Articles in support of Fenbendazole and articles expressing concerns and skepticism about it

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Category 1: In favor (articles 1-48 on pages 1-45)

[Jump to Category 2: Concerns and/or skeptical (articles 49-72, pages 45-65)]

Joe Tippens Blog

https://mycancerstory.rocks/the-blog/

1:

https://www.nature.com/articles/s41598-018-30158-6

Scientific Reports volume 8, Article number: 11926 (2018)

Title:

Fenbendazole acts as a moderate microtubule destabilizing agent and causes cancer cell death by modulating multiple cellular pathways

Abstract:

Drugs that are already clinically approved or experimentally tested for conditions other than cancer, but are found to possess previously unrecognized cytotoxicity towards malignant cells, may serve as fitting anti-cancer candidates. Methyl N-(6-phenylsulfanyl-1H benzimidazol-2-yl) carbamate [Fenbendazole, FZ], a benzimidazole compound, is a safe and inexpensive anthelmintic drug possessing an efficient anti-proliferative activity. In our earlier work, we reported a potent growth-inhibitory activity of FZ caused partially by impairment of proteasomal function. Here, we show that FZ demonstrates moderate affinity for mammalian tubulin and exerts cytotoxicity to human cancer cells at micromolar concentrations. Simultaneously, it caused mitochondrial translocation of p53 and effectively inhibited glucose uptake, expression of *GLUT* transporters as well as hexokinase (*HK II*) - a key glycolytic enzyme that most cancer cells thrive on. It blocked the growth of human xenografts in *nu/nu* mice model when mice were fed with the drug orally. The results, in conjunction with our earlier data, suggest that FZ is a

new microtubule interfering agent that displays anti-neoplastic activity and may be evaluated as a potential therapeutic agent because of its effect on multiple cellular pathways leading to effective elimination of cancer cells.

2:

https://pubmed.ncbi.nlm.nih.gov/2773308/

Vet Res Commun.1989;13(2):135-9

Title:

Comparative studies on the effect of fenbendazole on the liver and liver microsomal enzymes in goats, quail and rats

Abstract:

To compare the effect of fenbendazole on the liver and liver microsomal mono-oxygenases of goats, quail and rats, an oral dose of 25 mg/kg was administered to the animals daily for 9 consecutive days. On the tenth day, blood samples and livers were collected from both the control and the treated animals for preparation of serum and microsomes respectively. Determination of the activities of sorbitol dehydrogenase (SDH, alanine aminotransferase (ALT) and aspartate aminotransferase (AST) in the serum samples showed that there was no significant increase in the activities of these enzymes in the treated animals as compared to their corresponding controls, suggesting no liver damage. Similarly, no significant difference in the amount of microsomal cytochrome P-450 was found between the control and the treated animals of the same species. Compared to their respective controls, the activities of microsomal benzphetamine N-demethylase and aniline hydroxylase were almost unchanged in the treated goats and rats. However, fenbendazole treatment appeared to enhance the activity of these two microsomal enzymes in quail. The results indicate that fenbendazole is not liver toxic to goats, quail or rats at a dose rate of 25 mg/kg.

3:

https://www.scitechnol.com/peer-review/fenbendazole-enhancing-antitumor-effect-a-case-series-2Kms.php?article_id=14307&fbclid=IwAR0tYpTZb4fp2_AO8e_WGWM5mcqv-RNfI-5SID9OWDcRiwHyHmQBKsjeSKk

Case Report, Clin Oncol Case Rep Vol: 4 Issue: 2

Title:

Fenbendazole Enhancing Anti-Tumor Effect: A Case Series

Abstract:

Background: Fenbendazole (FBZ) is a cheap and readily available anti-parasitic commonly used in veterinary medicine. FBZ belongs to the benzimidazole drug class which destabilize microtubules through a mechanism similar to the anti-oncogenic vinca alkaloids. Although there are no reported cases in the literature, there have been several anecdotal stories published on website blogs with individuals praising its ability to treat a wide variety of cancers.

Case Presentations: Herein we describe the cases of three patients with various genitourinary malignancies who demonstrated complete response after receiving FBZ therapy as a single or supplementary chemotherapeutic agent. In two patient scenarios, they had experienced progression of metastatic disease despite multiple lines of therapy prior to initiation of FBZ. No side effects from FBZ were reported.

Conclusion: FBZ appears to be a potentially safe and effective antineoplastic agent that can be repurposed for human use in treating genitourinary malignancies. Further research is necessary to define the role of FBZ as a chemotherapeutic option.

4:

https://www.tandfonline.com/doi/full/10.1080/07391102.2023.2258419

Research article. 07 Sep 2023.

Title:

Network pharmacology and molecular docking study-based approach to explore mechanism of benzimidazole-based anthelmintics for the treatment of lung cancer

Abstract:

Emerging studies have reported the potential anticancer activity of benzimidazole-based anthelmintics (BBA) against lung cancer (LC). However, mechanism underlying the anticancer activity of BBA is unclear. Therefore, in the current study, network pharmacology and molecular docking-based approach were used to explore the potential molecular mechanism for the treatment of LC. The potential targets for BBA were obtained from multiple databases including SwissTargetPrediction, Drug Bank, Therapeutic Target Database, and Comparative Toxicogenomics Database while LC targets were collected from DisGeNet gene discovery platform, Integrated Genomic Database of NSCLC, Catalogue of Somatic Mutations in Cancer and Online Mendelian Inheritance in Man database. Protein-protein interaction (PPI) diagram of common targets was constructed using STRING online platform. Topological analysis was performed using Cytoscape and gene enrichment analysis was conducted using FunRich software. Highest degree targets were then confirmed using molecular docking and molecular dynamics simulations. The BBA were prioritized according to their S scores, with ricobendazole ranking highest followed by flubendazole, fenbendazole, mebendazole, triclabendazole, albendazole, oxibendazole, parbendazole, thiabendazole and oxfendazole. The potential targets of BBA identified using topological analysis and molecular docking were found to be CCND1 (cyclin D1), EGFR (Epidermal Growth Factor Receptor), ERBB2 (Erb-B2 Receptor Tyrosine Kinase 2/CD340), PTGS2 (Prostaglandin-endoperoxide synthase 2), and SRC (Proto-oncogene tyrosine-protein kinase). Furthermore, molecular dynamics confirmed that CCND1 and EGFR are the potential targets of ricobendazole for the treatment of LC. BBA can be further explored as a therapeutic strategy for the treatment of lung cancer under in vitro and in vivo studies.

5:

https://www.kjvr.org/journal/view.php?doi=10.14405/kjvr.2020.60.2.79

Korean Journal of Veterinary Research 2020;60(2):79-83.

Title:

Relevance of reactive oxygen species in the anticancer activity of Fenbendazole

Abstract:

Fenbendazole (FBZ) is a benzimidazole anthelmintic that has been widely used in treatments for gastrointestinal parasites including pinworms and roundworms in animals. Recently, some studies demonstrated that FBZ has anti-cancer effects related to disruption of microtubule polymerization. In this study, we investigated whether FBZ has anti-cancer activity in HL-60 cells, a human leukemia cell line, and assessed its relationship with the production of reactive oxygen species (ROS). FBZ treatment at 0.25-1 μM significantly decreased the metabolic activity of HL-60 cells. The mitochondrial membrane potential of FBZ-treated HL-60 cells decreased in a concentration-dependent manner. Apoptosis analysis using annexin V-FITC/propidium iodide staining demonstrated that 1 μM FBZ increased the percentages of cells in apoptosis and necrosis. In addition, Hoechst 33342 staining showed the presence of broken nuclei in HL-60 cells treated with 0.5 and 1 μM FBZ. To investigate the anti-cancer mechanism of FBZ, HL-60 cells were treated with FBZ in the absence or presence of N-acetyl cysteine (NAC), an inhibitor of ROS production. NAC significantly recovered the decreased metabolic activity of HL-60 induced by 0.5 and 1 μM FBZ treatments. This study provides evidence that FBZ has anti-cancer activity in HL-60 cells provided, in part, via ROS production.

6:

https://www.sciencedirect.com/science/article/abs/pii/S0304383519301442

Article. 1 June 2019, Pages 11-22

Title:

Drug library screen reveals benzimidazole derivatives as selective cytotoxic agents for KRAS-mutant lung cancer

Abstract:

KRAS is one of the most frequently mutated oncogenes in human non-small cell lung cancer (NSCLC). Mutations in KRAS are detected in 30% of NSCLC cases, with most of them occurring in codons 12 and 13 and less commonly in others. Despite intense efforts to develop drugs targeting mutant KRAS, no effective therapeutic strategies have been successfully tested in clinical trials. Here, we investigated molecular targets for KRAS-activated lung cancer cells using a drug library. A total of 1271 small molecules were screened in KRAS-mutant and wild-type lung cancer cell lines. The screening identified the cytotoxic effects of benzimidazole derivatives on KRAS-mutant lung cancer cells. Treatmentswith two benzimidazole derivatives, methiazole and fenbendazole—both of which are structurally specific—yielded significant suppression of the RAS-related signaling pathways in KRAS-mutated cells. Moreover, combinatorial therapy with methiazole and trametinib, a MEK inhibitor, induced synergistic effects in KRAS-mutant lung cancer cells. Our study demonstrates that these benzimidazole derivatives play an important role in suppressing KRAS-mutant lung cancer cells, thus offering a novel combinatorial therapeutic approach against such cancer cells.

7:

https://synapse.koreamed.org/articles/1516079963

Korean J. Physiol. Pharmacol. 2022;26(5):377-387.

Title:
Anti-cancer effects of fenbendazole on 5-fluorouracil-resistant colorectal cancer cells

Abstract:

Benzimidazole anthelmintic agents have been recently repurposed to overcome cancers resistant to conventional therapies. To evaluate the anti-cancer effects of benzimidazole on resistant cells, various cell death pathways were investigated in

5-fluorouracil-resistant colorectal cancer cells. The viability of wild-type and 5-fluorouracil-resistant SNU-C5 colorectal cancer cells was assayed, followed by Western blotting. Flow cytometry assays for cell death and cell cycle was also performed to analyze the anti-cancer effects of benzimidazole. When compared with albendazole, fenbendazole showed higher susceptibility to 5-fluorouracil-resistant SNU-C5 cells and was used in subsequent experiments. Flow cytometry revealed that fenbendazole significantly induces apoptosis as well as cell cycle arrest at G2/M phase on both cells. When compared with wild-type SNU-C5 cells, 5-fluorouracil-resistant SNU-C5 cells showed reduced autophagy, increased ferroptosis and ferroptosis-augmented apoptosis, and less activation of caspase-8 and p53. These results suggest that fenbendazole may be a potential alternative treatment in 5-fluorouracil-resistant cancer cells, and the anticancer activity of fenbendazole does not require p53 in 5-fluorouracil-resistant SNU-C5 cells.

8:

https://www.mdpi.com/1999-4923/12/10/1000

Pharmaceutics 2020, 12(10), 1000

Title:

Physicochemical, Pharmacokinetic, and Toxicity Evaluation of Soluplus® Polymeric Micelles Encapsulating Fenbendazole

Abstract:

Fenbendazole (FEN), a broad-spectrum benzimidazole anthelmintic, suppresses cancer cell growth through various mechanisms but has low solubility and achieves low blood concentrations, which leads to low bioavailability. Solubilizing agents are required to prepare poorly soluble drugs for injections; however, these are toxic. To overcome this problem, we designed and fabricated low-toxicity Soluplus®polymeric micelles encapsulating FEN and conducted toxicity assays in vitro and in vivo. FEN-loaded Soluplus® micelles had an average particle size of 68.3 ±0.6 nm, a zeta potential of −2.3 ±0.2 mV, a drug loading of 0.8 ±0.03%, and an encapsulation efficiency of 85.3 ±2.9%. MTT and clonogenic assays were performed on A549 cells treated with free FEN and FEN-loaded Soluplus® micelles. The in vitro drug release profile showed that the micelles released FEN more gradually than the solution. Pharmacokinetic studies revealed lower total

clearance and volume of distribution and higher area under the curve and plasma concentration at time zero of FEN-loaded Soluplus® micelles than of the FEN solution. The in vivo toxicity assay revealed that FEN-loaded Soluplus® micelle induced no severe toxicity. Therefore, we propose that preclinical and clinical safety and efficacy trials on FEN-loaded Soluplus® micelles would be worthwhile.

9:

https://www.ingentaconnect.com/content/aalas/cm/2022/00000072/00000004/art00001

Comparative Medicine, Volume 72, Number 4, August 2022, pp. 215-219(5)

Title:

An Update on the Biologic Effects of Fenbendazole

Abstract:

Fenbendazole remains the drug of choice to treat pinworm infection in laboratory rodents. When fenbendazole was last reviewed (15 y ago), the literature supported the drug's lack of toxic effects at therapeutic levels, yet various demonstrated physiologic effects have the potential to alter research outcomes. Although more recent reports continue to reflect an overall discordancy of results, several studies support the premise that fenbendazole affects the bone marrow and the immune system. No effects on reproduction were reported in an extensive study that assessed common treatment protocols in mice, and food intake was unchanged in rats. Behavioral studies are sparse, with only a single report of a subtle change in a rotarod performance in mice. Notably, unexpected results in tumor models during facility treatment with fenbendazole have prompted preclinical and clinical studies of the potential roles of benzimidazoles in cancer.

10:

https://www.sciencedirect.com/science/article/abs/pii/S0009279722001880

Volume 361, 1 July 2022, 109983

Title:
Fenbendazole and its synthetic analog interfere with HeLa cells ’proliferation and energy metabolism via inducing oxidative stress and modulating MEK3/6-p38-MAPK pathway

Abstract:

Fenbendazole, a broad-spectrum anti-parasitic drug, can be a potential anti-tumor agent. In this study, we synthesized and purified its derivative, analog 6, intending to achieve improved efficacy in cancer cells and decreased toxicity in normal cells.

To evaluate in vitro anti-tumor activities of fenbendazole and analog 6 in different cancer cell lines, a CCK-8 assay was performed, and we found that human cervical cancer HeLa cells were more sensitive to analog 6 than to fenbendazole. Furthermore, we explored the associated mechanism, and our results showed that analog 6 and fenbendazole could induce oxidative stress by accumulating ROS. It not only activated the p38-MAPK signaling pathway, thereby inhibiting the proliferation of HeLa cells and enhancing the apoptosis of HeLa cells, but also significantly induced impaired energy metabolism and restrained their migration and invasion. In addition, the modified analog 6 showed reduced toxicity to normal cells without decreased anti-cancer effect.

In conclusion, fenbendazole and analog 6 have multiple targets and strong anti-tumor effects on HeLa cells in vitro and in vivo. The optimized analog 6 could inhibit the viability of HeLa cells with lower toxicity than normal human cells, promising to be developed as an antitumor active compound.

11:

https://www.mdpi.com/1999-4923/13/10/1605

Pharmaceutics 2021, 13(10), 1605

Title:
PEGylated Mesoporous Silica Nanoparticles (MCM-41): A Promising Carrier for the Targeted Delivery of Fenbendazole into Prostate Cancer Cells

Abstract:

Low water solubility and thus low bioavailability limit the clinical application of fenbendazole (FBZ) as a potential anticancer drug. Solubilizing agents, such as Mobil Composition of Matter Number 41 (MCM) as a drug carrier, can improve the water solubility of drugs. In this study, PEGylated MCM (PEG-MCM) nanoparticles (NPs) were synthesized and loaded with FBZ (PEG-MCM-FBZ) to improve its solubility and, as a result, its cytotoxicity effect against human prostate cancer PC-3 cells. The loading efficiency of FBZ onto PEG-MCM NPs was 17.2%. The size and zeta potential of PEG-MCM-FBZ NPs were 366.3 ±6.9 nm and 24.7 ±0.4 mV, respectively. They had a spherical shape and released the drug in a controlled manner at pH 1.2 and pH 6.2. PEG-MCM-FBZ were found to inhibit the migration of PC-3 cells, increase the cytotoxicity effects of FBZ against PC-3 cells by 3.8-fold, and were more potent by 1.4-fold, when compared to the non-PEGylated NPs. In addition, PEG-MCM-FBZ promoted the production of reactive oxygen species by 1.3- and 1.2-fold, respectively, when compared to FBZ and MCM-FBZ. Overall, the results demonstrate that PEG-MCM-FBZ NPs enhanced FBZ delivery to PC-3 cells; therefore, they have the potential to treat prostate cancer after a comprehensive in vivo study.

12:

https://pubs.acs.org/doi/full/10.1021/acsomega.1c05519

ACS Omega 2022, 7, 1, 875–899

Title:

In Silico and In Vitro Studies for Benzimidazole Anthelmintics Repurposing as VEGFR-2 Antagonists: Novel Mebendazole-Loaded Mixed Micelles with Enhanced Dissolution and Anticancer Activity

Abstract:

Cancer is a leading cause of death worldwide and its incidence is unfortunately anticipated to rise in the next years. On the other hand, vascular endothelial growth factor receptor 2 (VEGFR-2) is highly expressed in tumor-associated endothelial cells, where it affects tumor-promoting angiogenesis. Therefore, VEGFR-2 is considered one of the most promising therapeutic targets for cancer treatment. Furthermore, some FDA-approved benzimidazole anthelmintics have already shown potential anticancer activities. Therefore, repurposing them against VEGFR-2 can provide a rapid and effective alternative that can be implicated safely for cancer treatment. Hence, 13 benzimidazole anthelmintic drugs were subjected to molecular docking against the VEGFR-2 receptor. Among the tested compounds, fenbendazole (FBZ, 1), mebendazole (MBZ, 2), and albendazole (ABZ, 3) were proposed as potential VEGFR-2 antagonists. Furthermore, molecular dynamics simulations were carried out at 200 ns, giving more information on their thermodynamic and dynamic properties. Besides, the anticancer activity of the aforementioned drugs was tested in vitro against three different cancer cell lines, including liver cancer (HUH7), lung cancer (A549), and breast cancer (MCF7) cell lines. The results depicted potential cytotoxic activity especially against both HUH7 and A549 cell lines. Furthermore, to improve the aqueous solubility of MBZ, it was formulated in the form of mixed micelles (MMs) which showed an enhanced drug release with better promising cytotoxicity results compared to the crude MBZ. Finally, an in vitro quantification for VEGFR-2 concentration in treated HUH7 cells has been conducted based on the enzyme-linked immunosorbent assay. The results disclosed that FBZ, MBZ, and ABZ significantly ($p < 0.001$) reduced the concentration of VEGFR-2, while the lowest inhibition was achieved in MBZ-loaded MMs, which was even much better than

the reference drug sorafenib. Collectively, the investigated benzimidazole anthelmintics could be encountered as lead compounds for further structural modifications and thus better anticancer activity, and that was accomplished through studying their structure–activity relationships.

13:

https://www.jbc.org/article/S0021-9258(20)63163-5/fulltext

VOLUME 287, ISSUE 36, P30625-30640, AUGUST 2012

Title:

Impairment of the Ubiquitin-Proteasome Pathway by Methyl N-(6-Phenylsulfanyl-1H-benzimidazol-2-yl)carbamate Leads to a Potent Cytotoxic Effect in Tumor Cells

Abstract:

In recent years, there has been a great deal of interest in proteasome inhibitors as a novel class of anticancer drugs. We report that fenbendazole (FZ) (methyl N-(6-phenylsulfanyl-1H-benzimidazol-2-yl)carbamate) exhibits a potent growth-inhibitory activity against cancer cell lines but not normal cells. We show here, using fluorogenic substrates, that FZ treatment leads to the inhibition of proteasomal activity in the cells. Succinyl-Leu-Leu-Val-Tyr-methylcoumarinamide (MCA), benzyloxycarbonyl-Leu-Leu-Glu-7-amido-4-MCA, and t-butoxycarbonyl-Gln-Ala-Arg-7-amido-4-MCA fluorescent derivatives were used to assess chymotrypsin-like, post-glutamyl peptidyl-hydrolyzing, and trypsin-like protease activities, respectively. Non-small cell lung cancer cells transiently transfected with an expression plasmid encoding pd1EGFP and treated with FZ showed an accumulation of the green fluorescent protein in the cells due to an increase in its half-life. A number of apoptosis regulatory proteins that are normally degraded by the ubiquitin-proteasome pathway like cyclins, p53, and IκBα were found to be accumulated in FZ-treated cells. In addition, FZ induced distinct ER stress-associated genes like GRP78, GADD153, ATF3, IRE1α, and NOXA in these cells. Thus, treatment of human NSCLC cells with fenbendazole induced endoplasmic reticulum stress, reactive oxygen species production, decreased mitochondrial membrane potential, and cytochrome c release that eventually led to cancer cell

death. This is the first report to demonstrate the inhibition of proteasome function and induction of endoplasmic reticulum stress/reactive oxygen species-dependent apoptosis in human lung cancer cell lines by fenbendazole, which may represent a new class of anticancer agents showing selective toxicity against cancer cells.

14:

https://www.mdpi.com/1422-0067/23/8/4315

Int. J. Mol. Sci. 2022, 23(8), 4315

Title:

Double Repositioning: Veterinary Antiparasitic to Human Anticancer

Abstract:

Drug repositioning, the approach of discovering different uses for existing drugs, has gained enormous popularity in recent years in the anticancer drug discovery field due to the increasing demand for anticancer drugs. Additionally, the repurposing of veterinary antiparasitic drugs for the treatment of cancer is gaining traction, as supported by existing literature. A prominent example is the proposal to implement the use of veterinary antiparasitics such as benzimidazole carbamates and halogenated salicylanilides as novel anticancer drugs. These agents have revealed pronounced anti-tumor activities and gained special attention for “double repositioning”, as they are repurposed for different species and diseases simultaneously, acting via different mechanisms depending on their target. As anticancer agents, these compounds employ several mechanisms, including the inhibition of oncogenic signal transduction pathways of mitochondrial respiration and the inhibition of cellular stress responses. In this review, we summarize and provide valuable information about the experimental, preclinical, and clinical trials of veterinary antiparasitic drugs available for the treatment of various cancers in humans. This review suggests the possibility of new treatment options that could improve the quality of life and outcomes for cancer patients in comparison to the currently used treatments.

15:

https://www.researchgate.net/profile/Nilambra-Dogra/publication/312205860_Methyl_N-6-Phenylsulfanyl-1h-Benzimidazol-2-Yl_Carbamate_A_Non-Toxic_Substitute_of_Colchicine_for_Quality_Metaphase_Chromosome_Preparation_from_Normal_and_Tumor_Cells_for_Cytogenetic_Analysis/links/5b858a3b92851c1e1238d3a4/Methyl-N-6-Phenylsulfanyl-1h-Benzimidazol-2-Yl-Carbamate-A-Non-Toxic-Substitute-of-Colchicine-for-Quality-Metaphase-Chromosome-Preparation-from-Normal-and-Tumor-Cells-for-Cytogenetic-Analysis.pdf

Biol Syst. Volum 5. Issue 2. 1000160.

Title:
Methyl N-(6-Phenylsulfanyl-1h-Benzimidazol-2-Yl) Carbamate: A Non-Toxic Substitute of Colchicine for Quality Metaphase Chromosome Preparation from Normal and Tumor Cells for Cytogenetic Analysis

Abstract:

Background: Methyl N-(6-phenylsulfanyl-1H-benzimidazol-2-yl) carbamate [Fenbendazole, FZ] is an anthelmintic drug which acts by selectively binding to β tubulin of nematodes, inhibiting the tubulin polymerization and blocking microtubule dependent glucose uptake. The anti-proliferative effect of Fenbendazole is partly due to its ability to affect microtubule dynamics and arrest cells at a pro-metaphase state with an intact mitotic spindle.

Findings: Here, we show that Fenbendazole - a benzimidazole anthelmintic drug, can be used as an alternative to colchicine for making high quality chromosome preparations for karyotyping and further cytogenetic analysis. This drug could efficiently block the proliferation of human tumor cell lines as well as peripheral blood lymphocytes in culture by arresting them at G2M phase. FZ treatment at 1uM concentration for 3 h resulted in high mitotic indices resulting in a number of well spread metaphasic plates in suspension as well as adherent cultures. The morphology of metaphase chromosomes obtained from FZ treated samples was at par with those prepared from colchicine.

Conclusion: Altogether, our results show FZ as an extremely efficient, relatively non-toxic and inexpensive G2/M blocker which may be utilized as a suitable alternative of colchicine for routine cytogenetic analysis.

16:

https://www.tandfonline.com/doi/full/10.2147/IJN.S315782

Volume 16, 2021

Title:

Optimization and Pharmacokinetic Evaluation of Synergistic Fenbendazole and Rapamycin Co-Encapsulated in Methoxy Poly(Ethylene Glycol)-b-Poly(Caprolactone) Polymeric Micelles

Abstract:

Purpose

We aimed to develop a nanocarrier formulation incorporating fenbendazole (FEN) and rapamycin (RAPA) with strong efficacy against A549 cancer cells. As FEN and RAPA are poorly soluble in water, it is difficult to apply them clinically in vivo. Therefore, we attempted to resolve this problem by encapsulating these drugs in polymeric micelles.

Methods

We evaluated drug synergy using the combination index (CI) values of various molar ratios of FEN and RAPA. We formed and tested micelles composed of different polymers. Moreover, we conducted cytotoxicity, stability, release, pharmacokinetic, and biodistribution studies to investigate the antitumor effects of FEN/RAPA-loaded mPEG-b-PCL micelles.

Results

We selected mPEG-b-PCL-containing FEN and RAPA at a molar ratio of 1:2 because these particles were consistent in size and had high encapsulation efficiency (EE, %) and drug loading (DL, %) capacity. The in vitro cytotoxicity was assessed for various FEN, RAPA, and combined FEN/RAPA formulations. After long-term exposures, both the solutions and the micelles had similar efficacy against A549 cancer cells. The in vivo pharmacokinetic study revealed that FEN/RAPA-loaded mPEG-b-PCL micelles had a relatively higher area under the plasma concentration–time curve from 0 to 2 h (AUC0–2 h) and 0 to 8 h (AUC0–8 h) and plasma concentration at time zero (Co) than that of the FEN/RAPA solution. The in vivo biodistribution assay revealed that the IV injection of FEN/RAPA-loaded mPEG-b-PCL micelles resulted in lower pulmonary FEN concentration than the IV injection of the FEN/RAPA solution.

Conclusion
When FEN and RAPA had a 1:2 molar ratio, they showed synergism. Additionally, using data from in vitro cytotoxicity, synergism between a 1:2 molar ratio of FEN and RAPA was observed in the micelle formulation. The FEN/RAPA-loaded mPEG-b-PCL micelle had enhanced bioavailability than the FEN/RAPA solution.

17:
https://www.sciencedirect.com/science/article/pii/S131901642100061X

Volume 29, Issue 5, May 2021, Pages 434-445

Title:
Anthelmintics for drug repurposing: Opportunities and challenges

Abstract:

Drug repositioning is defined as a process to identify a new application for drugs. This approach is critical as it takes advantage of well-known pharmacokinetics, pharmacodynamics, and toxicity profiles of the drugs; thus, the chance of their future failure decreases, and the cost of their development and the required time for their approval are reduced. Anthelmintics, which are antiparasitic drugs, have recently demonstrated promising anticancer effects in vitro and in vivo. This literature review focuses on the potential of anthelmintics for repositioning in the treatment of cancers. It also discusses their pharmacokinetics and pharmacodynamics as antiparasitic drugs, proposed anticancer mechanisms, present development conditions, challenges in cancer therapy, and strategies to overcome these challenges.

18:

https://www.tandfonline.com/doi/full/10.2147/IJN.S394712

Volume 18, 2023. May 2023.

Title:

Anticancer Evaluation of Methoxy Poly(Ethylene Glycol)-b-Poly(Caprolactone) Polymeric Micelles Encapsulating Fenbendazole and Rapamycin in Ovarian Cancer

Abstract:

Purpose

We aimed to inhibit ovarian cancer (OC) development by interfering with microtubule polymerization and inhibiting mTOR signaling. To achieve this, previously developed micelles containing fenbendazole and rapamycin were applied.

Methods

Herein, we prepared micelles for drug delivery using fenbendazole and rapamycin at a 1:2 molar ratio and methoxy poly(ethylene glycol)-b-poly(caprolactone)(mPEG-b-PCL) via freeze-drying. We revealed their long-term storage capacity of up to 120 days. Furthermore, a cytotoxicity test was performed on the OC cell line HeyA8, and an orthotopic model was established for evaluating in vivo antitumor efficacy.

Results

Fenbendazole/rapamycin-loaded mPEG-b-PCL micelle (M-FR) had an average particle size of 37.2 ±1.10 nm, a zeta potential of −0.07 ±0.09 mV, and a polydispersity index of 0.20 ±0.02. Additionally, the average encapsulation efficiency of fenbendazole was 75.7 ±4.61% and that of rapamycin was 98.0 ± 1.97%. In the clonogenic assay, M-FR was 6.9 times more effective than that free fenbendazole/rapamycin. The in vitro drug release profile showed slower release in the combination formulation than in the single formulation.

Conclusion

There was no toxicity, and tumor growth was suppressed substantially by our formulation compared with that seen with the control. The findings of our study lay a foundation for using fenbendazole and rapamycin for OC treatment.

19:

https://www.nature.com/articles/s41401-021-00752-y

Acta Pharmacologica Sinica 43, 194–208 (2022)

Title:

Benzimidazoles induce concurrent apoptosis and pyroptosis of human glioblastoma cells via arresting cell cycle

Abstract:

Glioblastoma multiforme (GBM) is the most malignant and lethal primary brain tumor in adults accounting for about 50% of all gliomas. The only treatment available for GBM is the drug temozolomide, which unfortunately has frequent drug resistance issue. By analyzing the hub genes of GBM via weighted gene co-expression network analysis (WGCNA) of the cancer genome atlas (TCGA) dataset, and using the connectivity map (CMAP) platform for drug repurposing, we found that multiple azole compounds had potential anti-GBM activity. When their anti-GBM activity was examined, however, only three benzimidazole compounds, i.e. flubendazole, mebendazole and fenbendazole, potently and dose-dependently inhibited proliferation of U87 and U251 cells with IC50 values below 0.26 μM. Benzimidazoles (0.125−0.5 μM) dose-dependently suppressed DNA synthesis, cell migration and invasion, and regulated the expression of key epithelial-mesenchymal transition (EMT) markers in U87 and U251 cells. Benzimidazoles treatment also dose-dependently induced the GBM cell cycle arrest at the G2/M phase via the P53/P21/cyclin B1 pathway. Furthermore, the drugs triggered pyroptosis of GBM cells through the NF-κB/NLRP3/GSDMD pathway, and might also concurrently induced mitochondria-dependent apoptosis. In a nude mouse U87 cell xenograft model, administration of flubendazole (12.5, 25, and 50 mg · kg−1 · d−1, i.p, for 3 weeks) dose-dependently suppressed the tumor growth without obvious adverse effects. Taken together, our results demonstrated that benzimidazoles might be promising candidates for the treatment of GBM.

20:

https://www.cabidigitallibrary.org/doi/full/10.5555/20123324904

Journal of Biological Chemistry, 2012, Vol. 287, No. 36, 30625-30640

Title:

Impairment of the ubiquitin-proteasome pathway by methyl n-(6-phenylsulfanyl-1h-benzimidazol-2-yl)carbamate leads to a potent cytotoxic effect in tumor cells. A novel antiproliferative agent with a potential therapeutic implication.

Abstract:

In recent years, there has been a great deal of interest in proteasome inhibitors as a novel class of anticancer drugs. We report that fenbendazole (FZ) (methyl N-(6-phenylsulfanyl-1H-benzimidazol-2-yl)carbamate) exhibits a potent growth-inhibitory activity against cancer cell lines but not normal cells. We show here, using fluorogenic substrates, that FZ treatment leads to the inhibition of proteasomal activity in the cells. Succinyl-Leu-Leu-Val-Tyr-methylcoumarinamide (MCA), benzyloxycarbonyl-Leu-Leu-Glu-7-amido-4-MCA, and t-butoxycarbonyl-Gln-Ala-Arg-7-amido-4-MCA fluorescent derivatives were used to assess chymotrypsin-like, post-glutamyl peptidyl-hydrolyzing, and trypsin-like protease activities, respectively. Non-small cell lung cancer cells transiently transfected with an expression plasmid encoding pd1EGFP and treated with FZ showed an accumulation of the green fluorescent protein in the cells due to an increase in its half-life. A number of apoptosis regulatory proteins that are normally degraded by the ubiquitin-proteasome pathway like cyclins, p53, and IκBα were found to be accumulated in FZ-treated cells. In addition, FZ induced distinct ER stress-associated genes like GRP78, GADD153, ATF3, IRE1α, and NOXA in these cells. Thus, treatment of human NSCLC cells with fenbendazole induced endoplasmic reticulum stress, reactive oxygen species production, decreased mitochondrial membrane potential, and cytochrome c release that eventually led to cancer cell death. This is the first report to demonstrate the inhibition of proteasome function and induction of endoplasmic reticulum stress/reactive oxygen species-dependent apoptosis in human lung cancer cell lines by fenbendazole, which may represent a new class of anticancer agents showing selective toxicity against cancer cells.

21:

https://www.mdpi.com/1420-3049/24/11/2152

Molecules 2019, 24(11), 2152
Title:
Benzimidazoles Downregulate Mdm2 and MdmX and Activate p53 in MdmX Overexpressing Tumor Cells

Abstract:

Tumor suppressor p53 is mutated in about 50% of cancers. Most malignant melanomas carry wild-type p53, but p53 activity is often inhibited due to overexpression of its negative regulators Mdm2 or MdmX. We performed high throughput screening of 2448 compounds on A375 cells carrying p53 activity luciferase reporter construct to reveal compounds that promote p53 activity in melanoma. Albendazole and fenbendazole, two approved and commonly used benzimidazole anthelmintics, stimulated p53 activity and were selected for further studies. The protein levels of p53 and p21 increased upon the treatment with albendazole and fenbendazole, indicating activation of the p53–p21 pathway, while the levels of Mdm2 and MdmX decreased in melanoma and breast cancer cells overexpressing these proteins. We also observed a reduction of cell viability and changes of cellular morphology corresponding to mitotic catastrophe, i.e., G2/M cell cycle arrest of large multinucleated cells with disrupted microtubules. In summary, we established a new tool for testing the impact of small molecule compounds on the activity of p53 and used it to identify the action of benzimidazoles in melanoma cells. The drugs promoted the stability and transcriptional activity of wild-type p53 via downregulation of its negative regulators Mdm2 and MdmX in cells overexpressing these proteins. The results indicate the potential for repurposing the benzimidazole anthelmintics for the treatment of cancers overexpressing p53 negative regulators.

22:

https://core.ac.uk/download/pdf/17355606.pdf

Title:

IN VITRO ANTI-CANCER EFFECTS OF BENZIMIDAZOLES ON THE CANINE OSTEOSARCOMA D17 CELL LINE

Abstract:

The high morbidity and mortality of canine osteosarcoma (OS) despite standard therapy warrants the need to investigate new treatment options. One avenue in exploring novel therapies is drug repurposing – using drugs with known dosing, toxicity profiles, and pharmacokinetics, and re-purposing them “off-label” for their pharmacologic effects for other diseases. In the search for novel therapies for canine osteosarcoma (OS), the benzimidazole (BZ) drugs, a class of safe and inexpensive anti-parasitics, were identified as potential novel therapeutics.

Benzimidazole (BZ) drugs are used routinely as effective anti-parasitics in both human and veterinary medicine. Their safety is well-established and side effects are minimal in most veterinary species including dogs. Safety has been described both with short-term high doses as well as long-term chronic dosing in dogs and other species with minimal adverse effects.

BZs have demonstrated in vitro and in vivo anti-cancer effects in both people and animal tumor models. The mechanism of BZs is thought to be similar to the microtubule inhibitory actions of traditional chemotherapeutic drug classes such as taxanes and vinca alkaloids, leading to metaphase arrest (G2/M phase) and tumor cell apoptosis. BZs also demonstrate indirect anti- cancer activity by vascular disruption of endothelial cells and reduction in cancer cell secretion of the angiogenic cytokine vascular endothelial growth factor (VEGF).

In human OS, mitotic spindle inhibitors are routinely used as an adjuvant chemotherapy agent, and similarly mitotic spindle inhibitors demonstrate effect for canine OS. Given the proposed activity at the mitotic apparatus, BZs may have similar activity in canine osteosarcoma. In addition to direct cytotoxic effects, BZs may possess indirect anti-angiogenic effects in canine OS, including modulation of VEGF. In human OS, increased VEGF expression is a negative prognostic factor and a strong predictor of metastasis and poor survival. Similarly serum VEGF is elevated in many canine cancers including OS and correlates with poor disease free interval. This supports a role for VEGF-induced angiogenesis in the development and progression of metastatic disease in dogs with OS and provides another potential anti-neoplastic mechanism for BZs.

We hypothesize that BZs have direct and indirect anti-neoplastic effects in vitro for canine OS. The aims of this study were to assess the in vitro effects of the clinically-used veterinary benzimidazoles [mebendazole (MBZ), fenbendazole (FBZ), and albendazole (ABZ)]

on a canine OS cell line. Cell lines were evaluated for dose-dependent anti-neoplastic effects on the functions of cell proliferation, cell-cycle phase distribution, and cell death. Soluble VEGF secretion and the effect on tubulin polymerization were also evaluated in vitro. Specifically, the in vitro effects of ABZ, FBZ and MBZ on D17 canine OS cells were investigated by characterizing 1) cell proliferation with an MTS assay, 2) apoptosis via flow cytometry, 3) VEGF

secretion via ELISA and 4) tubulin polymerization and 5) cell cycle distribution via flow cytometry.

The results of this study demonstrate that treatment with BZs inhibits cell proliferation in a dose and time dependent fashion. Flow cytometry demonstrates that BZ treatment induces cells arrest in G2/M and subsequently apoptosis. Mechanistically, the BZs affect microtubules by inhibition of polymerization. Additionally, exposure to the BZs results in decreased secretion of VEGF from D17 OS cells.

Our findings demonstrate that the clinically used veterinary BZs (ABZ, FBZ, and MBZ) possess anti-neoplastic activity in an OS cell line. In addition to direct effects on tubulin polymerization, cell cycle, proliferation, and cytotoxicity, BZs demonstrate indirect activity through modulation of a key pro-angiogenic cytokine. These findings are similar to what we would expect with a traditional mitotic spindle inhibitor such as a vinca alkaloid. In vitro effects are apparent at drug doses achievable in vivo with minimal expected adverse effects. This data supports the continued investigation into the use of BZs as an adjunctive therapy for canine osteosarcoma.

23:
https://www.sciencedirect.com/science/article/pii/S2211383522003999

Volume 13, Issue 2, February 2023, Pages 478-497

Title:
Benzimidazole and its derivatives as cancer therapeutics: The potential role from traditional to precision medicine

Abstract:

Cancer is the second leading cause of mortality globally which remains a continuing threat to human health today. Drug insensitivity and resistance are critical hurdles in cancer treatment; therefore, the development of new entities targeting malignant cells is considered a high priority. Targeted therapy is the

cornerstone of precision medicine. The synthesis of benzimidazole has garnered the attention of medicinal chemists and biologists due to its remarkable medicinal and pharmacological properties. Benzimidazole has a heterocyclic pharmacophore, which is an essential scaffold in drug and pharmaceutical development. Multiple studies have demonstrated the bioactivities of benzimidazole and its derivatives as potential anticancer therapeutics, either through targeting specific molecules or non-gene-specific strategies. This review provides an update on the mechanism of actions of various benzimidazole derivatives and the structure–activity relationship from conventional anticancer to precision healthcare and from bench to clinics.

24:

https://www.nature.com/articles/s41598-021-91629-x

Scientific Reports 11, Article number: 12537 (2021)

Title:

Transcriptional drug repositioning and cheminformatics approach for differentiation therapy of leukaemia cells

Abstract:

Differentiation therapy is attracting increasing interest in cancer as it can be more specific than conventional chemotherapy approaches, and it has offered new treatment options for some cancer types, such as treating acute promyelocytic leukaemia (APL) by retinoic acid. However, there is a pressing need to identify additional molecules which act in this way, both in leukaemia and other cancer types. In this work, we hence developed a novel transcriptional drug repositioning approach, based on both bioinformatics and cheminformatics components, that enables selecting such compounds in a more informed manner. We have validated the approach for leukaemia cells, and retrospectively retinoic acid was successfully identified using our method. Prospectively, the anti-parasitic compound fenbendazole was tested in leukaemia cells, and we were able to show that it can induce the differentiation of leukaemia cells to granulocytes in low concentrations of 0.1 μM and within as short a time period as 3 days. This work hence provides a systematic and validated approach for identifying small molecules for differentiation therapy in cancer.

25:

https://www.mdpi.com/1999-4923/14/8/1579

Pharmaceutics 2022, 14(8), 1579

Title:

Application of Mesoporous Silica Nanoparticles in Cancer Therapy and Delivery of Repurposed Anthelmintics for Cancer Therapy

Abstract:

This review focuses on the biomedical application of mesoporous silica nanoparticles (MSNs), mainly focusing on the therapeutic application of MSNs for cancer treatment and specifically on overcoming the challenges of currently available anthelmintics (e.g., low water solubility) as repurposed drugs for cancer treatment. MSNs, due to their promising features, such as tunable pore size and volume, ability to control the drug release, and ability to convert the crystalline state of drugs to an amorphous state, are appropriate carriers for drug delivery with the improved solubility of hydrophobic drugs. The biomedical applications of MSNs can be further improved by the development of MSN-based multimodal anticancer therapeutics (e.g., photosensitizer-, photothermal-, and chemotherapeutics-modified MSNs) and chemical modifications, such as poly ethyleneglycol (PEG)ylation. In this review, various applications of MSNs (photodynamic and sonodynamic therapies, chemotherapy, radiation therapy, gene therapy, immunotherapy) and, in particular, as the carrier of anthelmintics for cancer therapy have been discussed. Additionally, the issues related to the safety of these nanoparticles have been deeply discussed. According to the findings of this literature review, the applications of MSN nanosystems for cancer therapy are a promising approach to improving the efficacy of the diagnostic and chemotherapeutic agents. Moreover, the MSN systems seem to be an efficient strategy to further help to decrease treatment costs by reducing the drug dose.

26:

https://www.frontiersin.org/articles/10.3389/fnano.2021.693837/full

Front. Nanotechnol., 15 June 2021

Title:

Encapsulating Anti-Parasite Benzimidazole Drugs into Lipid-Coated Calcium Phosphate Nanoparticles to Efficiently Induce Skin Cancer Cell Apoptosis

Abstract:

Benzimidazole (BMZ) family of anti-worm drugs has been now repurposed as anti-cancer drugs. However, offering a general reformulation method for these drugs is essential due to their hydrophobicity and low aqueous solubility. In this work, we developed a general approach to load typical BMZ drugs as tiny nanocrystals within lipid-coated calcium phosphate (LCP) nanoparticles. BMZ drug-loaded LCP nanoparticles increased their solubility in PBS by 100–200% and significantly enhanced the anti-cancer efficacy in the treatment of B16F0 melanoma cells. These drug-LCP nanoparticles induced much more cancer cell apoptosis, generated much more reactive oxygen species (ROS) and inhibited Bcl-2 expression of cancer cells. Moreover, BMZ drug-loaded LCP nanoparticles caused morphological change and extension disruption of cancer cells, and significantly reduced migration activity, representing high possibility for inhibition of tumor dissemination and metastasis. Very advantageously, BMZ drug-loaded LCP nanoparticles did not show any obvious toxicity, Bcl-2 inhibition and morphological changes in HEK293T healthy cells. In conclusion, BMZ drug-incorporated LCP nanoformulations may be a valuable nanomedicine that is able to inhibit primary tumors and prevent tumor dissemination with minimum side effects on healthy cells and tissues.

27:

https://www.intechopen.com/chapters/85553

26 January 2023

Title:
Perspective Chapter: Prospects for Pharmacological Therapy of Hepatic Alveolar Echinococcosis

Abstract:

Often misdiagnosed as liver cancer at first, the Alveolar hydatid disease or hepatic alveolar echinococcosis is an uncommon but potentially harmful variant of the disease also synonymously known as Echinococcus multilocularis (E. Multilocularis). The major area being drastically affected is the liver, from where its later advances into the lung and brain, typically fatal if left untreated. Even if surgery is still the recommended course of treatment for the condition, drug therapy cannot be thwarted off and remains essential and vital for individuals with disease extremity. This chapter therefore aims to present a framework through which FDA-approved drugs and nano drug delivery technologies collaborate to manage progressive hepatic alveolar echinococcosis.

28:

https://www.nature.com/articles/s41598-019-42363-y

Scientific Reports 9, Article number: 6192 (2019)

Title:

Novel screening system revealed that intracellular cholesterol trafficking can be a good target for colon cancer prevention

Abstract:

In conventional research methods for cancer prevention, cell proliferation and apoptosis have been intensively targeted rather than the protection of normal or benign tumor cells from malignant transformation. In this study, we aimed to identify candidate colon cancer chemopreventive drugs based on the transcriptional activities of TCF/LEF, NF-κB and NRF2, that play important roles in the process of malignant transformation. We screened a “validated library” consisting of 1280 approved drugs to identify hit compounds that decreased TCF/LEF and NF-κB transcriptional activity and increased NRF2 transcriptional activity. Based on the evaluation of these 3 transcriptional activities, 8 compounds were identified as candidate chemopreventive drugs for colorectal cancer. One of those, itraconazole, is a clinically used anti-fungal drug and was examined in the Min mouse model of familial adenomatous polyposis. Treatment with itraconazole significantly suppressed intestinal polyp formation and the effects of itraconazole on

transcriptional activities may be exerted partly through inhibition of intracellular cholesterol trafficking. This screen represents one of the first attempts to identify chemopreventive agents using integrated criteria consisting of the inhibition of TCF/LEF, NF-κB and induction of NRF2 transcriptional activity.

29:

https://pubmed.ncbi.nlm.nih.gov/33738243/

Front Oncol. 2021 Mar 2:10:594141

Title:

Unbiased Phenotype-Based Screen Identifies Therapeutic Agents Selective for Metastatic Prostate Cancer

Abstract:

In American men, prostate cancer is the second leading cause of cancer-related death. Dissemination of prostate cancer cells to distant organs significantly worsens patients' prognosis, and currently there are no effective treatment options that can cure advanced-stage prostate cancer. In an effort to identify compounds selective for metastatic prostate cancer cells over benign prostate cancer cells or normal prostate epithelial cells, we applied a phenotype-based in vitrodrug screening method utilizing multiple prostate cancer cell lines to test 1,120 different compounds from a commercial drug library. Top drug candidates were then examined in multiple mouse xenograft models including subcutaneous tumor growth, experimental lung metastasis, and experimental bone metastasis assays. A subset of compounds including fenbendazole, fluspirilene, clofazimine, niclosamide, and suloctidil showed preferential cytotoxicity and apoptosis towards metastatic prostate cancer cells in vitro and in vivo. The bioavailability of the most discerning agents, especially fenbendazole and albendazole, was improved by formulating as micelles or nanoparticles. The enhanced forms of fenbendazole and albendazole significantly prolonged survival in mice bearing metastases, and albendazole-treated mice displayed significantly longer median survival times than paclitaxel-treated mice. Importantly, these drugs effectively targeted taxane-resistant tumors and bone metastases - two common clinical conditions in patients with aggressive prostate cancer. In summary, we find that metastatic prostate

tumor cells differ from benign prostate tumor cells in their sensitivity to certain drug classes. Taken together, our results strongly suggest that albendazole, an anthelmintic medication, may represent a potential adjuvant or neoadjuvant to standard therapy in the treatment of disseminated prostate cancer.

30:

https://www.sciencedirect.com/science/article/pii/S2468294222000910

Volume 32, 2022, 100601

Title:
Teaching an old dog new tricks: The case of Fenbendazole

Abstract:

The objective of this study is the assessment of the cytotoxic effect of fenbendazole and its commercially available formulation, which is used for its antihelmintic properties. The formulation was tested for its efficacy as well as the determination of the ingredients with proliferation assays and analytical techniques. HPLC, LC-MS and NMR confirmed the stated amount of active ingredient on the label. Dissolution studies were performed to simulate the ability of fenbendazole to dissolve adequately in the fluids of the Gastrointestinal tract, be absorbed in the circulation and reach certain areas of the human body. However, dissolution studies showed that both brands possess issues in their distribution. The in vitro drug screening exhibited potential cytotoxic effect in different types of human cancer cell lines and MDA-MB-231 human breast adenocarcinoma cells appeared to be the most sensitive with IC50 value lower than 10 μM.

31:

https://www.mdpi.com/2072-6694/11/12/2042

Cancers 2019, 11(12), 2042.

Title:
The Benzimidazole-Based Anthelmintic Parbendazole: A Repurposed Drug Candidate That Synergizes with Gemcitabine in Pancreatic Cancer

Abstract:

Pancreatic cancer (PC) is one of the most lethal, chemoresistant malignancies and it is of paramount importance to find more effective therapeutic agents. Repurposing of non-anticancer drugs may expand the repertoire of effective molecules. Studies on repurposing of benzimidazole-based anthelmintics in PC and on their interaction with agents approved for PC therapy are lacking. We analyzed the effects of four Food and Drug Administration (FDA)-approved benzimidazoles on AsPC-1 and Capan-2 pancreatic cancer cell line viability. Notably, parbendazole was the most potent benzimidazole affecting PC cell viability, with half maximal inhibitory concentration (IC50) values in the nanomolar range. The drug markedly inhibited proliferation, clonogenicity and migration of PC cell lines through mechanisms involving alteration of microtubule organization and formation of irregular mitotic spindles. Moreover, parbendazole interfered with cell cycle progression promoting G2/M arrest, followed by the emergence of enlarged, polyploid cells. These abnormalities, suggesting a mitotic catastrophe, culminated in PC cell apoptosis, are also associated with DNA damage in PC cell lines. Remarkably, combinations of parbendazole with gemcitabine, a drug employed as first-line treatment in PC, synergistically decreased PC cell viability. In conclusion, this is the first study providing evidence that parbendazole as a single agent, or in combination with gemcitabine, is a repurposing candidate in the currently dismal PC therapy.

32:

https://www.mdpi.com/2072-6694/15/4/1330

Cancers 2023, 15(4), 1330

Title:
Mebendazole Treatment Disrupts the Transcriptional Activity of Hypoxia-Inducible Factors 1 and 2 in Breast Cancer Cells

Abstract:

Breast cancer is the most diagnosed cancer in women in the world. Mebendazole (MBZ) has been demonstrated to have preclinical efficacy across multiple cancers, including glioblastoma multiforme, medulloblastoma, colon, breast, pancreatic, and thyroid cancers. MBZ was also well tolerated in a recent phase I clinical trial of adults diagnosed with glioma. The mechanisms of action reported so far for MBZ include tubulin disruption, inhibiting angiogenesis, promoting apoptosis, and maintaining stemness. To elucidate additional mechanisms of action for mebendazole (MBZ), we performed RNA sequencing of three different breast cancer cell lines treated with either MBZ or vehicle control. We compared the top genes downregulated upon MBZ treatment with expression profiles of cells treated with over 15,000 perturbagens using the clue.io online analysis tool. In addition to tubulin inhibitors, the gene expression profile that correlated most with MBZ treatment matched the profile of cells treated with known hypoxia-inducible factor (HIF-1α and -2α) inhibitors. The HIF pathway is the main driver of the cellular response to hypoxia, which occurs in solid tumors. Preclinical data support using HIF inhibitors in combination with standard of care to treat solid tumors. Therefore, we tested the hypothesis that MBZ could inhibit the hypoxia response. Using RNA sequencing and HIF-reporter assays, we demonstrate that MBZ inhibits the transcriptional activity of HIFs in breast cancer cell lines and in mouse models of breast cancer by preventing the induction of HIF-1α, HIF-2α, and HIF-1β protein under hypoxia. Taken together, our results suggest that MBZ treatment has additional therapeutic efficacy in the setting of hypoxia and warrants further consideration as a cancer therapy.

33:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8312413/

Aging (Albany NY). 2021 Jul 15; 13(13): 17407–17427

Title:
Antiparasitic mebendazole (MBZ) effectively overcomes cisplatin resistance in human ovarian cancer cells by inhibiting multiple cancer-associated signaling pathways

Abstract:

Ovarian cancer is the third most common cancer and the second most common cause of gynecologic cancer death in women. Its routine clinical management includes surgical resection and systemic therapy with chemotherapeutics. While the first-line systemic therapy requires the combined use of platinum-based agents and paclitaxel, many ovarian cancer patients have recurrence and eventually succumb to chemoresistance. Thus, it is imperative to develop new strategies to overcome recurrence and chemoresistance of ovarian cancer. Repurposing previously-approved drugs is a cost-effective strategy for cancer drug discovery. The antiparasitic drug mebendazole (MBZ) is one of the most promising drugs with repurposing potential. Here, we investigate whether MBZ can overcome cisplatin resistance and sensitize chemoresistant ovarian cancer cells to cisplatin. We first established and characterized two stable and robust cisplatin-resistant (CR) human ovarian cancer lines and demonstrated that MBZ markedly inhibited cell proliferation, suppressed cell wounding healing/migration, and induced apoptosis in both parental and CR cells at low micromole range. Mechanistically, MBZ was revealed to inhibit multiple cancer-related signal pathways including ELK/SRF, NFKB, MYC/MAX, and E2F/DP1 in cisplatin-resistant ovarian cancer cells. We further showed that MBZ synergized with cisplatin to suppress cell proliferation, induce cell apoptosis, and blunt tumor growth in xenograft tumor model of human cisplatin-resistant ovarian cancer cells. Collectively, our findings suggest that MBZ may be repurposed as a synergistic sensitizer of cisplatin in treating chemoresistant human ovarian cancer, which warrants further clinical studies.

34:

https://www.jstage.jst.go.jp/article/bpb/46/11/46_b23-00349/_html/-char/en

2023 Volume 46 Issue 11 Pages 1569-1575

Title:

Oxfendazole Induces Apoptosis in Ovarian Cancer Cells by Activating JNK/MAPK Pathway and Inducing Reactive Oxygen Species Generation

Abstract:

Ovarian cancer (OC) is one of the most common and high mortality type of cancer among women worldwide. The majority of patients with OC respond to

chemotherapy initially; however, most of them become resistant to chemotherapy and results in a high level of treatment failure in OC. Therefore, novel agents for the treatment of OC are urgently required. Benzimidazole anthelmintics might have the promising efficacy for cancer therapy as their selectively binding activity to β-tubulin. Recent study has shown that one of the benzimidazole anthelmintics oxfendazole inhibited cell growth of non-small cell lung cancer cells, revealing its anti-cancer activity; however, the pharmacological action and detailed mechanism underlying the effects of oxfendazole on OC cells remain unclear. Therefore, the present study investigated the cytotoxic effects of oxfendazole on OC cells. Our results demonstrated that oxfendazole significantly decreased the viability of OC cells. Oxfendazole inhibited the proliferation, induced G2/M phase arrest and apoptotic cell death in A2780 cells. The c-Jun N-terminal kinase (JNK)/mitogen-activated protein kinase (MAPK) pathway was activated and reactive oxygen species (ROS) generation was increased in OC cells treated with oxfendazole; oxfendazole-induced apoptosis was notably abrogated when co-treated with JNK inhibitor SP600125 and ROS scavenger N-acetyl-L-cysteine (NAC), indicating that JNK/MAPK pathway activation and ROS accumulation was associated with the oxfendazole-induced apoptosis of OC cells. Moreover, oxfendazole could also induce the proliferation inhibition and apoptosis of cisplatin resistant cells. Collectively, these results revealed that oxfendazole may serve as a potential therapeutic agent for the treatment of OC.

35:

https://www.mdpi.com/1420-3049/26/17/5118

Molecules 2021, 26(17), 5118

Title:
Anticancer Effect of Benzimidazole Derivatives, Especially Mebendazole, on Triple-Negative Breast Cancer (TNBC) and Radiotherapy-Resistant TNBC In Vivo and In Vitro

Abstract:

In this study, we aimed to evaluate the anticancer effect of benzimidazole derivatives on triple-negative breast cancer (TNBC) and investigate its underlying mechanism of action. Several types of cancer and normal breast cells including

MDA-MB-231, radiotherapy-resistant (RT-R) MDA-MB-231, and allograft mice were treated with six benzimidazole derivatives including mebendazole (MBZ). Cells were analyzed for viability, colony formation, scratch wound healing, Matrigel invasion, cell cycle, tubulin polymerization, and protein expression by using Western blotting. In mice, liver and kidney toxicity, changes in body weight and tumor volume, and incidence of lung metastasis were analyzed. Our study showed that MBZ significantly induced DNA damage, cell cycle arrest, and downregulation of cancer stem cell markers CD44 and OCT3/4, and cancer progression-related ESM-1 protein expression in TNBC and RT-R-TNBC cells. In conclusion, MBZ has the potential to be an effective anticancer agent that can overcome treatment resistance in TNBC.

36:

https://www.mdpi.com/1648-9144/58/9/1239

Medicina 2022, 58(9), 1239

Title:

Antidiabetics, Anthelmintics, Statins, and Beta-Blockers as Co-Adjuvant Drugs in Cancer Therapy

Abstract:

Over the last years, repurposed agents have provided growing evidence of fast implementation in oncology treatment such as certain antimalarial, anthelmintic, antibiotics, anti-inflammatory, antihypertensive, antihyperlipidemic, antidiabetic agents. In this study, the four agents of choice were present in our patients ’daily treatment for nonmalignant-associated pathology and have known, light toxicity profiles. It is quite common for a given patient’s daily administration schedule to include two or three of these drugs for the duration of their treatment. We chose to review the latest literature concerning metformin, employed as a first-line treatment for type 2 diabetes; mebendazole, as an anthelmintic; atorvastatin, as a cholesterol-lowering drug; propranolol, used in cardiovascular diseases as a nonspecific inhibitor of beta-1 and beta-2 adrenergic receptors. At the same time, certain key action mechanisms make them feasible antitumor agents such as for mitochondrial ETC inhibition, activation of the enzyme adenosine monophosphate-activated protein kinase, amelioration of endogenous hyperinsulinemia, inhibition of selective tyrosine kinases (i.e., VEGFR2, TNIK, and BRAF), and mevalonate

pathway inhibition. Despite the abundance of results from in vitro and in vivo studies, the only solid data from randomized clinical trials confirm metformin-related oncological benefits for only a small subset of nondiabetic patients with HER2-positive breast cancer and early-stage colorectal cancer. At the same time, clinical studies confirm metformin-related detrimental/lack of an effect for lung, breast, prostate cancer, and glioblastoma. For atorvastatin we see a clinical oncological benefit in patients and head and neck cancer, with a trend towards radioprotection of critical structures, thus supporting the role of atorvastatin as a promising agent for concomitant association with radiotherapy. Propranolol-related increased outcomes were seen in clinical studies in patients with melanoma, breast cancer, and sarcoma.

37:

https://www.mdpi.com/1999-4923/14/6/1201

Pharmaceutics 2022, 14(6), 1201

Title:
HPMA Copolymer Mebendazole Conjugate Allows Systemic Administration and Possesses Antitumour Activity In Vivo

Abstract:

Mebendazole and other benzimidazole antihelmintics, such as albendazole, fenbendazole, or flubendazole, have been shown to possess antitumour activity, primarily due to their microtubule-disrupting activity. However, the extremely poor water-solubility of mebendazole and other benzimidazoles, resulting in very low bioavailability, is a serious drawback of this class of drugs. Thus, the investigation of their antitumour potential has been limited so far to administering repeated high doses given peroral (p.o.) or to using formulations, such as liposomes. Herein, we report a fully biocompatible, water-soluble, HPMA copolymer-based conjugate bearing mebendazole (P-MBZ; Mw 28–33 kDa) covalently attached through a biodegradable bond, enabling systemic administration. Such an approach not only dramatically improves mebendazole solubility but also significantly prolongs the half-life and ensures tumour accumulation via an enhanced permeation and retention (EPR) effect in vivo. This P-MBZ has remarkable cytostatic and cytotoxic activities in EL-4 T-cell

lymphoma, LL2 lung carcinoma, and CT-26 colon carcinoma mouse cell lines in vitro, with corresponding IC50 values of 1.07, 1.51, and 0.814 µM, respectively. P-MBZ also demonstrated considerable antitumour activity in EL-4 tumour-bearing mice when administered intraperitoneal (i.p.), either as a single dose or using 3 intermittent doses. The combination of P-MBZ with immunotherapy based on complexes of IL-2 and anti-IL-2 mAb S4B6, potently stimulating activated and memory CD8+ T cells, as well as NK cells, further improved the therapeutic effect.

38:

https://bmcbioinformatics.biomedcentral.com/articles/10.1186/s12859-023-05271-7

BMC Bioinformatics 24, Article number: 149 (2023)

Title:

EZH2 as a prognostic-related biomarker in lung adenocarcinoma correlating with cell cycle and immune infiltrates

Abstract:

Backgrounds

It has been observed that high levels of enhancer of zeste homolog 2 (EZH2) expression are associated with unsatisfactory prognoses and can be found in a wide range of malignancies. However, the effects of EZH2 on Lung Adenocarcinoma (LUAD) remain elusive. Through the integration of bioinformatic analyses, the present paper sought to ascertain the effects of EZH2 in LUAD.

Methods

The TIMER and UALCAN databases were applied to analyze mRNA and protein expression data for EZH2 in LUAD. The result of immunohistochemistry was obtained from the HPA database, and the survival curve was drawn according to the library provided by the HPA database. The LinkedOmics database was utilized to investigate the co-expressed genes and signal transduction pathways with EZH2. Up- and down-regulated genes from The Linked Omics database were introduced to the CMap database to predict potential drug targets for LUAD using the CMap database. The association between EZH2 and cancer-infiltrating immunocytes was studied through TIMER and TISIDB. In addition, this paper explores the

relationship between EZH2 mRNA expression and NSCLC OS using the Kaplan–Meier plotter database to further validate and complement the research. Furthermore, the correlation between EZH2 expression and EGFR genes, KRAS genes, BRAF genes, and smoking from the Cancer Genome Atlas (TCGA) database is analyzed.

Results

In contrast to paracancer specimens, the mRNA and protein levels of EZH2 were higher in LUAD tissues. Significantly, high levels of EZH2 were associated with unsatisfactory prognoses in LUAD patients. Additionally, the coexpressed genes of EZH2 were predominantly associated with numerous cell growth-associated pathways, including the cell cycle, DNA replication, RNA transport, and the p53 signaling pathway, according to Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathways. The results of TCGA database revealed that the expression of EZH2 was lower in normal tissues than in lung cancer tissues ($p < 0.05$). Smoking was associated with elevated EZH2 expression ($p < 0.001$). EZH2 was highly expressed in lung cancers with positive KRAS expression, and the correlation was significant in lung adenocarcinoma ($r = 0.3129$, $p < 0.001$). CMap was applied to determine the top 15 positively correlated drugs/molecules and the top 15 negatively correlated drugs/molecules. MK-1775, MK-5108, fenbendazole, albendazole, BAY-K8644, evodiamine, purvalanol-a, mycophenolic-acid, PHA-793887, and cyclopamine are potential drugs for patients with lung adenocarcinoma and high EZH2 expression.

Conclusions

Highly expressed EZH2 is a predictor of a suboptimal prognosis in LUAD and may serve as a prognostic marker and target gene for LUAD. The underlying cause may be associated with the synergistic effect of KRAS, immune cell infiltration, and metabolic processes.

39:
https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2022.1037341/full

Front. Pharmacol., 29 November 2022

Title:

Targeting glycolysis in non-small cell lung cancer: Promises and challenges

Abstract:

Metabolic disturbance, particularly of glucose metabolism, is a hallmark of tumors such as non-small cell lung cancer (NSCLC). Cancer cells tend to reprogram a majority of glucose metabolism reactions into glycolysis, even in oxygen-rich environments. Although glycolysis is not an efficient means of ATP production compared to oxidative phosphorylation, the inhibition of tumor glycolysis directly impedes cell survival and growth. This review focuses on research advances in glycolysis in NSCLC and systematically provides an overview of the key enzymes, biomarkers, non-coding RNAs, and signaling pathways that modulate the glycolysis process and, consequently, tumor growth and metastasis in NSCLC. Current medications, therapeutic approaches, and natural products that affect glycolysis in NSCLC are also summarized. We found that the identification of appropriate targets and biomarkers in glycolysis, specifically for NSCLC treatment, is still a challenge at present. However, LDHB, PDK1, MCT2, GLUT1, and PFKM might be promising targets in the treatment of NSCLC or its specific subtypes, and DPPA4, NQO1, GAPDH/MT-CO1, PGC-1α, OTUB2, ISLR, Barx2, OTUB2, and RFP180 might be prognostic predictors of NSCLC. In addition, natural products may serve as promising therapeutic approaches targeting multiple steps in glycolysis metabolism, since natural products always present multi-target properties. The development of metabolic intervention that targets glycolysis, alone or in combination with current therapy, is a potential therapeutic approach in NSCLC treatment. The aim of this review is to describe research patterns and interests concerning the metabolic treatment of NSCLC.

40:

https://www.researchgate.net/profile/Baki-Bhaskar/publication/320182958_Synthesis_and_biological_evaluation_of_some_new_class_of_chromenoimidazole_derivatives_as_probable_anti_cancer_agents/lin

ks/5b4d9feaa6fdcc8dae249d5c/Synthesis-and-biological-evaluation-of-some-new-class-of-chromenoimidazole-derivatives-as-probable-anti-cancer-agents.pdf

Vol. 10 | No. 4 |1194-1212 |

Title:
SYNTHESIS AND BIOLOGICAL EVALUATION OF SOME NEW CLASS OF CHROMENOIMIDAZOLE DERIVATIVES AS PROBABLE ANTI CANCER AGENTS

Abstract:
A new series of compounds with benzimidazole moiety fused pyran ring derivatives were prepared by a simple chemical methodology. Here we have designed and reported a one pot condensation of 6-hydroxy-5-formyl benzimidazole with different N substituted cyano acetamide derivatives to get novel chromeno-benzimidazole molecules which were characterized by different analytical tools and docking study of these compounds against a lung cancer target protein(PDB Id : 3POZ). Most of the compounds exhibited good potency in inhibiting the cancer protein.

41:

https://www.sciencedirect.com/science/article/pii/S2211715623002527

Volume 6, December 2023, 101013

Title:
A critical review of benzimidazole: Sky-high objectives towards the lead molecule to predict the future in medicinal chemistry

Abstract:

Out of several heterocyclic templates, the use of a Benzimidazole (BZ) scaffold is immensely observed. This fused heterocycle comprises two ring nitrogen atoms placed at 1st and 3rd position, in which the 1st nitrogen is connected to hydrogen that gets released to exhibit the acidic property. The use of BZ for the purpose of

making clinically useful compounds was started in the year of 1944. BZ derivatives have been consistently used as effective chemotherapeutic agents to treat a diverse range of disorders. Apart from their clinical usefulness, BZ-based compounds also confer high safety, bio-availability, and stability. Out of several clinical conditions, cancer, and helminthiasis are a few where this template has been maximally utilized. The present review emphasizes chronologically the developments of BZ-based compounds in the entire scope of medicinal chemistry as antibacterial, anticancer, antifungal, anti-inflammatory, anti-HIV (human immunodeficiency virus), anticonvulsant, antioxidant, antidiabetic, antitubercular, antileishmanial, antimalarial, anti-histaminic. This review also covers patents on BZ of clinical importance till 2020. The primary objective of this review is to develop a comprehensive SAR (structure–activity relationship), which in turn assists the medicinal chemist to come up with novel ideas, while being implemented could produce novel compounds with enormous potential.

42:

https://www.mdpi.com/2072-6694/13/16/3946

Cancers 2021, 13(16), 3946

Title:
Drug Repurposing, an Attractive Strategy in Pancreatic Cancer Treatment: Preclinical and Clinical Updates

Abstract:
Pancreatic cancer (PC) is one of the deadliest malignancies worldwide, since patients rarely display symptoms until an advanced and unresectable stage of the disease. Current chemotherapy options are unsatisfactory and there is an urgent need for more effective and less toxic drugs to improve the dismal PC therapy. Repurposing of non-oncology drugs in PC treatment represents a very promising therapeutic option and different compounds are currently being considered as candidates for repurposing in the treatment of this tumor. In this review, we provide an update on some of the most promising FDA-approved, non-oncology, repurposed drug candidates that show prominent clinical and preclinical data in pancreatic cancer. We also focus on proposed mechanisms of action and known molecular targets that they modulate in PC. Furthermore, we provide an explorative bioinformatic analysis, which suggests that some of the PC repurposed drug candidates have additional, unexplored, oncology-relevant targets. Finally, we

discuss recent developments regarding the immunomodulatory role displayed by some of these drugs, which may expand their potential application in synergy with approved anticancer immunomodulatory agents that are mostly ineffective as single agents in PC.

43:

https://journals.sagepub.com/doi/full/10.1369/00221554211025482

Volume 69, Issue 12
Title:

Repurposing of Anticancer Stem Cell Drugs in Brain Tumors

Abstract:
Brain tumors in adults may be infrequent when compared with other cancer etiologies, but they remain one of the deadliest with bleak survival rates. Current treatment modalities encompass surgical resection, chemotherapy, and radiotherapy. However, increasing resistance rates are being witnessed, and this has been attributed, in part, to cancer stem cells (CSCs). CSCs are a subpopulation of cancer cells that reside within the tumor bulk and have the capacity for self-renewal and can differentiate and proliferate into multiple cell lineages. Studying those CSCs enables an increasing understanding of carcinogenesis, and targeting CSCs may overcome existing treatment resistance. One approach to weaponize new drugs is to target these CSCs through drug repurposing which entails using drugs, which are Food and Drug Administration–approved and safe for one defined disease, for a new indication. This approach serves to save both time and money that would otherwise be spent in designing a totally new therapy. In this review, we will illustrate drug repurposing strategies that have been used in brain tumors and then further elaborate on how these approaches, specifically those that target the resident CSCs, can help take the field of drug repurposing to a new level.

44:

https://pubs.acs.org/doi/full/10.1021/acs.jmedchem.2c00646

J. Med. Chem. 2022, 65, 19, 12883–12894

Title:

ID-Checker Technology for the Highly Selective Macroscale Delivery of Anticancer Agents to the Cancer Cells

Abstract:
Cancer cells deploy several glucose transport protein (GLUT) channels on the cell membranes to increase glucose uptake. Cancer cells die within 24 h in the absence of glucose. Thus, preventing the deployment of GLUT channels can deprive them of glucose, resulting in apoptosis within 24 h. Herein, we developed the ID-Checker with a glucose tag that ensures its highly specific macroscale delivery of anticancer agents to the cancer cells through the GLUT channels. ID-Checkerpresented here showed IC50 values of 0.17–0.27 and 3.34 μM in cancer and normal cell lines, respectively. ID-Checker showed a selectivity index of 12.5–20.2, which is about 10–20 times higher than that of known anticancer agents such as colchicine. ID-Checker inhibits the microtubule formation, which results in the prevention of the deployment of GLUT channels in 6 h and kills the cancer cells within 24 h without any damage to normal cells.

45:

https://www.mdpi.com/2072-6694/14/14/3368

Cancers 2022, 14(14), 3368

Title:
Drug Repurposing to Enhance Antitumor Response to PD-1/PD-L1 Immune Checkpoint Inhibitors

Abstract:

Monoclonal antibodies targeting the PD-1/PD-L1 immune checkpoint have considerably improved the treatment of some cancers, but novel drugs, new combinations, and treatment modalities are needed to reinvigorate immunosurveillance in immune-refractory tumors. An option to elicit antitumor

immunity against cancer consists of using approved and marketed drugs known for their capacity to modulate the expression and functioning of the PD-1/PD-L1 checkpoint. Here, we have reviewed several types of drugs known to alter the checkpoint, either directly via the blockade of PD-L1 or indirectly via an action on upstream effectors (such as STAT3) to suppress PD-L1 transcription or to induce its proteasomal degradation. Specifically, the repositioning of the approved drugs liothyronine, azelnidipine (and related dihydropyridine calcium channel blockers), niclosamide, albendazole/flubendazole, and a few other modulators of the PD-1/PD-L1 checkpoint (repaglinide, pimozide, fenofibrate, lonazolac, propranolol) is presented. Their capacity to bind to PD-L1 or to repress its expression and function offer novel perspectives for combination with PD-1 targeted biotherapeutics. These known and affordable drugs could be useful to improve the therapy of cancer.

46:

https://www.frontiersin.org/journals/pharmacology/articles/10.3389/fphar.2021.670081/full

Front. Pharmacol., 07 July 2021

Title:

Triclabendazole Induces Pyroptosis by Activating Caspase-3 to Cleave GSDME in Breast Cancer Cells

Abstract:

Pyroptosis is a form of programmed cell death, in which gasdermin E (GSDME) plays an important role in cancer cells, which can be induced by activated caspase-3 on apoptotic stimulation. Triclabendazole is a new type of imidazole in fluke resistance and has been approved by the FDA for the treatment of fascioliasis and its functions partially acting through apoptosis-related mechanisms. However, it remains unclear whether triclabendazole has obvious anti-cancer effects on breast cancer cells. In this study, to test the function of triclabendazole on breast cancer, we treated breast cancer cells with triclabendazole and found that triclabendazole induced lytic cell death in MCF-7 and MDA-MB-231, and the dying cells became swollen with evident large bubbles, a typical sign of pyroptosis. Triclabendazole activates apoptosis by regulating the apoptoic protein levels including Bax, Bcl-2, and enhanced cleavage of caspase-8/9/3/7 and PARP. In addition, enhanced cleavage of GSDME was also observed, which indicates the secondary

necrosis/pyroptosis is further induced by active caspase-3. Consistent with this, triclabendazole-induced GSDME–N-terminal fragment cleavage and pyroptosis were reduced by caspase-3–specific inhibitor (Ac-DEVD-CHO) treatment. Moreover, triclabendazole induced reactive oxygen species (ROS) elevation and increased JNK phosphorylation and lytic cell death, which could be rescued by the ROS scavenger (NAC), suggesting that triclabendazole-induced GSDME-dependent pyroptosis is related to the ROS/JNK/Bax-mitochondrial apoptotic pathway. Besides, we showed that triclabendazole significantly reduced the tumor volume by promoting the cleavage of caspase-3, PARP, and GSDME in the xenograft model. Altogether, our results revealed that triclabendazole induces GSDME-dependent pyroptosis by caspase-3 activation at least partly through augmenting the ROS/JNK/Bax-mitochondrial apoptotic pathway, providing insights into this on-the-market drug in its potential new application in cancer treatment.

47:

https://www.mdpi.com/2227-9059/9/5/579

Biomedicines 2021, 9(5), 579

Title:

Identifying Novel Actionable Targets in Colon Cancer

Abstract:

Colorectal cancer is the fourth cause of death from cancer worldwide, mainly due to the high incidence of drug-resistance toward classic chemotherapeutic and newly targeted drugs. In the last decade or so, the development of novel high-throughput approaches, both genome-wide and chemical, allowed the identification of novel actionable targets and the development of the relative specific inhibitors to be used either to re-sensitize drug-resistant tumors (in combination with chemotherapy) or to be synthetic lethal for tumors with specific oncogenic mutations. Finally, high-throughput screening using FDA-approved libraries of “known” drugs uncovered new therapeutic applications of drugs (used alone or in combination) that have been in the clinic for decades for treating non-cancerous diseases (re-positioning or re-purposing approach). Thus, several novel actionable targets have been identified and some of them are already being tested in clinical trials, indicating that high-throughput approaches, especially those involving drug

re-positioning, may lead in a near future to significant improvement of the therapy for colon cancer patients, especially in the context of a personalized approach, i.e., in defined subgroups of patients whose tumors carry certain mutations.

48:

http://www.ijper.org/sites/default/files/IndJPhaEdRes_54_2-432.pdf

Indian Journal of Pharmaceutical Education and Research | Vol 54 | Issue 2

Title:
N-(2-(1H-benzo[d]imidazol-2-yl)Phenyl)-2- (Substituted-styryl)Aniline as Anti-proliferative Agents: Rejuvenating the Importance of Low Molecular Weight Ligands in Oncotherapeutics

Abstract:

Background: The rationale behind the study involved that in individuality benzimidazole- based molecules demonstrates significant anti-proliferative activity; chalcone molecules like xanthohumol are known to express noteworthy anti-cancer activity; benzamide derived products show remarkable inhibition of HDAC (an emerging anti-proliferative target) and styrene-based compounds possesses notable anti-tumor activity. Materials and Methods: In this research, an attempt was made to synthesize and characterize a series of hybridized molecules of the prototype (E)-N-(2-(1H-benzo[d]imidazol-2-yl) phenyl)-2-(substituted-styryl)aniline which comprises of a benzimidazole function; along with a chalcone (or styryl) moiety linked by a benzamide. The study involved screening of the novel derivatives against non-small cell lung cancer cell line (H460; ATCC: HTB177) and human colorectal cancer cell line (HCT116; ATCC: CCL-247) using Propidium Iodide assay. In silico docking study was also performed against protein tyrosine kinase (PDB ID: 2J5F) to determine the probable mechanism of action of the novel compounds. Results: The study reflected the profound role and positions of substitution on the phenyl moiety of the benzimidazole system. The compound DSTYR4 displayed most potent anti- proliferative activity with IC50 values of 2.98 μM against HCT116 cell line and 5.15 μM against H460 cell line. Conclusion: The research fruitfully rejuvenates the potentials and importance of small molecular weight ligands for experimental oncology.

Category 2: Concerns and/or skpetical (articles 49-72)

[Jump to Category 1: In favor]

49:

https://karger.com/cro/article/14/2/886/820730

Case Rep Oncol (2021) 14 (2): 886–891.

Title:

Drug-Induced Liver Injury in a Patient with Nonsmall Cell Lung Cancer after the Self-Administration of Fenbendazole Based on Social Media Information

Abstract:

Fenbendazole is a benzimidazole anthelmintic agent, with a broad antiparasitic range in animals such as dogs and pigs. The agent is also reported to exert antitumor effects and inhibit microtubule-associated tubulin polymerization, but its safety and tolerability profile in humans remains unclear. An 80-year-old female patient with advanced nonsmall cell lung cancer (NSCLC) was started on pembrolizumab monotherapy. The patient experienced severe liver injury 9 months later. An interview with her and her family revealed that she had been taking fenbendazole for a month, solely based on social media reports suggesting its effectiveness against cancer. After discontinuation of the self-administration of fenbendazole, the patient's liver dysfunction spontaneously resolved. The antitumor inhibitory effects of fenbendazole have been reported; however, she did not experience tumor shrinkage. This is the first case report of a patient with advanced NSCLC who self-administered the anthelmintic, fenbendazole. Twitter and Facebook are online social media platforms which have been constructively used to exchange information among cancer patients. However, sources of medical information on these platforms are often unproven, and it is difficult for nonmedical professionals to accurately select and filter complex medical information. Physicians should enquire patients about self-administration of orally ingested products, including dietary supplements, herbs, or bioactive compounds, in cases of unexpected adverse reactions.

50:

https://onlinelibrary.wiley.com/doi/full/10.1002/bkcs.12519

Article. 08 April 2022.

Title:

Investigation of benzimidazole anthelmintics as oral anticancer agents

Abstract:

Recently, there has been social controversy regarding whether benzimidazole anthelmintic drugs can be used as anticancer drugs. On this note, we wish to address the use of current benzimidazole anthelmintic drugs for the treatment of cancer patients. We explored the anticancer efficacy of benzimidazole anthelmintic drugs in vitro and their mechanism of action. We also conducted pharmacokinetic studies of two benzimidazole anthelmintics and assessed the predictive systemic efficacy. Finally, we present the anticancer efficacy of benzimidazole anthelmintics' putative metabolites from hydrolysis. Our data suggest that benzimidazole anthelmintic drugs are not expected to show systemic anticancer efficacy in vivo due to poor pharmacokinetic parameters. Therefore, patients should not consider oxibendazole or fenbendazole as cancer treatment option.

51:

https://www.mdpi.com/1467-3045/44/10/338

Curr. Issues Mol. Biol. 2022, 44(10), 4977-4986

Title:
Exceptional Repositioning of Dog Dewormer: Fenbendazole Fever

Abstract:

Fenbendazole (FZ) is a benzimidazole carbamate drug with broad-spectrum antiparasitic activity in humans and animals. The mechanism of action of FZ is associated with microtubular polymerization inhibition and glucose uptake

blockade resulting in reduced glycogen stores and decreased ATP formation in the adult stages of susceptible parasites. A completely cured case of lung cancer became known globally and greatly influenced the cancer community in South Korea. Desperate Korean patients with cancer began self-administering FZ without their physician's knowledge, which interfered with the outcome of the cancer treatment planned by their oncologists. On the basis of presented evidence, this review provides valuable information from PubMed, Naver, Google Scholar, and Social Network Services (SNS) on the effects of FZ in a broad range of preclinical studies on cancer. In addition, we suggest investigating the self-administration of products, including supplements, herbs, or bioactive compounds, by patients to circumvent waiting for long and costly FZ clinical trials.

52:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8255490/

Korean J Parasitol. 2021 Jun; 59(3): 189–225.

Title:
Albendazole and Mebendazole as Anti-Parasitic and Anti-Cancer Agents: an Update

Abstract:

The use of albendazole and mebendazole, i.e., benzimidazole broad-spectrum anthelmintics, in treatment of parasitic infections, as well as cancers, is briefly reviewed. These drugs are known to block the microtubule systems of parasites and mammalian cells leading to inhibition of glucose uptake and transport and finally cell death. Eventually they exhibit ovicidal, larvicidal, and vermicidal effects on parasites, and tumoricidal effects on hosts. Albendazole and mebendazole are most frequently prescribed for treatment of intestinal nematode infections (ascariasis, hookworm infections, trichuriasis, strongyloidiasis, and enterobiasis) and can also be used for intestinal tapeworm infections (taeniases and hymenolepiasis). However, these drugs also exhibit considerable therapeutic effects against tissue nematode/cestode infections (visceral, ocular, neural, and cutaneous larva migrans, anisakiasis, trichinosis, hepatic and intestinal capillariasis, angiostrongyliasis, gnathostomiasis, gongylonemiasis, thelaziasis,

dracunculiasis, cerebral and subcutaneous cysticercosis, and echinococcosis). Albendazole is also used for treatment of filarial infections (lymphatic filariasis, onchocerciasis, loiasis, mansonellosis, and dirofilariasis) alone or in combination with other drugs, such as ivermectin or diethylcarbamazine. Albendazole was tried even for treatment of trematode (fascioliasis, clonorchiasis, opisthorchiasis, and intestinal fluke infections) and protozoan infections (giardiasis, vaginal trichomoniasis, cryptosporidiosis, and microsporidiosis). These drugs are generally safe with few side effects; however, when they are used for prolonged time (>14–28 days) or even only 1 time, liver toxicity and other side reactions may occur. In hookworms, Trichuris trichiura, possibly Ascaris lumbricoides, Wuchereria bancrofti, and Giardia sp., there are emerging issues of drug resistance. It is of particular note that albendazole and mebendazole have been repositioned as promising anti-cancer drugs. These drugs have been shown to be active in vitro and in vivo (animals) against liver, lung, ovary, prostate, colorectal, breast, head and neck cancers, and melanoma. Two clinical reports for albendazole and 2 case reports for mebendazole have revealed promising effects of these drugs in human patients having variable types of cancers. However, because of the toxicity of albendazole, for example, neutropenia due to myelosuppression, if high doses are used for a prolonged time, mebendazole is currently more popularly used than albendazole in anti-cancer clinical trials.

53:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10482585/

J Gynecol Oncol. 2023 Sep; 34(5): e58.

Title:

Anti-cancer effect of fenbendazole-incorporated PLGA nanoparticles in ovarian cancer

Abstract:

Objective

Fenbendazole (FZ) has potential anti-cancer effects, but its poor water solubility limits its use for cancer therapy. In this study, we investigated the anti-cancer effect of FZ with different drug delivery methods on epithelial ovarian cancer (EOC) in both in vitro and in vivo models.

Methods

EOC cell lines were treated with FZ and cell proliferation was assessed. The effect of FZ on tumor growth in cell line xenograft mouse model of EOC was examined according to the delivery route, including oral and intraperitoneal administration. To improve the systemic delivery of FZ by converting fat-soluble drugs to hydrophilic, we prepared FZ-encapsulated poly(D,L-lactide-co-glycolide) acid (PLGA) nanoparticles (FZ-PLGA-NPs). We investigated the preclinical efficacy of FZ-PLGA-NPs by analyzing cell proliferation, apoptosis, and in vivo models including cell lines and patient-derived xenograft (PDX) of EOC.

Results

FZ significantly decreased cell proliferation of both chemosensitive and chemoresistant EOC cells. However, in cell line xenograft mouse models, there was no effect of oral FZ treatment on tumor reduction. When administered intraperitoneally, FZ was not absorbed but aggregated in the intraperitoneal space. We synthesized FZ-PLGA-NPs to obtain water solubility and enhance drug absorption. FZ-PLGA-NPs significantly decreased cell proliferation in EOC cell lines. Intravenous injection of FZ-PLGA-NP in xenograft mouse models with HeyA8 and HeyA8-MDR significantly reduced tumor weight compared to the control group. FZ-PLGA-NPs showed anti-cancer effects in PDX model as well.

Conclusions

FZ-incorporated PLGA nanoparticles exerted significant anti-cancer effects in EOC cells and xenograft models including PDX. These results warrant further investigation in clinical trials.

54:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7458798/

Immune Netw. 2020 Aug; 20(4): e29.

Title:
The Antitumor Potentials of Benzimidazole Anthelmintics as Repurposing Drugs

Abstract:

The development of refractory tumor cells limits therapeutic efficacy in cancer by activating mechanisms that promote cellular proliferation, migration, invasion, metastasis, and survival. Benzimidazole anthelmintics have broad-spectrum action to remove parasites both in human and veterinary medicine. In addition to being antiparasitic agents, benzimidazole anthelmintics are known to exert anticancer activities, such as the disruption of microtubule polymerization, the induction of apoptosis, cell cycle (G2/M) arrest, anti-angiogenesis, and blockage of glucose transport. These antitumorigenic effects even extend to cancer cells resistant to approved therapies and when in combination with conventional therapeutics, enhance anticancer efficacy and hold promise as adjuvants. Above all, these anthelmintics may offer a broad, safe spectrum to treat cancer, as demonstrated by their long history of use as antiparasitic agents. The present review summarizes central literature regarding the anticancer effects of benzimidazole anthelmintics, including albendazole, parbendazole, fenbendazole, mebendazole, oxibendazole, oxfendazole, ricobendazole, and flubendazole in cancer cell lines, animal tumor models, and clinical trials. This review provides valuable information on how to improve the quality of life in patients with cancers by increasing the treatment options and decreasing side effects from conventional therapy.

55:

https://www.mdpi.com/1467-3045/45/11/560

Curr. Issues Mol. Biol. 2023, 45(11), 8925-8938

Title:
Fenbendazole Exhibits Differential Anticancer Effects In Vitro and In Vivo in Models of Mouse Lymphoma

Abstract:

Fenbendazole (FBZ) has been safely used as an antiparasitic agent in animals for decades, and the anticancer effects of FBZ have been studied through various mechanisms. However, there is a lack of in vivo studies that include lymphoma. Therefore, this study examined the effects of FBZ on EL-4 cells and a mouse T lymphoma model. FBZ induced G2/M phase arrest in EL-4 cells, resulting in cell death and decreased metabolic activity. However, FBZ had no anticancer effects on an EL-4 mouse lymphoma model in vivo, as evident by rapid weight loss and tumor growth comparable to the control. The FBZ-treated EL-4 cells expressed higher levels of PD-L1 and CD86, which are associated with T cell immunity in the tumor microenvironment (TME), than the controls. Furthermore, the hematoxylin and eosin staining of the FBZ-treated tumor tissues showed a starry sky pattern, which is seen in actively proliferating cancer tissues, and an immunohistochemical analysis revealed a high percentage of immunosuppressive M2 macrophages. These changes in the immune activity in the TME contradict the results of the in vitro experiments, and further studies are needed to determine the detailed mechanisms by which FBZ induces these responses.

56:

https://www.mdpi.com/2072-6694/14/19/4601

Cancers 2022, 14(19), 4601.

Title:
Repurposing of Benzimidazole Anthelmintic Drugs as Cancer Therapeutics

Abstract:

Benzimidazoles have shown significant promise for repurposing as a cancer therapy. The aims of this review are to investigate the possibilities and limitations of the anti-cancer effects of benzimidazole anthelmintics and to suggest ways to overcome these limitations. This review included studies on the anti-cancer effects of 11 benzimidazoles. Largely divided into three parts, i.e., preclinical anti-cancer effects, clinical anti-cancer effects, and pharmacokinetic properties, we examine the characteristics of each benzimidazole and attempt to elucidate its key properties. Although many studies have demonstrated the anti-cancer effects of benzimidazoles, there is limited evidence regarding their effects in clinical settings.

This might be because the clinical trials conducted using benzimidazoles failed to restrict their participants with specific criteria including cancer entities, cancer stages, and genetic characteristics of the participants. In addition, these drugs have limitations including low bioavailability, which results in insufficient plasma concentration levels. Additional studies on whole anti-cancer pathways and development strategies, including formulations, could result significant enhancements of the anti-cancer effects of benzimidazoles in clinical situations.

57:

https://www.jstage.jst.go.jp/article/bpb/45/2/45_b21-00697/_article

2022 Volume 45 Issue 2 Pages 184-193

Title:

Fenbendazole Suppresses Growth and Induces Apoptosis of Actively Growing H4IIE Hepatocellular Carcinoma Cells via p21-Mediated Cell-Cycle Arrest

Abstract:

Bendimidazole anthelmintics (BAs) have gained interest for their anticancer activity. The anticancer activity is mediated via multiple intracellular changes, which are not consistent under different conditions even in the same cells. We investigated the anticancer activity of fenbendazole (FZ, one of BAs) under two different growth conditions. The growth rate of H4IIE cells was dose-dependently decreased by FZ only in actively growing cells but not in fully confluent quiescent cells. Apoptosis-associated changes were also induced by FZ in actively growing cells. Markers of autophagy were not changed by FZ. The number of cells was markedly increased in sub-G1 phase but decreased in S- and G2/M phases by FZ. FZ up-regulated p21 (an inhibitor of cyclin-CDK) but suppressed the expression of cell cycle-promoting proteins (cyclin D1 and cyclin B1). FZ did not affect integrin αV or n-cadherin expression as well as cell migration. Glycolytic changes (glucose consumption and lactate production) and the generation of reactive oxygen species (ROS) were not affected by FZ. Although the activity of mitogen-activated protein kinases (MAPKs) was altered by FZ, the inhibition of MAPKs did not affect the pro-apoptotic activity of FZ. Taken together, FZ selectively suppressed the growth of cells via p21-mediated cell cycle arrest at G1/S and G2/M, and resulted in apoptosis only in actively growing cells but not in quiescent cells. Glucose

metabolism, ROS generation, and MAPKs are unlikely targets of FZ at least in H4IIE rat hepatocellular carcinoma cells used in this study.

58:

https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2022.942045/full

Front. Oncol., 27 October 2022

Title:
How cancer patients get fake cancer information: From TV to YouTube, a qualitative study focusing on fenbendazole scandle

Abstract:

Background: Korean society has faced challenges in communicating with cancer patients about false information related to complementary alternative medicine. As the situation has become severe with the 2020 fenbendazole scandal, the demand for reliable information from health authorities has increased.
Objectives: This study aimed to examine patients ʼacquisition patterns and perception of false information by presenting empirical evidence to help health authorities enable effective preemptive responses in the cancer communication context.

Method: We conducted a focus group interview with 21 lung cancer patients who were informed about fenbendazole based on a semi-structured questionnaire with three categories: 1) acquisition channel of the general cancer information and the false information, 2) quality of obtained information, and 3) perception toward it. The interviewees, comprising 13 men and eight women, were aged 50 or older. Participants ʼcurrent stages of cancer were stages one, three, and four and there were seven people in each stage.

Results: 1) Acquisition channel: Participants had their first encounter with false information through the TV, while the channels to obtain general cancer information were through Internet communities or portal sites. YouTube was a second channel to actively search for information regardless of the information type. 2) Information quality: participants had only fragmented information through media. 3) Perception: Most patients had a negative attitude toward complementary and alternative medicine information such as fenbendazole. They perceive that it

needs to be verified by experts and filtered according to their arbitrary criteria. They had vague expectations based on a hope for “what if” at the same time.

Conclusions: Despite the complex media environment, traditional or legacy media is an important channel to encounter information. YouTube is independent of other media as an “active” information-seeking channel. Patients required the appropriate intervention of experts and governments because they perceived that they had obtained irrational and unreliable information from the media. Suggestions are made about how health authorities can construct an effective communication system focusing on the user to prevent patients from getting false cancer information.

59:

https://www.mdpi.com/2072-6694/11/9/1284

Cancers 2019, 11(9), 1284

Title:

Mebendazole as a Candidate for Drug Repurposing in Oncology: An Extensive Review of Current Literature

Abstract:

Anticancer treatment efficacy is limited by the development of refractory tumor cells characterized by increased expression and activity of mechanisms promoting survival, proliferation, and metastatic spread. The present review summarizes the current literature regarding the use of the anthelmintic mebendazole (MBZ) as a repurposed drug in oncology with a focus on cells resistant to approved therapies, including so called “cancer stem cells”. Mebendazole meets many of the characteristics desirable for a repurposed drug: good and proven toxicity profile, pharmacokinetics allowing to reach therapeutic concentrations at disease site, ease of administration and low price. Several in vitro studies suggest that MBZ inhibits a wide range of factors involved in tumor progression such as tubulin polymerization, angiogenesis, pro-survival pathways, matrix metalloproteinases, and multi-drug resistance protein transporters. Mebendazole not only exhibits direct cytotoxic activity, but also synergizes with ionizing radiations and different

chemotherapeutic agents and stimulates antitumoral immune response. In vivo, MBZ treatment as a single agent or in combination with chemotherapy led to the reduction or complete arrest of tumor growth, marked decrease of metastatic spread, and improvement of survival. Further investigations are warranted to confirm the clinical anti-neoplastic activity of MBZ and its safety in combination with other drugs in a clinical setting.

60:

https://academic.oup.com/neuro-oncology/article/13/9/974/1096119

Neuro-Oncology, Volume 13, Issue 9, September 2011, Pages 974–982

Title:

Antiparasitic mebendazole shows survival benefit in 2 preclinical models of glioblastoma multiforme

Abstract:

Glioblastoma multiforme (GBM) is the most common and aggressive brain cancer, and despite treatment advances, patient prognosis remains poor. During routine animal studies, we serendipitously observed that fenbendazole, a benzimidazole antihelminthic used to treat pinworm infection, inhibited brain tumor engraftment. Subsequent in vitro and in vivo experiments with benzimidazoles identified mebendazole as the more promising drug for GBM therapy. In GBM cell lines, mebendazole displayed cytotoxicity, with half-maximal inhibitory concentrations ranging from 0.1 to 0.3 μM. Mebendazole disrupted microtubule formation in GBM cells, and in vitro activity was correlated with reduced tubulin polymerization. Subsequently, we showed that mebendazole significantly extended mean survival up to 63% in syngeneic and xenograft orthotopic mouse glioma models. Mebendazole has been approved by the US Food and Drug Administration for parasitic infections, has a long track-record of safe human use, and was effective in our animal models with doses documented as safe in humans. Our findings indicate that mebendazole is a possible novel anti-brain tumor therapeutic that could be further tested in clinical trials.

61:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4096024/

Ecancermedicalscience. 2014; 8: 443.
Title:
Repurposing Drugs in Oncology (ReDO)—mebendazole as an anti-cancer agent

Abstract:

Mebendazole, a well-known anti-helminthic drug in wide clinical use, has anti-cancer properties that have been elucidated in a broad range of pre-clinical studies across a number of different cancer types. Significantly, there are also two case reports of anti-cancer activity in humans. The data are summarised and discussed in relation to suggested mechanisms of action. Based on the evidence presented, it is proposed that mebendazole would synergise with a range of other drugs, including existing chemotherapeutics, and that further exploration of the potential of mebendazole as an anti-cancer therapeutic is warranted. A number of possible combinations with other drugs are discussed in the Appendix.

62:

https://journals.lww.com/ajg/fulltext/2023/10001/s3542_is_it_safe_to_take_your_dog_s_medication__a.3769.aspx

The American Journal of Gastroenterology 118(10S):p S2316-S2317, October 2023.

Title:

S3542 Is It Safe to Take Your Dog's Medication? A Case of Severe Drug-Induced Liver Injury Due to Self-Administration of Fenbendazole

Abstract:
Fenbendazole is an anthelmintic agent with a broad antiparasitic range in animals like dogs. It has been gaining popularity on social media for anticancer effects; however, these, along with its safety profile in humans have not been scientifically established. We report a case of severe drug-induced liver injury (DILI) from self-administration of fenbendazole.

63:

https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0275620

October 4, 2022

Title:

Experience with and perceptions of non-prescription anthelmintics for cancer treatments among cancer patients in South Korea: A cross-sectional survey

Abstract:

Although non-prescription anthelmintics are used by many patients as cancer treatment in South Korea, data regarding the experiences or perceptions of these drugs are lacking. This study aimed to investigate the repercussions of non-prescription anthelmintics for cancer treatment and evaluate their perceived effectiveness and adverse effects. This survey included 86 cancer patients, aged 19 years and older, who underwent anthelmintic therapy for cancer. They were recruited from two online communities in South Korea through a structured questionnaire that was provided online. Cancer patients under non-prescription anthelmintic therapy for cancer in South Korea were mostly in their advanced stages and had started the treatment in 2019. About half of the cancer patients had taken non-prescription anthelmintics during their chemotherapy, and 96.5% of them did not inform the clinicians. These participants had a positive perception (79.1%) toward the effectiveness of anthelmintics, as they felt it improved their physical condition. Data on the adverse effects of anthelmintics showed that more than two-third of the participants did not report experiencing any adverse effects. Communication between the clinicians and cancer patients regarding the use of non-prescription anthelmintics should be enhanced to prevent adverse effects.

64:

https://synapse.koreamed.org/articles/1142467

Journal of Korean Medical Science 2020; 35(6): e75

Title:
Anthelmintics as Potential Anti-Cancer Drugs?

Abstract:

The news that caught the attention of Korean cancer patients recent months was not about new anti-cancer drug development but about “animal anthelmintics.” A YouTube video of a US patient diagnosed with small cell lung cancer claimed he had been cured by fenbendazole (animal anthelmintic), while attending a clinical trial with other anti-cancer drug at the MD Anderson Cancer Center. When fenbendazole became difficult to obtain on the market, even the human anthelmintic (albendazole) was sold out.

65:

https://www.mdpi.com/2072-6643/15/19/4245

Nutrients 2023, 15(19), 4245

Title:
Cancer Metabolism as a Therapeutic Target and Review of Interventions

Abstract:

Cancer is amenable to low-cost treatments, given that it has a significant metabolic component, which can be affected through diet and lifestyle change at minimal cost. The Warburg hypothesis states that cancer cells have an altered cell metabolism towards anaerobic glycolysis. Given this metabolic reprogramming in cancer cells, it is possible to target cancers metabolically by depriving them of glucose. In addition to dietary and lifestyle modifications which work on tumors metabolically, there are a panoply of nutritional supplements and repurposed drugs associated with cancer prevention and better treatment outcomes. These interventions and their evidentiary basis are covered in the latter half of this review to guide future cancer treatment.

66:

https://www.mdpi.com/2073-4360/13/15/2530

Polymers 2021, 13(15), 2530

Title:

HPMA-Based Polymer Conjugates for Repurposed Drug Mebendazole and Other Imidazole-Based Therapeutics

Abstract:

Recently, the antitumor potential of benzimidazole anthelmintics, such as mebendazole and its analogues, have been reported to have minimal side effects, in addition to their well-known anti-parasitic abilities. However, their administration is strongly limited owing to their extremely poor solubility, which highly depletes their overall bioavailability. This study describes the design, synthesis, and physico-chemical properties of polymer-mebendazole nanomedicines for drug repurposing in cancer therapy. The conjugation of mebendazole to water-soluble and biocompatible polymer carrier was carried out via biodegradable bond, relying on the hydrolytic action of lysosomal hydrolases for mebendazole release inside the tumor cells. Five low-molecular-weight mebendazole derivatives, differing in their inner structure, and two polymer conjugates differing in their linker structure, were synthesized. The overall synthetic strategy was designed to enable the modification and polymer conjugation of most benzimidazole-based anthelmintics, such as albendazole, fenbendazole or albendazole, besides the mebendazole. Furthermore, the described methodology may be suitable for conjugation of other biologically active compounds with a heterocyclic N-H group in their molecules.

67:

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10493385/

Front Vet Sci. 2023; 10: 1231769

Title:

Pharmacokinetics of mebendazole in plasma and cerebrospinal fluid following a single oral dose in healthy dogs

Abstract:

Novel therapies are needed for treatment of gliomas. Mebendazole previously demonstrated anti-neoplastic effects on canine glioma cell lines at in vitro mean inhibitory concentrations (IC50) of 10 ng/mL. Our study aimed to titrate the oral dose of mebendazole necessary to achieve concentrations ≥10 ng/mL in cerebrospinal fluid (CSF) of healthy dogs. We hypothesized that an oral dose up to 200 mg/kg would be necessary. Phase one was a dose titration study using a total of 6 mixed breed dogs that described dose vs. plasma concentrations for 72 h after single oral dosing of either 50 mg/kg (n = 2), 100 mg/kg (n = 2), or 200 mg/kg (n = 2). Based on phase one, phase two dogs (total of 9) received 100 mg/kg (n = 4) or 200 mg/kg (n = 5) orally and blood samples were collected intermittently for 60 h with CSF samples collected intermittently for 24 h. Mebendazole was quantitated in plasma and CSF using high performance liquid chromatography. Median peak plasma concentrations (Cmax) were reached at 7 ± 2 h (100 mg/kg) of 220 ng/mL (81, 283) and at 15 ± 4 h (200 mg/kg) of 147 ng/ml (112, 298). The respective area under the curve (AUC: ng/ml/h) reported as a median was 2,119 (1,876, 3,288) vs. 3,115 (1,559, 4,972). Median plasma concentrations (ng/ml) for 100 vs. 200 mg/kg were 47 (32, 52) vs. 65 (35, 104), respectively. For CSF, the median value for Cmax (at 100 mg/kg vs. 200 mg/kg) was 8 (2, 28) vs. 21 (12, 27) and AUC was 87 (22, 157) vs. 345 (92, 372), respectively. Relative bioavailability in CSF vs. plasma was 4 to 10%. Although several animals demonstrated clinical signs indicative of gastrointestinal upset [i.e., vomiting (n = 2), diarrhea (n = 2), or both (n = 1)], these events were not considered serious. The in vitro IC50 for gliomas can be reached in CSF at 100 mg/kg (n = 1), however a 200 mg/kg dose yielded more consistent concentrations.

68:

https://www.sciencedirect.com/science/article/abs/pii/S009082582034018X

Volume 160, Issue 1, January 2021, Pages 302-311

Title:
Potential and mechanism of mebendazole for treatment and maintenance of ovarian cancer

Abstract:
Objective

Mebendazole and other anti-parasitic drugs are being used off-prescription based on social media and unofficial accounts of their anti-cancer activity. The purpose of this study was to conduct a controlled evaluation of mebendazole's therapeutic efficacy in cell culture and in vivo models of ovarian cancer. The majority of ovarian cancers harbor p53 null or missense mutations, therefore the effects of p53 mutations and a mutant p53 reactivator, PRIMA-1MET (APR246) on mebendazole activity were evaluated.

Methods

Mebendazole was evaluated in cisplatin-resistant high grade serous stage 3C ovarian cancer patient derived xenograft (PDX) models: PDX-0003 (p53 null) and PDX-0030 (p53 positive), and on ovarian cancer cell lines: MES-OV (p53 R282W), ES2 (p53 S241F), A2780 (p53 wild type), SKOV3 parental (p53 null) and isogenic sublines, SKOV3 R273H p53 and SKOV3 R248W p53. Drug synergy and mechanisms were evaluated in cell cultures using isobolograms, clonogenic assays and western blots. Prevention of tumor establishment was studied in a MES-OV orthotopic model.

Results

Mebendazole inhibited growth of ovarian cancer cell culturesat nanomolar concentrations and PDXs at doses up to 50 mg/kg, and reduced orthotopic tumor establishment at 50 mg/kg. The mechanism of mebendazole was associated with p53-independent induction of p21 and tubule depolymerization. PRIMA-1MET also inhibited tumor establishment and worked synergistically with mebendazole in cell culture to inhibit growth and induce intrinsic apoptosisthrough a p53- and tubule destabilization-independent mechanism.

Conclusion

This work demonstrates the therapeutic potential of repurposing mebendazole and supports clinical development of mebendazole for ovarian cancer therapy and maintenance.

69:

https://media.sparx-ip.net/AACR2020EPd/508.pdf
Title:

A novel orally available Wnt-pathway inhibitor for the treatment of metastatic cancers

Abstract:
We have developed a novel drug compound (OBD9) which blocks growth of metastatic cancer cells both in vitro and in vivo. We now identify OBD9 as an effective Wnt-signaling inhibitor targeting TNIK (TRAF2 And NCK Interacting Kinase) and we hypothesize that OBD9 represents a novel therapeutic option for patients with tumors that have an activated Wnt signaling pathway.
To find novel drug candidates that selectively inhibit metastatic tumor cell viability, a drug screen was first performed, and results of the screen identified members of the FDA-approved benzimidazole methylcarbamate family (e.g. mebendazole (MBZ) and albendazole (ALB)) as potential therapies for metastatic cancer. Earlier work also supports a role for this chemical family in the potential treatment of multiple cancers, but progress has been stalled by their poor water solubility and poor bioavailability for systemic delivery to disseminated tumors. We therefore synthesized a novel compound (OBD9) containing the scaffold of MBZ coupled to an oxetane group to enhance aqueous solubility to 361μM. OBD9 demonstrates significant cytotoxicity toward a variety of cancer cell types including colon, lung, and prostate cancers (IC50: 0.9-2μM). In a mouse xenograft model using highly aggressive PC3MLN4 prostate cancer cells, OBD9 at 30 mg/kg significantly repressed growth of established tumors with no visible toxicity. In a mouse xenograft model of human A549 lung cancer cell line, orally delivered OBD9 also dramatically inhibited the growth of established tumors at 30 or 90mg/kg without noticeable toxicity.
Mechanistically, we find that OBD9 treatment significantly reduces TNIK levels as early as 4 hours at 1uM via an autophagy-dependent protein degradation pathway. TNIK functions as an activator of Wnt signaling pathway via phosphorylation of the beta-catenin/TCF4 complex that regulates Wnt downstream targets. We show that OBD9 treatment inhibits colon cancer cell growth and both qPCR and Western blot data suggest that Wnt signaling downstream targets, such as TCF4, AXIN2 and cMyc, are all significantly suppressed by OBD9 via the inhibition of TNIK. Overall, our in vitro and in vivo data suggest that OBD9 potentially represents a novel therapeutic option for multiple cancers including but not limited to colon, lung and prostate cancer

70:

https://aacrjournals.org/mcr/article/6/8/1308/90323/Mebendazole-Induces-Apoptosis-via-Bcl-2

Mol Cancer Res (2008) 6 (8): 1308–1315.

Title:
Mebendazole Induces Apoptosis via Bcl-2 Inactivation in Chemoresistant Melanoma Cells

Abstract:

Most metastatic melanoma patients fail to respond to available therapy, underscoring the need for novel approaches to identify new effective treatments. In this study, we screened 2,000 compounds from the Spectrum Library at a concentration of 1 μmol/L using two chemoresistant melanoma cell lines (M-14 and SK-Mel-19) and a spontaneously immortalized, nontumorigenic melanocyte cell line (melan-a). We identified 10 compounds that inhibited the growth of the melanoma cells yet were largely nontoxic to melanocytes. Strikingly, 4 of the 10 compounds (mebendazole, albendazole, fenbendazole, and oxybendazole) are benzimidazoles, a class of structurally related, tubulin-disrupting drugs. Mebendazole was prioritized to further characterize its mechanism of melanoma growth inhibition based on its favorable pharmacokinetic profile. Our data reveal that mebendazole inhibits melanoma growth with an average $IC_{50}$of 0.32 μmol/L and preferentially induces apoptosis in melanoma cells compared with melanocytes. The intrinsic apoptotic response is mediated through phosphorylation of Bcl-2, which occurs rapidly after treatment with mebendazole in melanoma cells but not in melanocytes. Phosphorylation of Bcl-2 in melanoma cells prevents its interaction with proapoptotic Bax, thereby promoting apoptosis. We further show that mebendazole-resistant melanocytes can be sensitized through reduction of Bcl-2 protein levels, showing the essential role of Bcl-2 in the cellular response to mebendazole-mediated tubulin disruption. Our results suggest that this screening approach is useful for identifying agents that show promise in the treatment of even chemoresistant melanoma and identifies mebendazole as a potent, melanoma-specific cytotoxic agent. (Mol Cancer Res 2008;6(8):1308–15)

71:
https://www.tandfonline.com/doi/full/10.2147/IDR.S141468

Title:

Treatment-refractory giardiasis: challenges and solutions

Abstract:

Giardia is the commonest parasitic diarrheal pathogen affecting humans and a frequent cause of waterborne/foodborne parasitic diseases worldwide. Prevalence of giardiasis is higher in children, living in poor, low hygiene settings in developing countries, and in travelers returning from highly endemic areas. The clinical picture of giardiasis is heterogeneous, with high variability in severity of clinical disease. It can become chronic or be followed by post-infectious sequelae. An alarming increase in cases refractory to the conventional treatment with nitroimidazoles (ie, metronidazole) has been reported in low prevalence settings, such as European Union countries, especially in patients returning from Asia. In view of its relevance, we aim in this review to recapitulate present clinical knowledge about Giardia, with a special focus on the challenge of treatment-refractory giardiasis. We propose a working definition of clinically drug-resistant giardiasis, summarize knowledge regarding resistance mechanisms, and discuss its clinical management according to research-based evidence and medical practice. Advances in development and identification of novel drugs and potential non-pharmacological alternatives are also reviewed with the overall aim to define knowledge gaps and suggest future directions for research.

72:

https://www.mdpi.com/2076-0817/10/4/454

Pathogens 2021, 10(4), 454

Title:
Cat Respiratory Nematodes: Current Knowledge, Novel Data and Warranted Studies on Clinical Features, Treatment and Control

Abstract:
The nematodes Aelurostrongylus abstrusus, Troglostrongylus brevior and Capillaria aerophila are the most important parasites inhabiting the airways of cats. They are receiving growing attention from academia, pharmaceutical companies and veterinarians, and are now considered a primary cause of respiratory diseases

in feline clinical practice and parasitology. In the past few years, several studies have been conducted in both natural and experimental settings to increase knowledge, provide new insights and fill gaps on respiratory parasitoses of cats. Awareness and knowledge of clinical scenarios towards appropriate and timely diagnosis and prompt and efficacious treatment options have become a priority to investigate. At the same time, chemopreventative approaches have been evaluated to assess the geographical spreading of these parasites and the rise in the number of clinical cases in cat populations of different countries. Given the intense accumulation of novel data, this review presents and discusses the state of the art and the latest updates on the clinical features, treatment, and control of major respiratory parasitoses of cats. Moreover, food for thought is also provided with the aim of spurring on new studies in the near future.