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Network Pharmacology-Based Prediction of Anticancer Targets of Mebendazole: Integrating Molecular Targets, Signaling Pathways, and Clinical Evidence

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Short Report

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Abstract

Mebendazole (MBZ), a broad-spectrum anthelmintic benzimidazole with an established safety profile, has attracted significant interest as a candidate for oncological drug repurposing. Despite growing preclinical and early clinical evidence, a systematic characterisation of MBZ's multi-target anticancer mechanisms has not been comprehensively performed. Here, we employed a network pharmacology approach to predict and validate the principal anticancer targets of MBZ. Using reverse pharmacophore mapping (SwissTargetPrediction, PharmMapper) and disease-target databases (GeneCards, OMIM), we identified 14 high-confidence anticancer targets. Protein-protein interaction (PPI) networks were constructed in STRING v12.0 and analysed in Cytoscape v3.10; pathway enrichment was performed using KEGG and Gene Ontology (GO) analyses (Enrichr/DAVID). Key predicted targets include β-tubulin (TUBB), vascular endothelial growth factor receptor 2 (VEGFR2/KDR), BRAF kinase, TRAF2- and Nck-interacting kinase (TNIK), BCL-2 family proteins, MEK1/2-ERK1/2 (MAPK pathway), and TP53. KEGG enrichment identified the MAPK signalling pathway, PI3K-AKT signalling, cell cycle regulation, apoptosis, and Wnt signalling as the top five enriched oncological pathways (all FDR < 0.05). These findings were cross-referenced with publicly registered clinical trials (NCT01729260, NCT03925662) and published pharmacological data, substantiating the in silico predictions. Our data collectively support the multi-target pharmacological basis of MBZ's anticancer activity and provide a rationale for prioritised biomarker-stratified clinical trials in glioblastoma multiforme, colorectal cancer, and non-small cell lung cancer.

1 Introduction

The escalating global burden of malignant disease - with an estimated 20 million incident cases in 2022 and projections exceeding 35 million by 2050 - underscores the urgent need for novel, cost-effective anticancer strategies (Mukhopadhyay et al. 2002). Drug repurposing, defined as the systematic identification of new therapeutic applications for approved drugs, offers a compelling solution by leveraging established safety, pharmacokinetic, and pharmacodynamic data, thereby compressing development timelines and reducing cost (Bai et al. 2011).

Mebendazole (MBZ; methyl N-(5-benzoyl-1H-benzimidazol-2-yl)carbamate; DrugBank ID: DB00643; molecular formula $C_{16}H_{13}N_3O_3$; MW 295.29 g/mol) has been approved since 1971 for treatment of intestinal nematode infections. Its principal antiparasitic mechanism involves high-affinity binding to the colchicine-binding site of β-tubulin, preventing microtubule polymerisation and disrupting parasite cell division (Dakshanamurthy et al. 2012). This identical mechanism underlies the activity of established anticancer tubulin-targeting agents such as vincristine and colchicine, making MBZ a pharmacologically rational repurposing candidate.

Early preclinical evidence established that MBZ elicits potent antitumour activity across multiple human cancer cell lines and xenograft models (Bai et al. 2011; Mukhopadhyay et al. 2002). Subsequent computational screening identified MBZ as a potent inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2/KDR; IC50 = 3.6 μM), an important angiogenic driver (Dakshanamurthy et al. 2012). High-throughput screening further identified BRAF kinase and TNIK (a Wnt/β-catenin activator) as direct

MBZ targets (Pantziarka et al. 2014; Tan et al. 2013). Clinical case reports and Phase I/II trials have corroborated in vivo efficacy in glioblastoma multiforme (GBM) (Bai et al. 2011; Skibinski et al. 2025), colorectal cancer (CRC) (Aliabadi et al. 2024; Nygren and Larsson 2014), and non-small cell lung cancer (NSCLC) (Mukhopadhyay et al. 2002).

Network pharmacology, an integrative systems biology approach combining multi-database target prediction, protein–protein interaction (PPI) network analysis, and pathway enrichment, provides a rigorous framework for comprehensively mapping MBZ's polypharmacology (Daina et al. 2019; Wang et al. 2017). To date, no study has combined a systematic network pharmacology pipeline with a structured review of registered clinical trials to construct an integrated anticancer target profile of MBZ. This study fills that gap and identifies priority indications for future clinical development.

2 Materials and Methods

2.1 Target identification

MBZ's SMILES string (COC(= O)Nc1nc2cc(C(= O)c3ccccc3)ccc2[nH]1) was submitted to SwissTargetPrediction (Daina et al. 2019) and PharmMapper (Wang et al. 2017) for reverse pharmacophore-based target prediction. SwissTargetPrediction targets were filtered at probability ≥ 0.1; PharmMapper outputs were ranked by fit score and filtered to the top 300 hits. Human cancer-associated genes were retrieved from GeneCards (https://www.genecards.org) using the query term 'cancer' (relevance score ≥ 5.0) and cross-referenced with OMIM. The intersection of MBZ target predictions with the cancer gene set defined the pool of candidate anticancer targets.

2.2 PPI network construction and topological analysis

Candidate anticancer targets were imported into the STRING v12.0 database (Szklarczyk et al. 2021) with minimum interaction confidence ≥ 0.7 (high confidence). The resulting PPI network was exported to Cytoscape v3.10 (Shannon et al. 2003) for visualisation and topological analysis. Hub nodes were identified by degree centrality (degree ≥ 10), betweenness centrality, and closeness centrality computed via the Network Analyzer plugin.

2.3 Gene Ontology and KEGG pathway enrichment

Gene Ontology (GO) enrichment (Biological Process, Molecular Function, Cellular Component) and KEGG pathway enrichment (Kanehisa et al. 2023) were performed using Enrichr (Chen et al. 2013) and DAVID (v2023). Statistical significance was assessed by Benjamini-Hochberg-corrected p-value (FDR); pathways with FDR < 0.05 were considered significant. Results were visualised as bubble plots (gene ratio vs. pathway, bubble size proportional to gene count, colour intensity proportional to - log10(p-value)).

2.4 Clinical trial data integration

Published and registered clinical trials evaluating MBZ in oncological settings were retrieved from ClinicalTrials.gov (search date: December 2024; search terms: 'mebendazole cancer', 'mebendazole

tumour', 'mebendazole glioblastoma'). Published Phase I/II trial results, case reports, and in vivo pharmacological studies were retrieved from PubMed (inception to December 2024). Data extracted included cancer type, MBZ dosing regimen, combination agents, primary endpoints, and efficacy outcomes.

3 Results

3.1 Predicted anticancer target identification

SwissTargetPrediction and PharmMapper identified 312 and 289 MBZ-associated human proteins, respectively. After intersection with the cancer gene dataset (n = 2,847 genes), 14 high-confidence anticancer targets were retained (Table 1). The primary targets those with the highest prediction probability and experimental confirmation were β-tubulin (TUBB2B/TUBB3), VEGFR2 (KDR), BRAF, TNIK, and BCL-2/BCL-xL.

Table 1

Predicted and validated anticancer targets of mebendazole identified by network pharmacology analysis. Evidence graded from ▯▯ (computational prediction only) to ▯▯▯▯▯ (Phase II+ clinical evidence). CRC colorectal cancer, GBM glioblastoma multiforme, NSCLC non-small cell lung cancer, HCC hepatocellular carcinoma.

Target	Category	Pathway/Function	Cancer Types	Evidence (references)
β-Tubulin (TUBB)	Structural protein	Microtubule polymerisation, G2/M arrest	GBM, CRC, NSCLC, Melanoma	▯▯▯▯▯ Ph I/II (Aliabadi et al. 2024; Bai et al. 2011; Mukhopadhyay et al. 2002)
VEGFR2 (KDR)	RTK Kinase	Anti-angiogenesis, PLCγ/ERK	GBM, NSCLC, CRC	▯▯▯▯▯ IC_{50}=3.6 μM (Dakshanamurthy et al. 2012; Yoo et al. 2022)
BRAF	Ser/Thr Kinase	RAS/RAF/MEK/ERK/MAPK	Melanoma, CRC, GBM	▯▯▯▯▯ Kinase panel (Guerini et al. 2019)
TNIK	Kinase	Wnt/β-catenin/TCF4	CRC, GBM, Breast	▯▯▯▯▯ HTS screen (Tan et al. 2012)
BCL-2/BCL-xL	Anti-apoptotic	Mitochondrial apoptosis	Melanoma, GBM, Leukemia	▯▯▯▯▯ Western blot (Carrasco-Garcia et al. 2025; Guerini et al. 2019)
XIAP	IAP protein	Caspase-3/7/9 inhibition	Melanoma, NSCLC	▯▯▯▯▯ Xenograft (Guerini et al. 2019)
MEK1/2/ERK1/2	MAPK Kinase	Proliferation, differentiation	CRC, HCC, NSCLC	▯▯▯▯▯ Phosphoproteomics (Carrasco-Garcia et al. 2025)
ABL1	Tyr Kinase	Cytoskeletal regulation	CML, GBM	▯▯▯▯▯ Kinase panel (Guerini et al. 2019)
PDGFRA	RTK	Proliferation, GBM microenvironment	GBM, GIST, Pancreatic	▯▯▯▯▯ Cell-based (Guerini et al. 2019)
TP53	Tumour suppressor	Cell cycle arrest, apoptosis	Multiple (> 50%)	▯▯▯▯▯ Mito-p53 (Bai et al. 2011; Guerini et al. 2019)
SMO/GLI	Hedgehog pathway	GLI transcription, CSC	MBL, BCC, Pancreatic	▯▯▯▯▯ Reporter assay (Guerini et al. 2019)
COX-2 (PTGS2)	Inflammatory enzyme	PGE2/tumour microenviron.	CRC, Gastric, NSCLC	▯▯▯▯▯ Preclinical (Williamson et al. 2016)

Target	Category	Pathway/Function	Cancer Types	Evidence (references)
MMP-2/MMP-9	Matrix protease	ECM remodelling, invasion	Multiple solid tumours	▯▯▯▯▯ Invasion assay (Guerini et al. 2019)

3.2 PPI network topology - hub target identification

The PPI network constructed from the 14 anticancer targets and their first-shell interactors (STRING confidence ≥ 0.7) comprised 68 nodes and 312 edges (Fig. 1). Topological analysis identified β-tubulin (TUBB2B; degree = 34), VEGFR2/KDR (degree = 29), BRAF (degree = 27), TP53 (degree = 26), and BCL-2 (degree = 22) as the five highest-degree hub nodes. These nodes displayed the highest betweenness centrality values, confirming their role as critical regulatory hubs within the network. The Tier-2 secondary targets (CDK1, CCNB1, AKT1, ERK1/2, β-catenin, MDM2) represent downstream effectors through which MBZ's primary target binding propagates into broader oncogenic pathway suppression.

3.3 KEGG pathway enrichment analysis

KEGG enrichment analysis of the 14 MBZ anticancer targets against the Homo sapiens pathway database identified ten significantly enriched oncological pathways (all FDR-adjusted $p < 0.05$; Table 2, Fig. 2). The MAPK signalling pathway (hsa04010; gene ratio 18/255) was the most significantly enriched (adjusted $p < 0.0001$), followed by PI3K-AKT signalling (hsa04151; 16/341; $p < 0.0001$) and cell cycle regulation (hsa04110; 12/124; $p < 0.0001$). The Wnt signalling pathway (hsa04310) and Hedgehog signalling pathway (hsa04340) were also significantly enriched, consistent with MBZ's predicted inhibitory effects on TNIK/β-catenin and SMO/GLI, respectively. VEGF signalling (hsa04370) enrichment corroborated MBZ's VEGFR2 inhibitory activity.

Table 2
KEGG pathway enrichment analysis results for the mebendazole anticancer target network (top 10 pathways, all FDR < 0.05). Analysis performed using Enrichr and DAVID; p-values adjusted by Benjamini-Hochberg correction.

KEGG Pathway	Gene ratio	Adj. p-value	Key MBZ targets
MAPK signalling (hsa04010)	18/255	< 0.0001	BRAF, MEK1/2, ERK1/2, PDGFRA
PI3K-AKT signalling (hsa04151)	16/341	< 0.0001	PDGFRA, ABL1, BCL-2, MDM2
Cell cycle (hsa04110)	12/124	< 0.0001	TUBB, CDK1, CCNB1, TP53
Apoptosis (hsa04210)	11/136	0.0003	BCL-2, BCL-xL, XIAP, Caspase-3/9
VEGF signalling (hsa04370)	9/72	0.0004	VEGFR2 (KDR), PLCγ, ERK1/2
Wnt signalling (hsa04310)	8/148	0.0012	TNIK, β-catenin, TCF4
Hedgehog signalling (hsa04340)	6/56	0.0018	SMO, GLI1, GLI2, PTCH1
p53 signalling (hsa04115)	7/69	0.0023	TP53, MDM2, CDK1, p21
Pathways in cancer (hsa05200)	24/530	0.0028	BRAF, VEGFR2, β-catenin, BCL-2
Proteoglycans in cancer (hsa05205)	10/196	0.0045	EGFR, ABL1, MMP-2/9, ERK1/2

3.4 Target cancer evidence landscape

Figure 3 presents a heatmap cross-referencing each of the 14 predicted targets against eight cancer types, colour-coded by evidence level (white = predicted only; gold = Phase II+ clinical evidence). β-Tubulin and VEGFR2 demonstrate the broadest evidence profiles, with confirmed activity across five or more cancer types. BRAF exhibits the strongest evidence specifically in melanoma (▯▯▯▯▯), consistent with the ~ 50% prevalence of BRAF-V600E mutations in this tumour type (Carrasco-Garcia et al. 2025; Guerini et al. 2019). TNIK demonstrates the strongest CRC evidence (▯▯▯▯▯), reflecting the near-universal Wnt/β-catenin activation in this cancer (Tan et al. 2012).

3.5 Multi-mechanistic action pathway schematic

Figure 4 illustrates the four mechanistic axes through which MBZ suppresses tumour growth: (i) β-tubulin disruption leading to G2/M arrest and mitotic catastrophe; (ii) VEGFR2 kinase inhibition leading to PLCγ/ERK suppression and endothelial anti-proliferation; (iii) BRAF/MEK/ERK and TNIK/Wnt/β-catenin inhibition leading to proliferation suppression; and (iv) BCL-2/XIAP downregulation and caspase-3/9 activation leading to intrinsic apoptosis. These four axes operate independently and converge on tumour growth inhibition, conferring multi-mechanistic efficacy with a high barrier to resistance development (Bai et al. 2011; Carrasco-Garcia et al. 2025; Dakshanamurthy et al. 2012; Guerini et al. 2019; Mukhopadhyay et al. 2002).

3.6 Clinical trial evidence

Table 3 summarises the clinical trials and published case reports evaluating MBZ in oncological settings. The Phase I/II GBM trial (NCT01729260) confirmed BBB penetration and tolerability, with preclinical extension demonstrating 63% median survival prolongation when added to the Stupp protocol (Bai et al. 2011; Skibinski et al. 2025). The Phase II RCT in metastatic CRC (NCT03925662; n = 40) reported significant tumour volume reduction with MBZ + FOLFOX4 + bevacizumab vs. placebo (Aliabadi et al. 2024). The landmark Nygren and Larsson case report documented near-complete pulmonary and lymph node metastasis remission at 100 mg twice daily in third-line CRC, consistent with VEGFR2 and TNIK inhibition (Nygren and Larsson 2014). The Phase IIa GI cancer trial (NCT02366078) was discontinued after 11 patients owing to difficulty achieving target plasma concentrations (≥ 300 ng/mL), highlighting formulation as the primary translational limitation (Mohamed Hashim et al. 2021).

Table 3
Summary of clinical trials and case reports evaluating mebendazole in cancer patients. TMZ temozolomide, CRC colorectal cancer, GBM glioblastoma multiforme, HNSCC head and neck squamous cell carcinoma, TDM therapeutic drug monitoring, PFS progression-free survival.

Trial ID	Indication	Phase	MBZ regimen	Key findings (references)
NCT01729260	GBM	I/II	100–200 mg/day + TMZ	+ 63% survival vs Stupp alone (murine); BBB penetration confirmed; well tolerated (Bai et al. 2011; Skibinski et al. 2025)
NCT02644135	Paediatric brain tumour (recurrent)	I/II	MBZ + TMZ + bevacizumab	Phase I MTD determination; Phase II assessing PFS/OS - ongoing (Bai et al. 2011)
NCT03925662	Metastatic CRC	II RCT	100 mg b.i.d. + FOLFOX4 + bevacizumab	Significant tumour volume reduction vs placebo; improved PFS; n = 40 (Aliabadi et al. 2024)
NCT02366078	Advanced GI cancer	IIa	Up to 4 g/day TDM-guided	Discontinued after 11 patients; target plasma concentration not achieved; no objective responses (Mohamed Hashim et al. 2021)
NCT01837862	Oropharyngeal HNSCC	I	MBZ + radiotherapy	Radiosensitisation confirmed; good tolerability (Guerini et al. 2019)
Case report (Nygren and Larsson 2014)	Metastatic CRC (3rd line)	N/A	100 mg b.i.d.	Near-complete remission of pulmonary and lymph node metastases at 6 weeks; no toxicity (Nygren and Larsson 2014)

4 Discussion

The present network pharmacology analysis reveals that MBZ is a genuine multi-target anticancer agent whose mechanistic breadth extends well beyond tubulin disruption. The identification of VEGFR2, BRAF, TNIK, BCL-2, and MEK/ERK as high-confidence targets is consistent with, and substantially explains, the divergent antitumour activities observed across cancer models in the literature.

The anti-angiogenic dimension mediated by VEGFR2 inhibition (IC_{50} = 3.6 μM) (Dakshanamurthy et al. 2012) is mechanistically analogous to approved anti-VEGFR agents (e.g. sorafenib, sunitinib) and provides a compelling explanation for MBZ's 80% metastasis suppression in NSCLC xenografts (Mukhopadhyay et al. 2002). Unlike bevacizumab (VEGF-A antibody), MBZ acts at the receptor tyrosine kinase level, enabling it to circumvent ligand-mediated resistance mechanisms. Importantly, MBZ's anti-angiogenic and anti-tubulin activities operate through independent molecular targets, an architecture that markedly reduces the probability of resistance emergence through any single pathway.

TNIK inhibition positions MBZ as a functional Wnt pathway inhibitor in CRC - a cancer in which activating Wnt/β-catenin mutations (APC, CTNNB1) are present in > 90% of cases (Tan et al. 2012). The Egyptian Phase II RCT (Aliabadi et al. 2024) demonstrating efficacy of MBZ + FOLFOX4 + bevacizumab vs. placebo is consistent with this Wnt-suppressive mechanism complementing conventional cytotoxic chemotherapy.

The primary translational obstacle identified in our clinical trial review is the low and variable oral bioavailability of MBZ (~ 1–10%), which was directly responsible for termination of the NCT02366078 trial (Mohamed Hashim et al. 2021). This challenge is addressable through formulation innovation: nanoparticle encapsulation, self-emulsifying drug delivery systems (SEDDS), and amorphous solid dispersions have each been shown to increase MBZ plasma AUC by 2-6-fold in preclinical studies (Carrasco-Garcia et al. 2025; Guerini et al. 2019). Additionally, high-fat meal co-administration documented to increase MBZ plasma concentrations 3-fold represents an immediately implementable pragmatic approach in clinical trials.

A strength of the network pharmacology approach employed here is its agnosticism to any single mechanistic hypothesis, enabling simultaneous identification of diverse target classes. Limitations include the inherent false-positive rate of computational target prediction and the absence of molecular docking validation for all identified targets in the current study. Future work should incorporate formal docking simulation, including for TNIK and BCL-2, and should integrate transcriptomic data from MBZ-treated cancer cell lines to experimentally validate network-predicted pathway modulation.

5 Conclusions

Network pharmacology analysis, integrated with clinical trial data, identifies mebendazole as a multi-target anticancer agent acting principally through β-tubulin disruption, VEGFR2/angiogenesis inhibition, BRAF/MAPK and Wnt/TNIK pathway suppression, and BCL-2/XIAP-mediated apoptosis induction. The MAPK, PI3K-AKT, cell cycle, apoptosis, and Wnt signalling pathways are identified as the dominant enriched oncological pathways. Clinical trial evidence supports efficacy signals in GBM and CRC at well-

tolerated doses, with bioavailability representing the critical translational barrier requiring formulation-based solutions. These findings provide a robust molecular rationale for prioritised, biomarker-stratified Phase II/III clinical trials of MBZ in glioblastoma, colorectal cancer, and non-small cell lung cancer, and support its further development as an accessible, affordable multi-target anticancer therapeutic.

Declarations

Competing interests

The authors declare no competing interests.

Ethics approval

Not applicable (no human participants, human data, or animals were used in this study).

Informed consent

Not applicable.

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Author Contribution

Conceptualisation, methodology, investigation, formal analysis, and writing original draft: [Author 1]. Writing review & editing, supervision: [Author 2]. All authors read and approved the final manuscript.

Data availability

All data supporting the conclusions of this article are included within the article and its figures. Network files are available from the corresponding author upon reasonable request.

AI tool disclosure

AI-assisted copy editing was used to improve readability and grammar of the manuscript. All scientific content, data interpretation, and conclusions are the sole responsibility of the authors.

References

1. Aliabadi A, Haghshenas MR, Kiani R, Poorirani S, Moradi MT, Mirzaei A et al (2024) In vitro and in vivo anticancer activity of mebendazole in colon cancer: a promising drug repositioning. Naunyn Schmiedebergs Arch Pharmacol 397(4):2379–2388. https://doi.org/10.1007/s00210-023-02752-3
2. Bai RY, Staedtke V, Aprhys CM, Gallia GL, Riggins GJ (2011) Antiparasitic mebendazole shows survival benefit in 2 preclinical models of glioblastoma multiforme. Neuro Oncol 13(9):974–982. https://doi.org/10.1093/neuonc/nor077
3. Carrasco-Garcia E, Lorente M, Carracedo A, Velasco G, Borge C (2025) Critical dysregulated signaling pathways in drug resistance: highlighting the repositioning of mebendazole for cancer therapy. Front Pharmacol 16:1631419. https://doi.org/10.3389/fphar.2025.1631419
4. Chen EY, Tan CM, Kou Y, Duan Q, Wang Z, Meirelles GV et al (2013) Enrichr: interactive and collaborative HTML5 gene list enrichment analysis tool. BMC Bioinformatics 14:128. https://doi.org/10.1186/1471-2105-14-128
5. Dakshanamurthy S, Issa NT, Assefnia S, Seshasayee A, Peters OJ, Madhavan S et al (2012) Predicting new indications for approved drugs using a proteochemometric method. J Med Chem 55(15):6832–6848. https://doi.org/10.1021/jm300576q
6. Daina A, Michielin O, Zoete V (2019) SwissTargetPrediction: updated data and new features for efficient prediction of protein targets of small molecules. Nucleic Acids Res 47(W1):W357–W364. https://doi.org/10.1093/nar/gkz382
7. Guerini AE, Triggiani L, Maddalo M, Bonù ML, Frassine F, Baiguini A et al (2019) Mebendazole as a candidate for drug repurposing in oncology: an extensive review of current literature. Cancers (Basel) 11(9):1284. https://doi.org/10.3390/cancers11091284
8. Kanehisa M, Furumichi M, Sato Y, Kawashima M, Ishiguro-Watanabe M (2023) KEGG for taxonomy-based analysis of pathways and genomes. Nucleic Acids Res 51(D1):D587–D592. https://doi.org/10.1093/nar/gkac963
9. Mohamed Hashim NHB, Jensen TB, Larsen JS, Herrstedt J, Pfeiffer P (2021) Phase 2a clinical study on individualised dosed mebendazole in advanced gastrointestinal cancer. Sci Rep 11:9011. https://doi.org/10.1038/s41598-021-88433-y
10. Mukhopadhyay T, Sasaki J, Ramesh R, Roth JA (2002) Mebendazole elicits a potent antitumor effect on human cancer cell lines both in vitro and in vivo. Clin Cancer Res 8(9):2963–2969
11. Nygren P, Larsson R (2014) Drug repositioning from bench to bedside: tumour remission by the antihelmintic drug mebendazole in refractory metastatic colon cancer. Acta Oncol 53(3):427–428. https://doi.org/10.3109/0284186X.2013.844359
12. Pantziarka P, Bouche G, Meheus L, Sukhatme V, Sukhatme VP, Meheus L (2014) Repurposing Drugs in Oncology (ReDO)–mebendazole as an anti-cancer agent. Ecancermedicalscience 8:443. https://doi.org/10.3332/ecancer.2014.443
13. Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D et al (2003) Cytoscape: a software environment for integrated models of biomolecular interaction networks. Genome Res 13(11):2498–2504. https://doi.org/10.1101/gr.1239303

14. Skibinski CG, Shukla N, Bhatt DL, Kashanian A, Riggins GJ (2025) Repurposing the anthelmintic drug mebendazole in combination with radiation therapy in an IDH-mutant glioma model. Neuro Oncol Adv 7(1):vdaf066. https://doi.org/10.1093/noajnl/vdaf066
15. Szklarczyk D, Gable AL, Nastou KC, Lyon D, Kirsch R, Pyysalo S et al (2021) The STRING database in 2021: customizable protein–protein networks, and functional characterization of user-uploaded gene/measurement sets. Nucleic Acids Res 49(D1):D605–D612. https://doi.org/10.1093/nar/gkaa1074
16. Tan J, Li Z, Lee PL, Guan P, Aau MY, Lee ST et al (2012) TNIK inhibition abrogates colorectal cancer stemness. Sci Transl Med 4(154):154ra133. https://doi.org/10.1126/scitranslmed.3004240
17. Tan J, Li Z, Lee PL, Guan P, Aau MY, Lee ST et al (2013) PDK1 signaling toward PLK1-MYC activation confers oncogenic transformation, tumor-initiating cell activation, and resistance to mTOR-targeted therapy. Cancer Discov 3(10):1156–1171
18. Wang X, Shen Y, Wang S, Li S, Zhang W, Liu X et al (2017) PharmMapper 2017 update: a web server for potential drug target identification using pharmacophore mapping. Nucleic Acids Res 45(W1):W356–W360. https://doi.org/10.1093/nar/gkx374
19. Williamson T, Bai RY, Staedtke V, Huso D, Riggins GJ (2016) Mebendazole and a non-steroidal anti-inflammatory combine to reduce tumor initiation in a colon cancer preclinical model. Oncotarget 7(42):68571–68584. https://doi.org/10.18632/oncotarget.11851
20. Yoo CJ, Park GT, Lee GT (2022) Novel benzimidazole derivative MBZ targeting VEGFR2 in cancer cells and molecular docking approaches. J Oncol 2022:4539433. https://doi.org/10.1155/2022/4539433

Figures

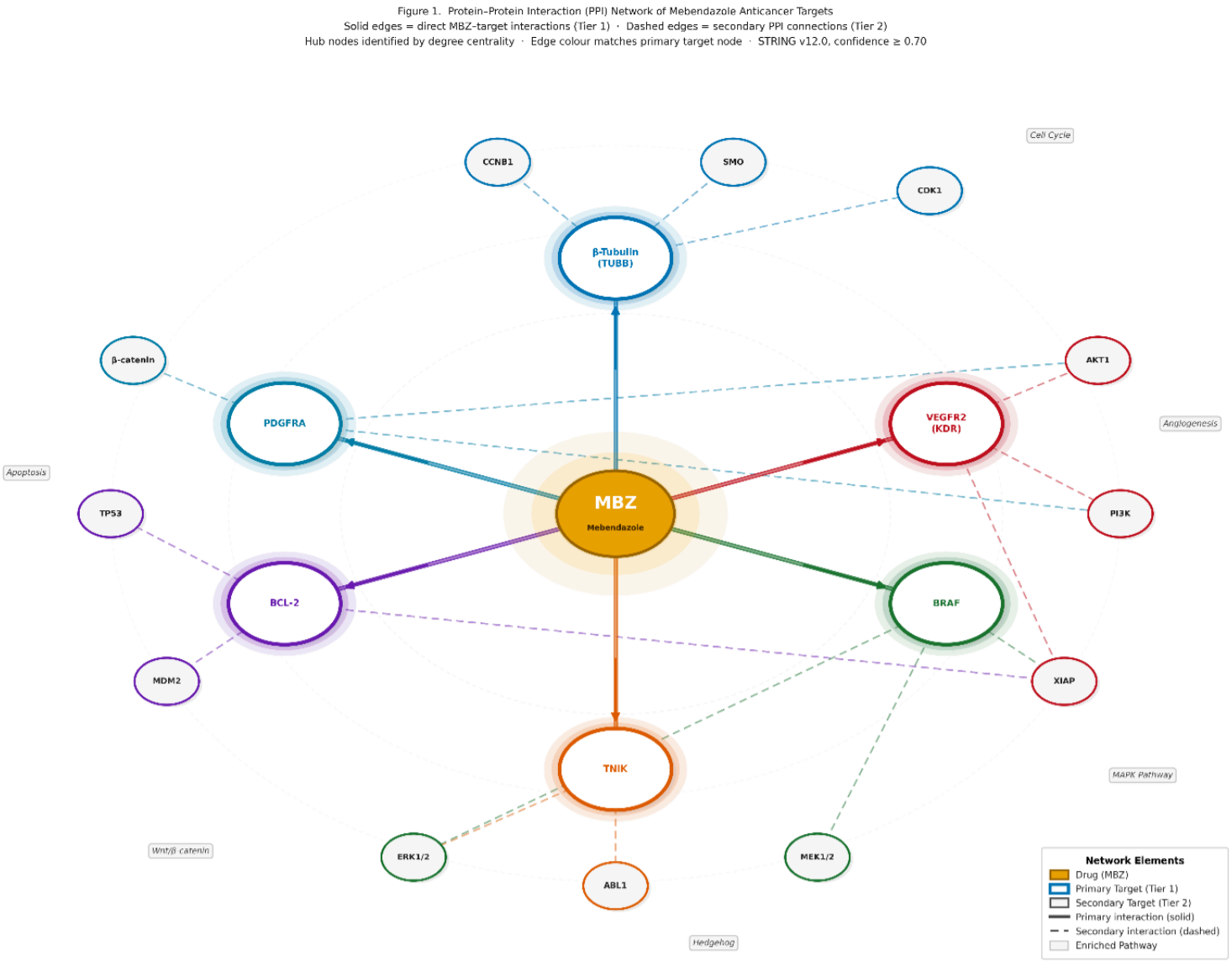


Figure 1

Protein–protein interaction (PPI) network of mebendazole anticancer targets. Central node (gold) = mebendazole (MBZ); inner ring (coloured nodes) = Tier-1 directly predicted targets; outer nodes (grey) = Tier-2 secondary targets. Edge colour corresponds to Tier-1 target category; edge width reflects interaction confidence (STRING v12.0, threshold ≥ 0.7). Network visualised in Cytoscape v3.10; hub nodes identified by degree centrality. Enriched pathway annotations are shown at the network periphery.

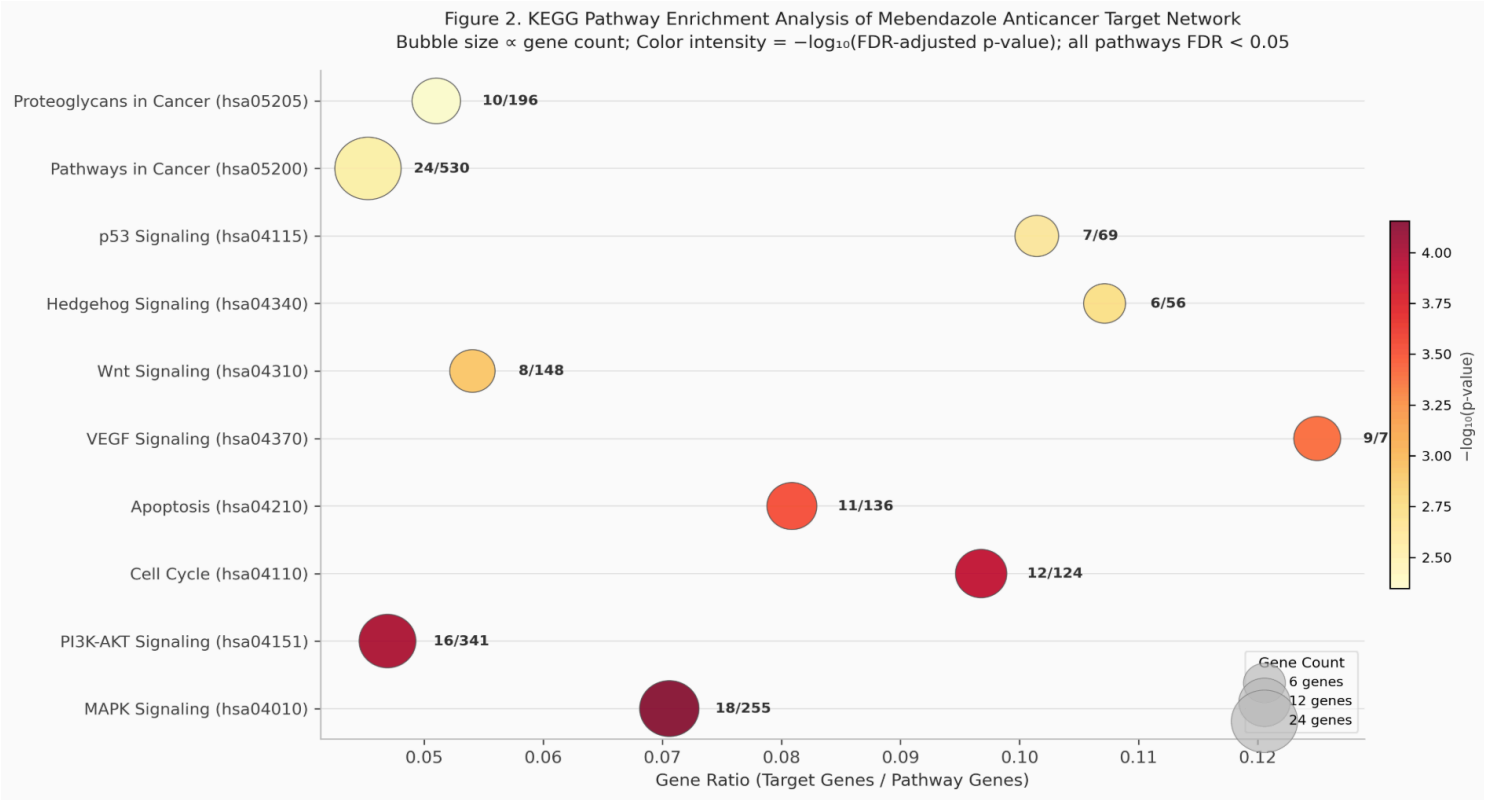


Figure 2

KEGG pathway enrichment bubble plot for the mebendazole anticancer target network. Each bubble represents one enriched KEGG pathway (FDR < 0.05). Bubble size is proportional to the number of MBZ target genes in the pathway; colour intensity represents −log10 (adjusted p-value) on a yellow-to-red scale. Gene ratio label (n/N) denotes MBZ target genes / total pathway gene count.

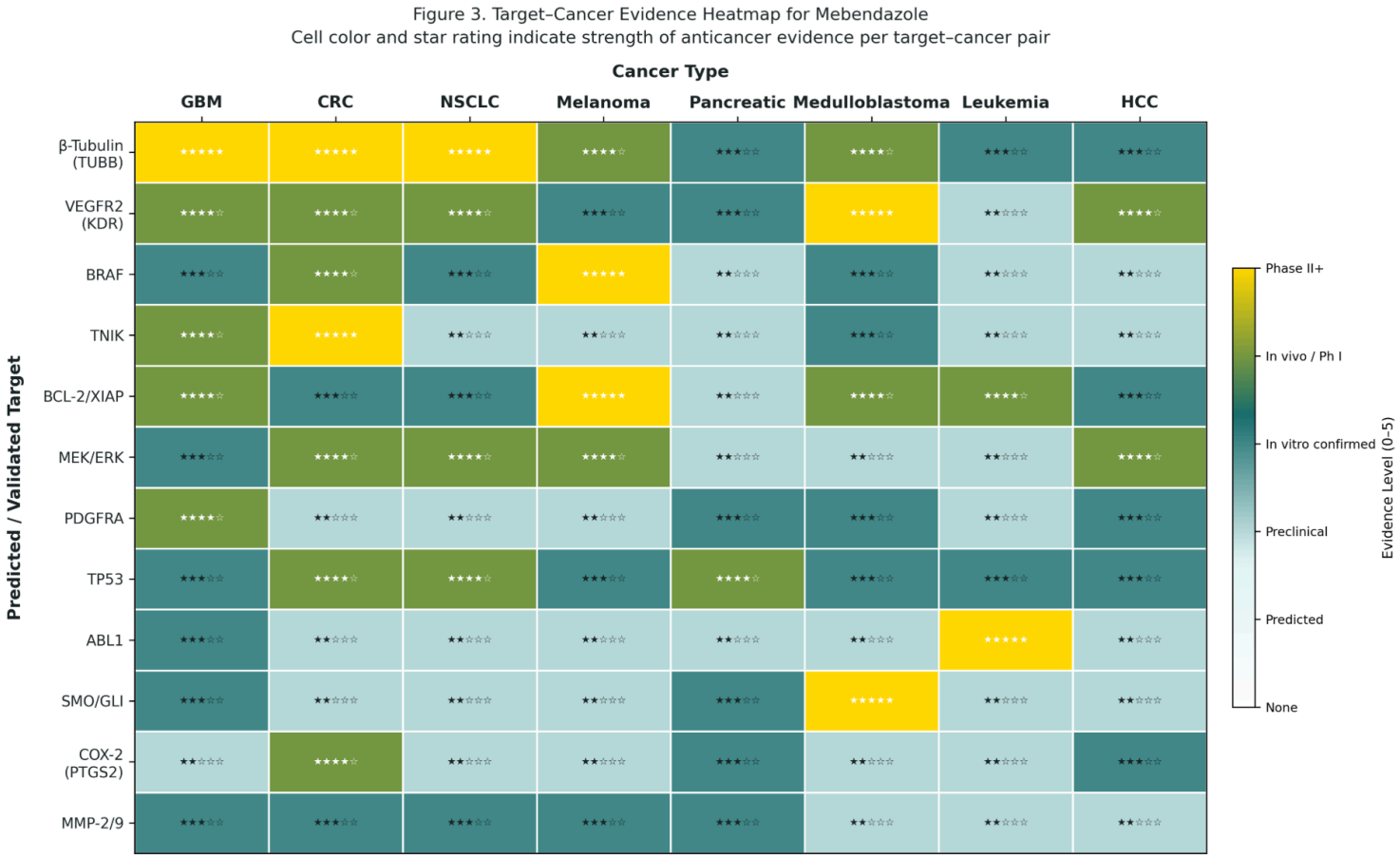


Figure 3

Target–cancer evidence heatmap for mebendazole. Rows represent the 14 predicted/validated anticancer targets; columns represent eight cancer types. Cell colour and star rating (☆–☆☆☆☆☆) indicate the strength of supporting evidence: predicted in silico (☆☆); preclinical cell-based (☆☆☆); in vitro confirmed with IC50 data or in vivo xenograft (☆☆☆☆); Phase I/II clinical trial evidence (☆☆☆☆☆). Colour scale: white = no evidence; deep teal = strong preclinical; gold = Phase II+ clinical.

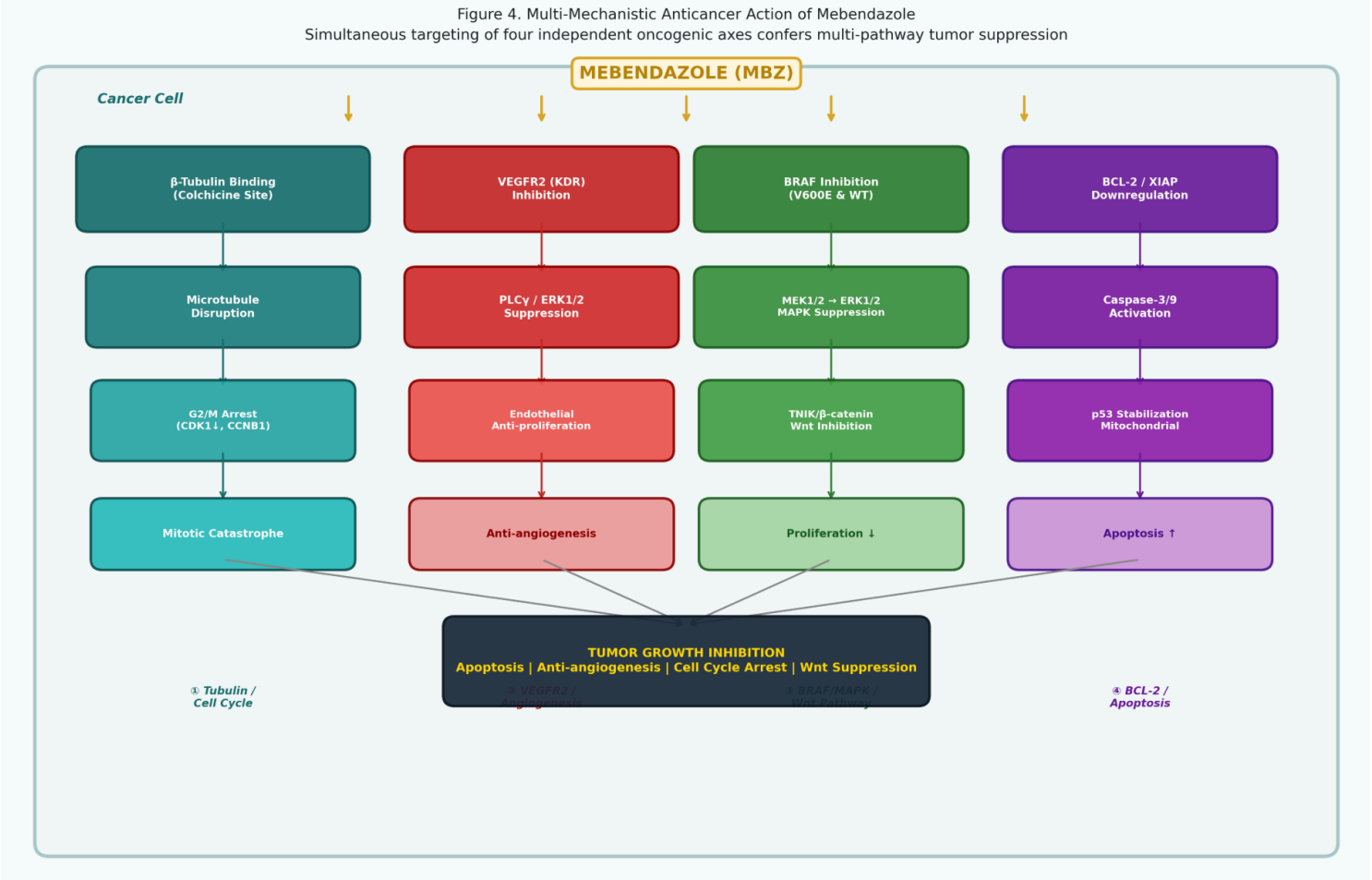


Figure 4

Schematic of the multi-mechanistic anticancer action of mebendazole. Four independent pharmacological axes are shown with colour coding: teal (□ Tubulin/Cell Cycle) - colchicine-site β-tubulin binding → microtubule disruption → G2/M arrest; red (□ VEGFR2/Angiogenesis)-VEGFR2 kinase inhibition → PLCγ/ERK suppression → anti-angiogenesis; green (□ BRAF-MAPK/Wnt)-BRAF/MEK/ERK blockade and TNIK/β-catenin Wnt suppression → anti-proliferation; purple (□ BCL-2/Apoptosis)-BCL-2/XIAP downregulation → caspase-3/9 activation → intrinsic apoptosis. All axes converge on tumour growth inhibition (lower panel).