities through gain-of-function pathways, these mutants lose the typical tumor-suppressive features of p53 to variable degrees. The gain-of-function impact of stabilized mutant p53 causes tumor-specific dependency and resistance to therapy. P53 is a prospective target for cancer therapy because of its tumor-suppressive qualities and the numerous alterations that it experiences in tumors. Phenotypic abnormalities in breast cancer, notably poorly differentiated basal-like tumors are frequently linked to high-grade tumors. By comparing data from cell and animal models with clinical outcomes in breast cancer, this study investigates the molecular mechanisms that convert gene alterations into the pathogenic consequences of mutant p53's tumorigenic activity. The study delves into current and novel treatment approaches aimed at targeting p53 mutations, taking into account the similarities and differences in p53 regulatory mechanisms between mutant and wild-type forms, as well.

Keywords Breast cancer, Mutp53, Gain-of-function, HSP90, Ferroptosis, Metabolic reprogramming

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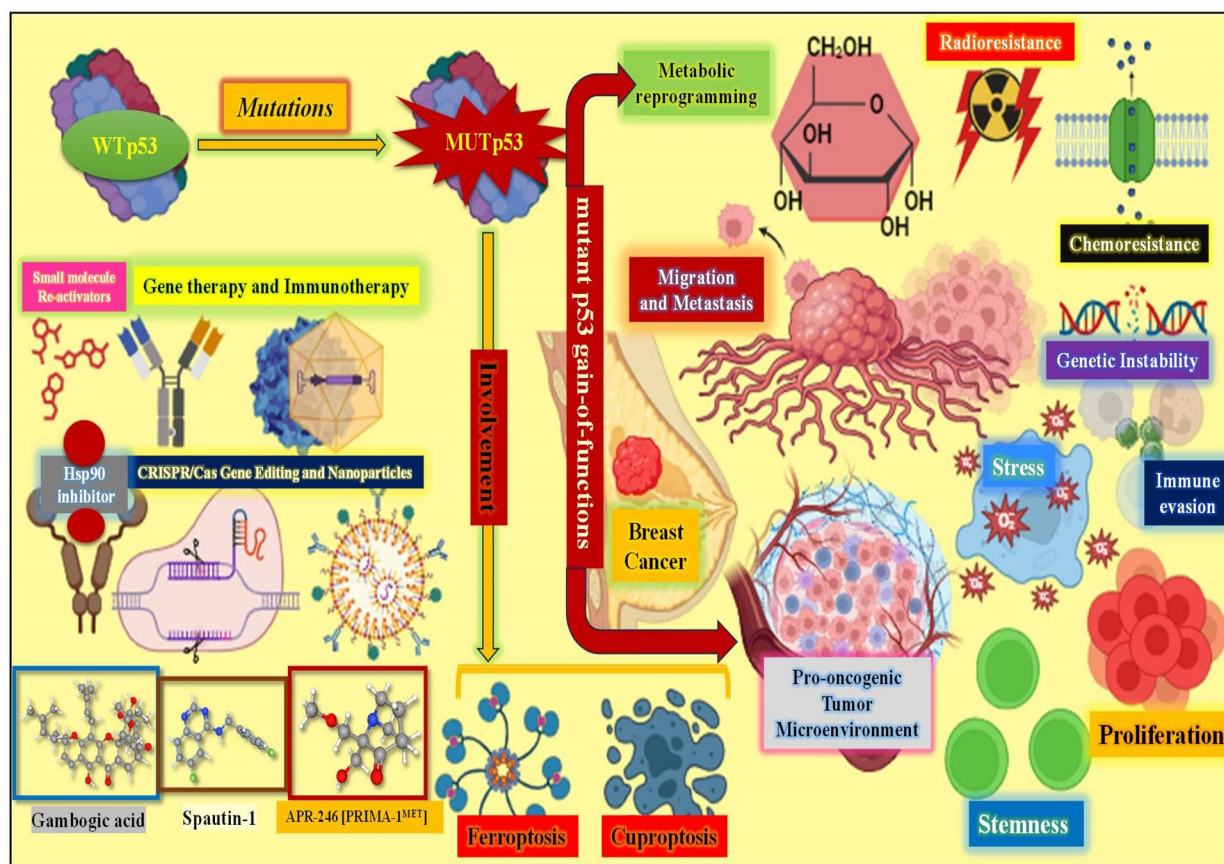
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Graphical Abstract



Introduction

The breast cancer is characterized by a high global incidence and besides affecting the breast tissue, it has the ability to metastasize to lungs and bones [1, 2]. The genome instability represents one of the cancer hallmarks [3, 4]. The frequently altered gene in cancers in humans is the tumor suppressor TP53, in almost 50% of all cancers. The mutation in TP53 has a strong connection with cancer risk [5]. Located at 17p13.1 locus, the human tumor suppressor gene TP53 encodes a 393 amino acid-long protein, the p53 [6]. P53 is a transcription factor that can be activated by internal and external stressors such as UV radiation and oncogenes. These stressors trigger signals that modify the P53 protein post-translationally, freeing it from its interaction with the MDM2 protein and resulting in P53 activation [7]; Subsequently, p53 may reach the nucleus and stimulate the production of several target genes [8] (Fig. 1). Reported findings suggest that P53 has

non-transcriptional activities as well that may contribute to tumor suppression action [9].

P53 is an essential tumor suppressor because it represents an important modulator of DNA repair and DNA replication stress [10–12] to achieve the maintenance in genome stability. Be it the DNA damage, oncogenic signaling or oxidative stress, the p53 responds to all these varied cellular stresses [12, 13]. p53's functional role and expression are hindered by its negative modulator MDM2 protein to be balanced at a low level in case of unstressed, non-transformed cells [14–16]. On the other hand, the interaction of p53-MDM2 is lost and in stressed cells p53 expression upregulation is witnessed [17]. In order to eliminate the damaged cells, upregulated p53 mediates the arrest of cell cycle as well as apoptosis [18]. There is a complex connection of p53 with the survival or death of tumor cells via metabolism modulation [19].

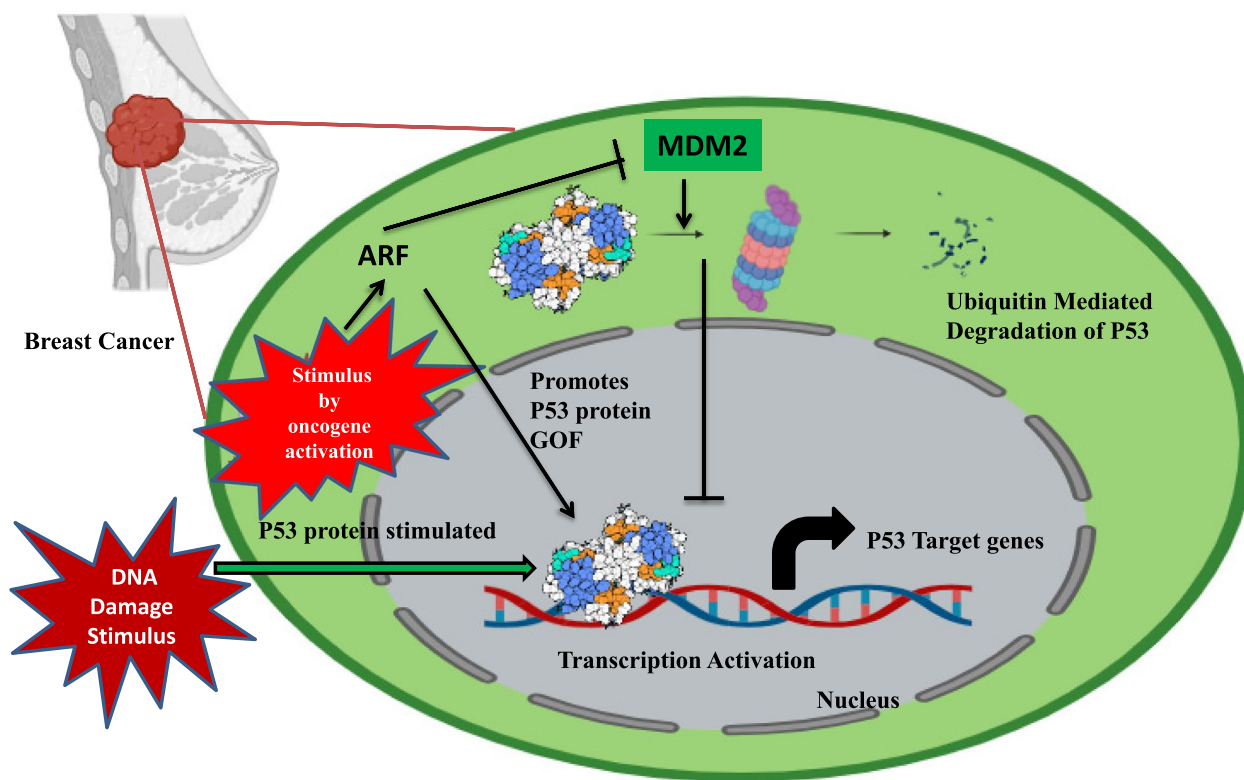


Fig. 1 The regulation of p53 by MDM2: Highlighting the p53-Mdm2 negative feedback loop, wherein p53 transcriptionally activates Mdm2, which in turn aims p53 for degradation

In addition to being a tumor suppressor, the transcription factor p53 is regarded as one of the chief potential targets for curing cancer at molecular level. This is because it modulates a plethora of intracellular metabolic pathways like apoptosis and senescence in addition to DNA damage repair (Fig. 2). Regarded as the “Guardian of the genome”, the p53 protein hampers the cell proliferation carrying genetic anomalies, especially oncogenic mutations. Be it ubiquitination, acetylation, phosphorylation or methylation, the p53 undergoes post-translational modifications in both stressed and unstressed cells. These post-translational modifications help modulate the stability, transcriptional activity as well as cytoplasmic or nuclear localization of p53 protein. And in response to the cellular stress, the Ser or Thr residues undergo phosphorylation and correlates with enhanced p53 activity [20]. The p53’s activation in response to several stresses is significant for normal cells to survive and protect themselves from the process of carcinogenesis. But TP53 is often altered in maximum human cancers ending up in loss of functions (LOFs), important for suppressing tumor and even gain of functions (GOFs) important for growth of tumor [21, 22]. The missense mutation represents the chief type of p53 alteration in the DNA-binding domain

(DBD), affecting a solo amino acid in the p53 protein but possessing huge impact on p53’s role in breast cancer [23]. The growing data suggests that additional processes, such as regulating cancer cell metabolism, ferroptosis, and cell stemness, play a significant part in supporting p53’s anti-cancer function [19, 24].

The ways through which mutant p53 facilitates cancer progression

There are several ways, through which mutant p53 facilitates cancer progression like inducing genetic instability, high proliferation, metabolism regulation, promoting metastasis, Pro-oncogenic Tumor Microenvironment Facilitation as well as Chemo- and Radio-Resistance Induction. The same are discussed here:

1. Genetic instability induction

Mutp53 has the capacity to cause a genomic abnormality by stopping the replication of DNA. Similar to how some mutp53 proteins trigger Cyclin A to encourage the growth of the intra-S phase checkpoint and the DNA replication origin kinase CHK1 to help duplicate aberrant genomic DNAs by stabilising replication forks [25].

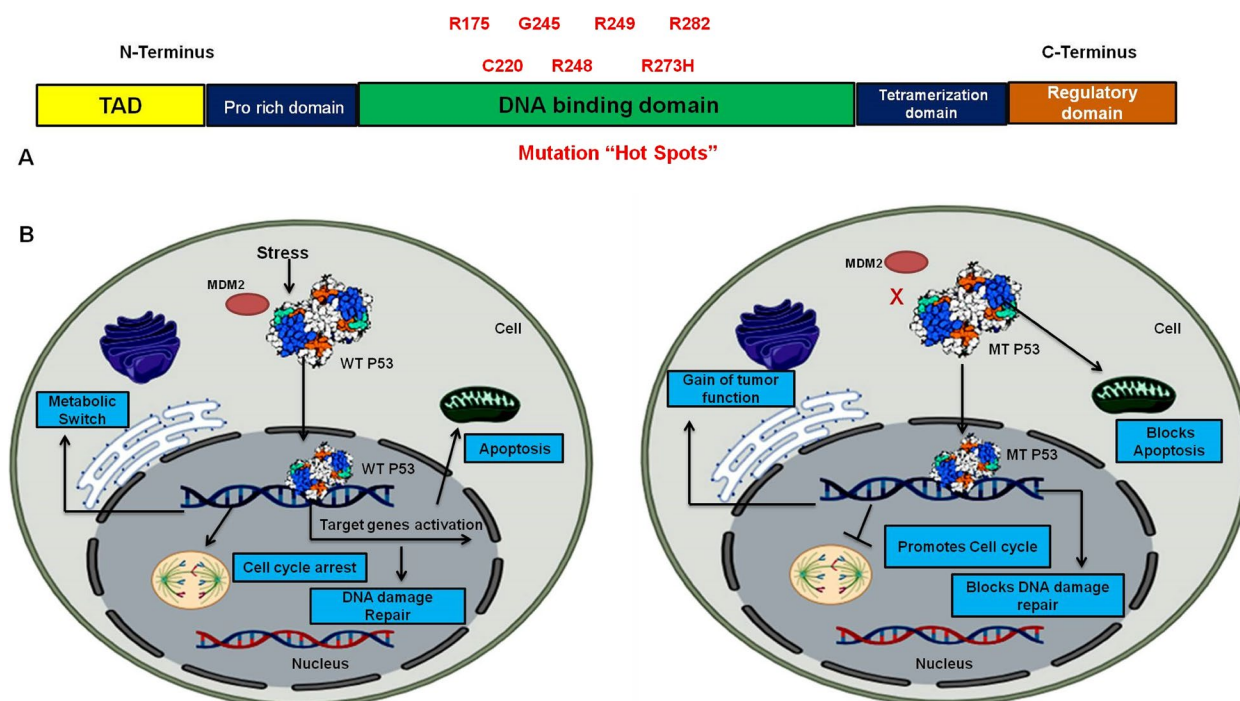


Fig. 2 **A** Representing protein sequence of P53 protein where DNA binding domain is mutated with seven hot spot mutations. **B** Diagrammatic representation of the functional attributes of wild type (WT) P53 and Mutant (MT) P53

2. Heightened proliferation and metastasis
 Numerous studies have demonstrated that the mutp53 increases two of the primary "hallmarks of cancer"—the unbounded ability for replication and the insensitivity to anti-growth signals—during the malignant transformation of a normal cell [4, 26]. To over 90% of cancer-associated deaths are contributed by metastasis, which represents another "hallmark of cancer" [27, 28]. The primary and the most important step in metastasis is represented by EMT (Epithelial-to-mesenchymal transition), and it permits the cells to modify their structure so to further enhance their migration and invasion abilities [29, 30]. Furthermore, it has been observed that mutp53, perhaps in a cell type-dependent manner, stimulates the expression of many important EMT-related transcription factors, including ZEB1, SLUG, and TWIST1, through transcriptional, post-translational, and epigenetic modifications [31–34].
3. Metabolism modulation
 The metabolism of glucose, lipids, and nucleotides is the traditional basis for cell viability; during malignant transformation, all of these systems experience dynamic changes. New research indicates that mutp53 proteins are involved in a number of the previously stated processes [35, 36]. The hyperactivation of oncogenic pathways directly affects the metabolic

processes that promote tumor development. Interestingly, it has been observed that mutp53 amplifies the Warburg effect, a phenomenon marked by increased absorption of glucose and lactate production even in the presence of oxygen [35, 37]. Furthermore, research indicates that wtp53 promotes oxidative phosphorylation and counteracts the Warburg effect [38, 39]. Furthermore, mutp53-related metabolic alterations and GOF raise ROS levels in cancer cells, which encourage the buildup of ROS [40]. Additionally, p53 functions as a significant metabolic modulator that regulates the glycolysis to oxidative phosphorylation transition, amplifies the biogenesis of Fe-S cluster and coordinates the level of copper chelator GSH (glutathione) [41].

4. Chemo- and radio-resistance induction
 The p53 gene mutation is one of the key attempts made by the tumour cells to establish mechanisms to develop radio- and chemotherapy-resistance in order to survive such treatments [42]. A number of radio- and chemotherapy-resistant genes have their expression altered by the mutp53 proteins. Mutp53 proteins cause MDR1 expression to be greatly elevated. MDR1 encodes an energy-dependent efflux pump that helps cancer cells become resistant to a variety of hydrophobic cytotoxic agents [43, 44] (Fig. 3). Mutp53 has also been shown to be associated with angiogenesis

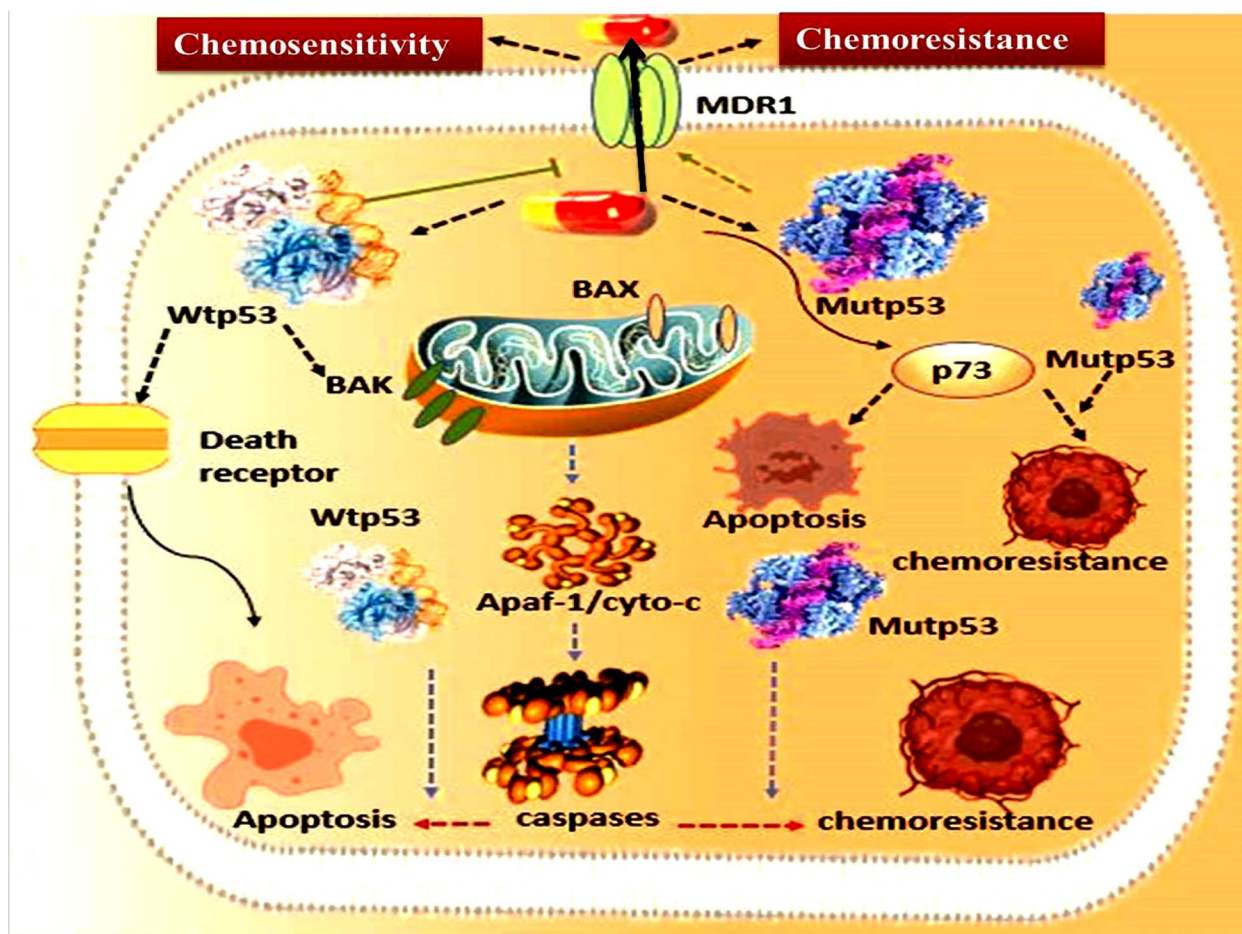


Fig. 3 The involvement of mutp53 towards the development of drug resistance: The mutp53 proteins highly upregulate expression of MDR1, which codes for the efflux pumps that facilitates tumor cell resistance to several hydrophobic cytotoxic agents

and inflammation. Similar to the GOF mutant, p53 has been shown to promote chronic inflammation and has the capacity to modify the TME [45]. Additionally, the mutp53 encourages angiogenesis within the tumor by altering the pro-angiogenic protein VEGF [46].

5. Pro-oncogenic tumor microenvironment facilitation

The TME, which is comprised chiefly of immune cells, ECM, stromal cells, and blood vessels displays a significant role in the process of carcinogenesis and drug resistance abilities [47, 48]; And mutp53 can regulate the TME by prompting the secretion of pro-inflammatory cytokines as well as angiogenesis [49, 50].

Mutational landscape of p53 in breast cancer

As to the most recent version of the International Agency for Research on Cancer (IARC) TP53 database (<http://www-p53.iarc.fr/>), which is a part of COSMIC, missense mutations account for over 70% of TP53 changes linked to breast cancer [51]. This ratio matches the p53 mutational pattern seen in other tumors, as does the range of altered codons (the hotspots). There are some significant variations, though. For example, codon 220 ranks seventh in other malignancies (2%), whereas it is the fourth most common missense mutation in breast cancer (3.6%). Corresponding to this, codon 163 is more prevalent in breast cancer (2%) than in other malignancies (1%) [52]. While the reasons for these differences in mutation patterns are not fully explained, geographic or ethnic factors may control the prevalence of specific mutations, potentially due to environmental mutagens [53, 54]. Furthermore, correlations between BRCA1/2 germline mutations and TP53 mutations have been found, most likely as a result of a bias in defective DNA repair pathways [55, 56]. High

frequency of TP53 mutations have been substantially associated with two particular polymorphisms in sporadic breast cancers: the presence of the highly active G allele of glutathione-S-transferases (GSTs) [57] and the homozygous Arginine at codon 72 of p53 [58].

The variety and tissue specificity of TP53 mutations in human breast tumors are noteworthy. The DNA binding domain (DBD) has a significant enrichment of mutations, the majority of which are missense (around 80%) [59, 60]. Moreover, variations in specific TP53 mutations are seen across different breast cancer types and grades, and these mutations can impact patient survival, particularly those with certain hotspot mutations. The incidence of missense mutations differs among distinct subclasses of tumours within the same organ, for example. Significant discrepancies have been identified in the occurrence of particular TP53 mutations among different breast cancer kinds and grades. For instance, TP53 point mutations are nearly universally present in luminal breast cancers, but p53 truncations are more commonly observed in basal breast tumours [61]. Additionally, the presence of particular hotspot mutations can influence patient survival outcomes as well.

Molecular Insights into p53 mutations and breast cancer

Tumorigenesis frequently involves the inactivation of the p53 tumor suppressor. Usually, a mutation in the p53 gene produces a persistent mutant protein, which accumulates to be recognized as a characteristic of cancerous cells. In addition to losing their ability to control tumor growth, these mutant p53 proteins frequently take on new carcinogenic properties that aid in cell survival. It is noteworthy that mutations in the p53 gene can arise at different phases of the complex process of malignant transformation, meaning that they influence tumor development, aggressiveness, and metastasis in distinct ways [62].

The TP53 gene in human tumors frequently experiences missense mutations, which are alterations in which one nucleotide is substituted for another. This is in contrast to most tumor suppressor genes, such as RB, APC, or BRCA1, which are normally rendered inactive over the course of cancer by deletions or truncating mutations [63].

With only one amino acid changed, a whole protein is generated. The positions of the cancer-associated TP53 mutations within the p53 coding sequence and how they affect the protein's thermodynamic stability differ significantly. Notwithstanding this variation, the great majority of these mutations result in p53 losing its capacity to bind DNA in a way that is particular to a certain sequence and to halt the transcription of classical p53 target genes [64].

The most often changed residues in breast cancer are R248Q and R273H, also known as "contact mutants," which affect how p53 interacts with DNA. On the other hand, alterations such as Y220C and R175H result in "structural mutants" of p53, which under physiological circumstances cause the DNA binding domain (DBD) structure to be deformed. Comprehensive biophysical investigations conducted *in vitro* have demonstrated a gradient in the level of p53 DBD destabilization resulting from certain hotspot TP53 mutations, suggesting that separate proteins may be functionally associated with different mutants [65]. To assess the activity of mutant p53 proteins, transactivation experiments have been used in yeast or human cultured cells. Numerous mutant p53 variants have been demonstrated to display different promoter activation patterns in research focusing on TP53 mutations frequently seen in breast cancer. The Y220C mutant, for instance, is still able to activate the most sensitive wild-type p53 response element, which is derived from the p21 gene's promoter (WAF1), but it is unable to activate other response elements [66].

A growing body of research using a variety of models, including breast cancer cells, suggests that mutant p53 has specific transactivation and DNA-binding abilities. Hotspot p53 mutants directly control a large number of loci devoid of p53-responsive elements [67, 68].

Furthermore, mutant p53 has the ability to directly stimulate the transcription of certain microRNAs and obstruct microRNA processing, which may change the total amount of microRNAs in cells [69, 70]. Blandino et al., for example, found 40 promoters bound *de novo* by the R175H p53 mutant utilising studies employing breast cancer cell lines [71]. However, ten more genes regulated and bound by the R280K p53 mutant were found by another group [72].

Despite the widespread belief that all p53 mutants are equal, there is growing evidence that certain mutants have unique profiles in terms of how much of their activity is lost compared to wild-type p53, how well they are able to suppress wild-type p53, and how they acquire gain-of-function characteristics [73].

Controversies regarding the gain-of-function of P53 mutation

Since all TP53 mutations are believed to impair the activity of wild-type p53, a great deal of study has been done to determine the function of the ensuing mutant p53 proteins due to the high frequency and recurrence of missense TP53 alleles. Research points to three separate, albeit potentially overlapping, processes by which various p53 mutations affect cancer: They exhibit three main characteristics: (i) they partially or completely lose the capacity to perform the tumor-suppressive functions

of wild-type p53; (ii) they operate as dominant negative (DN) inhibitors of these activities; and (iii) they may acquire novel oncogenic roles in addition to p53 inactivation. The gain of function (GOF) theory is the most discussed of these processes, in part because to the variety of biological roles that various mutant p53 proteins are thought to have [74].

It has been discussed for almost thirty years whether mutant p53 proteins may have gain-of-function (GOF) consequences. Levine et al.'s discovery that ectopic expression of certain TP53 mutant alleles could trigger the production of a multidrug resistance gene reporter, but wild-type p53 could not, provided the first clue that p53 mutant proteins could have GOF function. Various TP53 mutants displayed a variety of behaviors, indicating early on that not all TP53 mutations work in the same way [75]. Subsequently, researchers from two different labs found that mice generated with germline missense mutations (R175H and R273H) formed tumor at a rate comparable to that of p53 null mice, but that they had a greater variety of tumor forms and a higher percentage of invasion [76, 77]. These results were seen as undisputed evidence of a gain-of-function (GOF) impact.

Following those first investigations, countless more recent publications have shown further proof that mutant p53 may affect a range of biological processes, including metastasis, stemness, the shift from epithelial to mesenchymal tissue, and more [78–80].

Further evidence supporting the gain-of-function (GOF) acquired by mutant p53 comes from the observation that patients with a TP53 missense mutation (i.e., expressing a mutant p53 protein) in the germline develop cancer substantially earlier than patients with TP53 mutations which culminate in the loss of p53 protein expression [81].

Accordingly, *in vivo* studies have shown that, in comparison to p53 null or p53 wild-type mice, animals expressing mutant p53 have a more aggressive and metastatic tumor profile [82]. Further research, however, suggests that this impact may be tissue specific. Specifically, when comparable p53 mutations were introduced into the lung, no discernible gain-of-function (GOF) activity was observed in comparison to p53 loss [83]. However, a multitude of *in vitro* and xenograft models has validated mutant p53's capacity to induce increased invasion and motility. It has been demonstrated that mutant p53 can improve signalling via receptors including MET, TGF- β , and epidermal growth factor receptor [84, 85]. Nevertheless, the community has not yet agreed upon a coherent paradigm to account for these alarming findings. A plethora of effectors have been found, despite the fact that many putative GOF pathways include mutant p53

working with other transcriptional regulators to modify gene expression [86].

Certain TP53 mutations seem to have different GOF capacities, and depending on the situation, even the same mutant may function through different methods [87] indicating that certain discrepancies may be influenced by a person's genetic history. This intricacy is especially noticeable because most research only looks at one or a small number of mutations. With models exhibiting gain-of-function (GOF) activity and displaying R172H or R270H mutations (corresponding to R175H and R273H mutations in humans), some researchers have started to question how well p53 GOF plays a meaningful role in cancer biology. As a result, they are beginning to adopt extensive methods to tackle this question [76, 77]. However, neither the humanized G245S mutant p53 mice nor the mouse version of the human R249S mutation showed any signs of GOF activity. Nevertheless, R246S might still function as a dominant-negative inhibitor of wild-type p53, enhancing cell survival following radiation exposure [88, 89]. In comparison to p53 null mice, humanized R248Q p53 knock-in mice had an earlier start of tumor growth and a considerably shorter longevity [88], a decrease not observed in other mutant p53 models. Patients with Li-Fraumeni who carry the R248Q mutation typically develop cancer earlier than those who have inherited null mutations or the G245S mutation [88]. These results imply that the function of R248Q p53 differs from that of other p53 mutants under investigation. R248W and R248Q are structural mutations, which is noteworthy, however the humanized R248W p53 knock-in mice does not exhibit a shorter lifetime or an earlier start of illness [90]. Thus, it is a very difficult task to comprehend how each p53 mutation affects the course of the disease and the effectiveness of therapy [91].

Different strategies to target mutant P53 in breast cancer

With the aim to eradicate the p53-mutant cancer cells, the general methods are implemented either by reverting the WT onco-suppressor features of p53 or by aiming on elimination of tumor by altering main components of the immune system [92] (Fig. 4). The strategies employed to address same include:

Restoring p53 activity in cells with wild-type and mutant p53

The promising small molecules, which possess the ability to revert or restore the function of mutant p53 are the PRIMA-1 (p53 reactivation and induction of massive apoptosis) and its methyl analog APR-246 [PRIMA-1^{MET}] and these two small molecules achieve same by associating with the DNA binding domain, enhancing

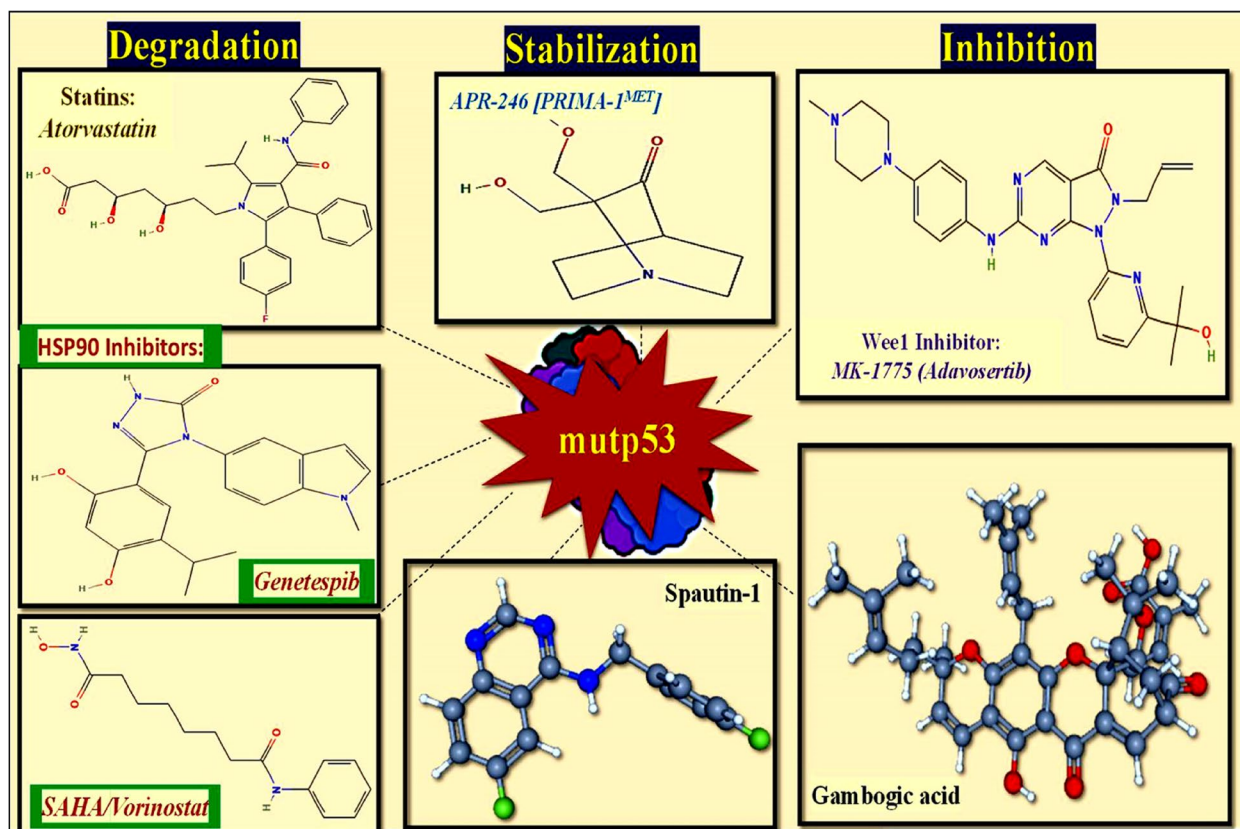


Fig. 4 The various compounds that have been used against mutp53 either by inhibiting; degrading the mutp53 protein or stabilizing the WTP53 protein

proper folding/function [93]. As a consequence, there is an increase in the production of pro-apoptotic genes such as Puma, Noxa, and Bax in cells with mutated p53 (Fig. 4). This also leads to the activation of cell-cycle genes and PARP cleavage, regardless of the mutation status of p53. Similar findings were observed in many trials that included multiple forms of cancer such as Breast, Myeloma, and Thyroid [94].

As an example, tiny molecules like PK7088 and Phi-Kan083, which bind to a particular location in the p53 protein generated by the Y220C mutation, stabilize the structure of this mutant p53. The amount of p53 with a wild-type structure and function is increased by this stabilization [95].

Misfolded p53 may adopt a wild-type shape when metallothioneins, which bind and store intracellular zinc, are lost [96].

Furthermore, it has been demonstrated that incorporating zinc into conformational mutants such as G245C and G245D p53 can partially restore their wild-type shape [97]. As a result, research into the possibility of using zinc to restore wild-type folding has been conducted, and it has been shown that using this strategy

can make cells containing endogenous mutant p53 more sensitive to chemotherapy [98]. Furthermore, it has been discovered that the thiosemicarbazone metal ion chelator NSC31926 restores wild-type activity in a variety of cell lines expressing mutant p53, perhaps by making zinc more bioavailable to the mutant p53 [99].

While p53 activity restoration is an intriguing therapeutic strategy, a number of problems must be fixed in order to optimize these treatments' effectiveness for potential clinical use. A hurdle lies in the many biological consequences (such as cell cycle arrest, apoptosis, senescence, or differentiation) that arise from p53 activation, which seem to be contingent upon the kind of cell and its surroundings. Surprisingly, research on p53 has mostly concentrated on the advantages of restoring its activity. However, there is evidence to suggest that prolonged p53 activation may be just as damaging as its inactivation. Hyperactivation of p53 has been associated with ischaemic damage from strokes or cardiac arrest [100], as well as cell death in degenerative illnesses such as arthritis, multiple sclerosis [101], and neuropathies [102].

Under these circumstances, it was discovered that p53 pathway overexpression caused apoptotic death

that resulted in the loss of important cell types, whereas p53 function suppression provided protection. It is still unknown if newly developed substances meant to increase p53 activity have these harmful consequences in entire animals. But when p53-restoring medications enter clinical trials, it would be wise to investigate any possible side effects these medications could have in non-target tissues.

Inhibiting and degrading mutant forms of p53

To efficiently remove the mutant p53 proteins, increasing its turnover is an alternate strategy for targeting it. The ubiquitin ligase MDM2 has the ability to target both wild-type and mutant p53 for proteasomal destruction in otherwise normal cells. The overexpression of mutant p53 seen in cancer cells is thought to be caused by inhibition of MDM2, which is also responsible for the activation of wild-type p53 in response to stress. In fact, it seems that the stabilization of mutant p53 brought on by stress is required for its gain-of-function (GOF) consequences [103]. Apart from MDM2, it has been demonstrated that CHIP, an additional chaperone-associated E3 ubiquitin ligase, plays a crucial role in the breakdown of mutant p53 [104, 105]. Mutant p53 interacts with the Hsp70 and Hsp90 chaperone complex for stabilization; however, normal functioning of this complex requires interaction with HDAC6 [106]. Heat shock proteins (HSP) separate from mutant p53 when HDAC6 interaction is disrupted, enabling MDM2 and CHIP to degrade p53 [106]. HDAC inhibitors that stop HDAC6 from interacting with Hsp90, like SAHA, have the potential to destabilize mutant p53 [107].

Nevertheless, it has recently been demonstrated that SAHA and the pan-HDAC inhibitor NaB control both the transcription and stability of mutant p53 through the p53 activator HoxA5 [108]. When employing HDAC inhibitors as therapeutic drugs, caution should be used to ascertain the p53 status of tumors since this action was not limited to reducing the expression of mutant p53 but also decreased the expression of wild-type p53 [108]. It has also been demonstrated that small molecule SIRT1 activators cause p53 to become deacetylated and lower the total amount of mutant p53 [109]. Furthermore, in previous investigations, Stathmin—a transcriptional target of both mutant and wild-type p53—boosted the activity of mutant p53 in ovarian tumors by controlling its phosphorylation and stability (by the control of miR-223) [110].

Autophagy has a multifaceted function in cancer, as it may either stimulate or impede the growth of tumors based on the targets of the autophagic process and the stage at which the tumor is evolving [111]. Mutant p53

was specifically encouraged to be degraded by macroautophagy triggered by glucose restriction, but wild-type p53 was stabilized in comparable circumstances [112]. Protease inhibition also aided in the degradation of mutant p53, which also required the presence of functioning autophagy machinery [113].

In addition, a specialized kind of autophagy called chaperone-mediated autophagy may facilitate the degradation of mutant p53 when glucose shortage and confluent growth conditions are present [114]. Interestingly, the degradation of mutant p53 via this specific autophagy route was improved by the suppression of macroautophagy, indicating that glucose-deprived mutant p53 degradation is conditional, in contrast to the findings of Rodriguez et al. (2012) [112, 114]. Moreover, when located in the cytoplasm, both mutant and wild-type p53 may suppress autophagy [115], suggesting a complicated interaction between autophagy and mutant p53.

Consequently, even while it is possible to target mutant p53 for degradation, there are still questions regarding the efficacy of merely eliminating mutant p53 without substituting it with wild-type p53 that is resistant to degradation in order to trigger a therapeutic response. Nevertheless, a number of investigations have demonstrated that increasing apoptosis follows reductions in mutant p53 levels (either by siRNA or spautin treatment), suggesting that these cells may have grown reliant on mutant p53 for survival [116–118]. More research is needed to determine whether lowering mutant p53 levels is adequate for long-term and in vivo treatment.

P53-oriented cancer immunotherapy to inhibit GOF activity

Recently, cancer immunotherapy has attracted a lot of interest because of its exceptional efficacy in treating a variety of malignancies. There is a revived interest in p53-based therapies as well, especially those that improve the immune system's capacity to identify and destroy cancer cells that have p53 deregulation. These tactics are justified by the fact that cancer cells harbouring TP53 missense mutations frequently overexpress p53, which may result in an increased amount of p53-derived peptides being presented on their surface via major histocompatibility complexes (MHCs). But a major problem is that, rather than just increased p53 mRNA expression and translation, the excess of mutant p53 (mutp53) proteins in cancer cells is mostly caused by their poor degradation by the ubiquitin–proteasome system. Since the immunoproteasome uses proteolytic degradation to create MHC-displayed peptides, ineffective mutp53 degradation may actually lessen the presentation of p53-derived peptides. Despite this, studies conducted over the previous

20 years give promise that p53-based immunotherapy may eventually find use in clinical settings [119–121].

It is generally anticipated that the overexpression of missense mutp53 proteins in cancer cells will highlight different peptides from the whole p53 protein. Normal cells produce relatively low quantities of p53, which underlies the immune system's preference for cancer cells, even if some of these peptides may overlap with those from wild-type p53 (wtp53) [122]. The fact that natural self-tolerance does not restrict the T cell response to p53 adds credence to the viability of this strategy. But it's dangerous to assume that healthy cells won't be impacted. Rapidly growing normal progenitor cells may have more TP53 mRNA expression than differentiated cells, which may have little p53 mRNA and thus less p53 protein production [123].

Bispecific antibodies represent a highly promising avenue in cancer immunotherapy [124]. A newly created synthetic single-chain bispecific antibody targets the TCR–CD3 complex and a neo-antigen produced from the p53(R175H) hotspot mutant [125]. Neo-antigens on cancer cell surfaces provide a problem because of their low density, which usually impedes efficient immune clearance. This bispecific antibody, however, gets around this challenge by binding with great affinity to the TCR–CD3 complex on T cells as well as the p53(R175H) peptide–HLA complex on cancer cells. Both in vitro and in vivo, this dual binding efficiently reroutes T lymphocytes to identify and assault cancer cells presenting the mutant peptide, producing remarkably specific cytotoxicity against p53(R175H)-expressing cancer cells [125]. These encouraging results suggest that mutp53-selective immunotherapy strategies—like the use of this bispecific antibody—will become more and more common in the years to come.

Issues and considerations of p53 treatment strategies

Despite ongoing advancements in p53-based cancer therapies, numerous challenges persist, and the quest for effective and selective drugs that can eventually be used in clinical settings continues. One major issue with p53-based treatments, as with all anticancer therapies, is the risk of developing resistance. Although knowledge in this area is still limited, some potential resistance mechanisms are already predictable. For instance, mutations in the TP53 gene could lead to resistance to MDM2 inhibitors, as demonstrated in experiments with prolonged nutlin treatment [126]. Other mechanisms could include activation of anti-apoptotic genes, inherent resistance to apoptosis, and increased levels of MDM4 [127]. The impact of these factors on the effectiveness of p53-based therapies remains uncertain.

Furthermore, p53-based medications are not expected to work well as stand-alone therapies. The goal of research has been to find efficient medication combinations. For example, nutlin 3a plus a BET inhibitor increased p53 activation in a wild-type p53 acute myeloid leukaemia (AML) mouse model [128]. In a similar vein in primary AML cells, combining the BCL-2 inhibitor venetoclax with idasanutlin produced encouraging outcomes, surpassing resistance to either medication alone by reducing the apoptotic threshold [129]. Clinical trials for young adults and children with solid tumors and relapsed or refractory leukaemia have been initiated using this combination (NCT04029688). Furthermore, p53 activation with immunotherapy is a compelling combination that may minimize required medication dosages and, in certain situations, overcome resistance [130]. The fact that mice models are used largely for in vivo testing of p53-based medications presents another difficulty. Although mice are commonly used in drug development, there are notable distinctions between mice and humans, such as variances in the p53, MDM2, and MDM4 protein sequences and variations in the p53 signalling pathway [8]. Cutting-edge methods like organ-on-a-chip and other ex vivo models might help resolve these interspecies variations and speed up the development of p53-targeted medications for clinical use [131, 132].

Our limited comprehension of human biology and the intricate cellular mechanisms induced by medication administration is a significant obstacle. While screening techniques are becoming more sophisticated and producing a greater number of compounds targeted to the p53, it is still difficult to anticipate off-target effects and possible harmful on-target effects. Unacceptable toxicity is frequently only identified in patient trials. More precise testing models and a greater comprehension of these processes are desperately needed.

Discussion

There are very significant roles associated with WT-p53 within breast cancer cells. And the resulting mutations in p53 from varied causes could lead to several types of malignancies. Thus, particular therapeutic ways to aim at p53 anomalies and pathways linked with this protein have drawn significant focus in recent times. Here we have reviewed the recent advances in the understanding of p53 roles and associated anomalies as well as the role it primarily plays as a tumor-suppressor in the body, with special focus on breast cancer. Over half of all human tumors and seventy-five percent of tumors with changed transitions have p53 missense mutations, which are pro-tumorigenic factors. The aberrant stabilization and accumulation of p53 mutations in tumor cells is one of the primary factors contributing to the malignant growth

of tumors. Our lab has recently suggested through an *in silico* approach the two PhiKan-083 analogues, which could possibly address the p53 misfolding after performing proper *in vitro* and *in vivo* experiments and validate the same [133]. We think that these methods have promising clinical application prospects and that significant developments based on them are about to come. New advances in the area of mutp53 cancer treatment will become physically apparent if they pass the pre-clinical and clinical tests, which will be difficult but very rewarding. The resurgence of tumor immunotherapy is also igniting interest in p53-based tactics, primarily those that try to strengthen the immune system's capacity to identify and eliminate cancer cells that have p53 that is dysregulated. Overall, TP53 represents an important therapeutic target for cancer and since more treatments aiming at p53 are being explored, it will be suitable to develop personalized treatment plans as per the patients' p53 mutation status. Future studies will shed more light on the full mechanisms of the complex modulatory interplay between the cancer TP53 status and the pathways that get engaged in the overall pathophysiology of cancers especially Breast Cancer.

Tumor-specific dependency and chemotherapy resistance are induced by the GOF effect, which is brought on by mutant p53 stabilization. When malignant tumors have heterozygous mutant/wild-type p53 alleles, the oncogenic effects of the GOF impact of mutant p53 are effectively mitigated by p53 degradation. Consequently, there is considerable promise for enhancing prognosis, extending cancer patient survival, and advancing cancer therapy through controlled degradation of mutant p53 protein. Due to its inherent tumor suppressor role and the high prevalence of p53 mutations in tumors, p53 is a potentially attractive target for cancer therapy. Cancer-related stress is caused by a relatively small number of factors, including nutritional imbalance, hypoxia, reactive oxygen or nitrogen compounds, DNA damage, and somatic mutations. However, the situation is extremely complex due to the multiple pathways involved and the changing conditions a tumor encounters during its clinical evolution. It will need further research and careful assessment of experimental conditions to determine the best individualized treatment plans for cancer patients. To sum up, p53 is an extremely topical therapeutic target for BC and needs more research at clinical level, particularly for patients with high p53 mutational burden who also have TNBC and HER2-positive subtypes. An important future focus will be the optimization of p53-associated treatment techniques, including logical combinations.

Abbreviations

TNBC Triple-negative breast cancer

CRISPR/Cas9	Clustered regularly interspaced short palindromic repeats/ Caspase 9
ROS	Reactive oxygen species
HDAC	Histone deacetylase
Bid	BH3 interacting-domain death agonist
Bax	Bcl-2 Associated X-protein
Bim	Bcl-2 Interacting Mediator of cell death
CHK1	Checkpoint kinase 1
ZEB1	Zinc finger E-box binding homeobox 1
SNAI2/SLUG	Snail Family Transcriptional Repressor 2
TWIST1	Twist-related protein 1
MDR1	Multidrug resistance mutation 1
TME	Tumour microenvironment
ECM	Extracellular matrix
PARP	Poly (ADP-ribose) polymerases
STAT	Signal Transducer and Activator of Transcription
PRIMA-1	P53 reactivation and induction of massive apoptosis-1
DSF	Disulfiram
MEFs	Mouse Embryonic Fibroblasts
CSCs	Cancer Stem Cells
VEGF	Vascular endothelial growth factor
ABC Transporters	ATP binding cassette
SAHA	Suberoylanilide Hydroxamic Acid
DM2	Type II diabetes mellitus
CHIP	Carboxyl terminus of Hsp70-interacting Protein

Acknowledgements

The author Burhan Ul Haq would like to thank the Department of Science and Technology, Government of India for supporting this work under INSPIRE Fellowship Program [Research Student- IF220332]. The authors would also like to thank BioRender for Figures and PubChem for structures of the compounds used in this Review.

Authors' contributions

M.A.M designed and supervised the work; B.U.H, H.Q and S.S contributed equally to the work. M.A.M and B.U.H prepared Graphical Abstract and Figures 1 and 4; H.Q, S.S and N.J prepared Figures 2 and 3. All the authors edited and reviewed the manuscript.

Funding

This work has been sponsored by the Science Engineering and Research Board (SERB-DST) Govt of India vide grant No. SERB/CRG/2023/008460 sanctioned to Dr Manzoor Ahmad Mir.

Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All contributing authors agree to the publication of this article.

Competing interests

The authors declare no competing interests.

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Received: 14 March 2024 Accepted: 30 September 2024

Published online: 10 October 2024

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