A Overview of Pharmacological Activities of Mebendazole as a potential Anthelmintic drug

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ABSTRACT: Mebendazole is a broad-spectrum antibiotic belongs to benzimidazole group, is partially insoluble in water and other organic solvents. Mebendazole is a medication that is mostly used to treat helmintic infections, including as roundworms, which are treated by inhibiting microtubule polymerization, hookworm and pinworm by inhibits glucose uptake and glycogen synthesis in worm. Additionally, this medication is used to treat Severe acute respiratory infections (SARS-CoV) and to treat filariasis, toxocariasis, benign tumors, and malignant tumors. Mebendazole has poor bioavailability. Only about 17-20% of the dose reaches the systemic circulation after oral administration due to incomplete absorption and extensive first-pass metabolism. Mebendazole exerts its pharmacodynamics activity primarily by inhibiting microtubule polymerization in the parasite by binding to β-tubulin. Thus its effectiveness against all these conditions shows significant outcomes when administered accurately.

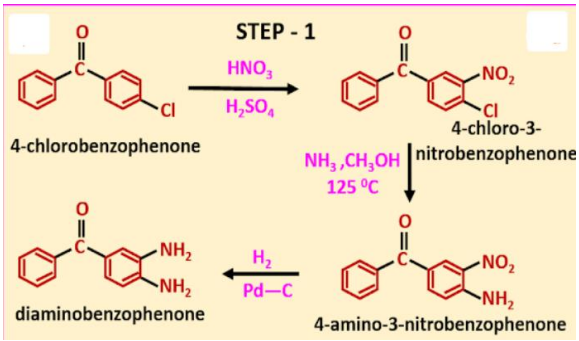
KEYWORDS: Mebendazole, helmintics, tumors, benzimidazole.

1. INTRODUCTION

In human beings and animals ascarasis, hookworm infections, taeniases, enterobiasis, hymenolepiasis, and Enterobius vermicularis are known to cause infections[1,2,3,4,5]. Hence the drug Mebendazole was chosen to treat these conditions and also it is known as an anti- worm medication which is given first to people in 1971[6]. Mebendazole is a synthetic derivative of benzimidazole, a carbamate esteramine[7]. Numerous research on mebendazole's antihelmintic activities against different nematodes, trematodes, cestodes, and even protozoans have been conducted since the drug was initially used to treat a number of intestinal helminth species in humans[8,9]. Mebendazole has a lot of potential for treating hydatid illnesses and capillary asthenia among its non-administered uses[10]. Mebendazole works by preventing the parasite from absorbing glucose, which immobilizes and kills it[11,12]. ethylbenzene (MBZ) has demonstrated preclinical efficacy in treating a number of malignancies, including thyroid, colon, breast, pancreatic, multiform glioblastoma, and melaloblastoma. [13,14,15].

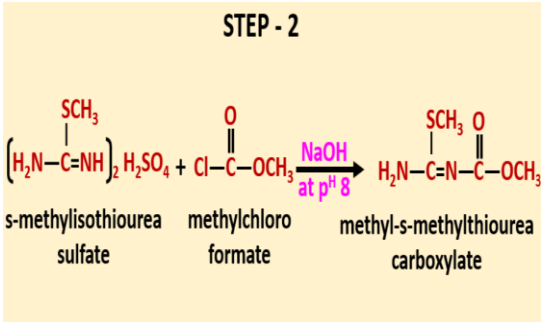
2. SYNTHESIS OF MEBENDAZOLE

First step:



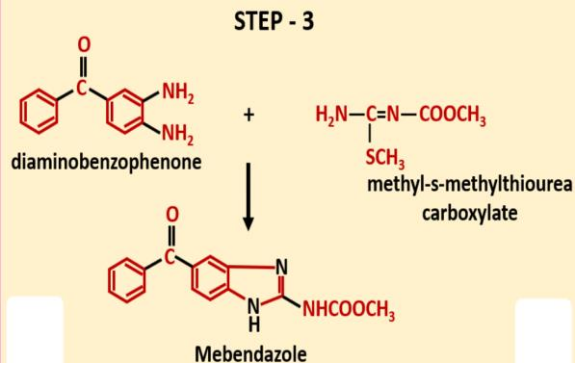
In the first step, 4-chlorobenzophenone reacted with mixed acid (HNO_3+H_2SO_4), as a result 4-chloro-3-nitrobenzne is formed. Now 4-chloro-3-nitrobenzophenone reacted with ammonia in presence of methanol as a result 4-amino 3- nitrobenzophenone is produced. The nitro group present at 3 in 4-amino-3-nitrbenzophenone is reduced by hydrogen in presence of palladium on carbon as a result diaminobenzophenone is formed.

Second step:



In this step, s-methylisothiourea sulphate and methylchloro formate reacted in the presence of NaOH and forms methyl-s-methylthiourea carboxylate.

Third step:



In this last step diaminobenzophenone and methyl-s-methylthiourea carboxylate reacted each other and forms Mebendazole.

3. VARIOUS MARKETED DOSAGE FORMS OF MEBENDAZOLE

1) Oral suspension:

Fig 1: Marketed dosage forms of Mebendazole drops and suspension

2) Tablets:

Fig 2: Marketed dosage forms of Mebendazole tablet

4. PHARMACOLOGY OF DRUG IN VARIOUS DISEASES

Causative agents & Disease name	MOA	References
Roundworms (Ascariasis, cestodes)	▪ Mebendazole binds to tutbuline, a protein in microtubules, and inhibits microtubule polymerization. ▪ This discrupts the worms cytoskeleton, causing paralysis and death.	16,17,18
Wipworm (Trichuriasis)	▪ Mebendazole damages the worms cuticle and causes muscle connraction. ▪ This leads to expulsion of the worm from the intestine.	6,19,20
Pinworm (Enterobiasis), Hookworm, Hymenolepiasis	▪ Mebendazole inhibits glucose uptake and glycogen synthesis in worm. ▪ This leads to energy depletion, paralysis, and death.	21,22
Benign tumors	▪ Mebendazole inhibits formation of blood vessels that feeds the tumor. ▪ It also induce apoptosis means cell death in tumor cells.	23
Malignant tumors (Giloblastoma, Breast cancer, Lung cancer, Ovarian cancer)	▪ Mebendazole inhibits cell division and proliferation as well as apoptosis and angiogenesis. ▪ It also targets the tumor microenvironment, reducing inflammation and immune suppression.	13,14,24

Toxocariasis	▪ Mebendazole may disrupt critical cellular functions, such as DNA replication or protein synthesis, causing metabolic dysfunction and parasite death.	30,31
Filariasis	▪ Mebendazole inhibiting the production of microtubule via binding to colchicine binding site of beta tubulin and thereby blocking polymerization of tubulin dimer in the intestinal cells of parasites.	25,26
Metastatic adrenocortical carcinoma	▪ Drug also inhibited the growth of these tumor cells in nude mice and reduced their invasive properties.	27,28
SARS-CoV	▪ Inhibition of viral penetration , uncoating ,nucleic with synthesis ,integration of viral dna geneme,maturation and exit from host cells.	32

5. PHARMACOKINETIC ACTIVITY OF MEBENDAZOLE

a) ABSORPTION:

The bioavailability of mebendazole is generallyb reported to be less than 10%, indicating poor oral absorption. When taken with fatty meals, the absorption can be enhanced however it is highly variable[33].

b) DISTRIBUTION:

Mebendazole is extensively disseminated throughout the body following absorption. It is about 90-95% protein bound and has a strong affinity for plasma proteins. The drugs main effects are felt in the liver, bile, and intestinal wall, where it tends to concentrated.

c) METABOLISM:

The liver extensively metabolizes mebendazole through first-pass metabolism. Oxidation is the main metabolic route, which is followed by the synthesis of hydroxyl and carboxy metaboliets. 2-amino-5(6)-bezoylbenzimidazole, the primary metabolite, is not active[34] .

d) EXCRETION:

Bile and feces are the main organs where mebendazole and it metabolites are eliminated urine only excretes a small fraction (5-10%) of it. Mebendazole has a half-life of between 2.5 to 5.5 hours[35].

6. PHARMACODYNAMIC ACTIVITY OF MEBENDAZOLE

Mebendazole exerts its pharmacodynamics activity primarily by inhibiting microtubule polymerization in the parasite by binding to β-tubulin, which disrupts the nematode's cytoskeleton, causing nutrient malabsorption, starvation and reproductive failure. Consequently, the worms cannot maintain their structure or reproduce effectively, resulting in their death and clearance from the host[36].

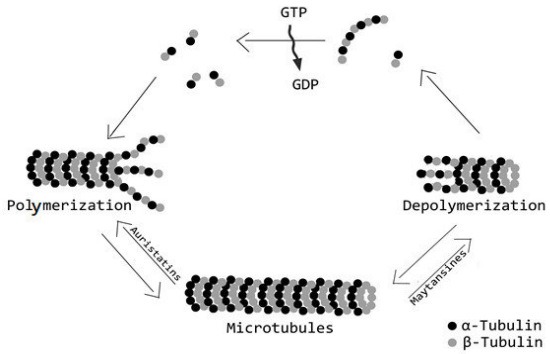


Fig 3: Schematic representation of Inhibition of Microtubulin

7. CONCLUSION

Mebendazole is described as highly versatile broad-spectrum drug that is effective both as an anti-parasitic and anti-cancer agent. This article highlights its usefulness in treating various conditions,
including:

1) Nematode infestations
2) Tissue and intestinal helminthiases
3) Some protozoal infections

It also emphasizes safety of Mebendazole when used at recommended doses for different ailments. The authors refers to it as “very safe” under these conditions, suggesting a favourable risk-benefit profile for its intended uses.

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