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A.C.Camargo Cancer Center
Especializado em Vida

IN SILICO AND *IN VITRO* EVALUATION OF MODULATION OF THE ENZYME LACTATE DEHYDROGENASE (LDH) BY THE DRUG MEBENDAZOLE IN GASTRIC TUMOR METABOLISM

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Introduction

The enzyme Lactate Dehydrogenase (LDH) is widely associated with tumor metabolic reprogramming, an essential process responsible for maintaining the proliferative profile, and thus an ideal target for the development of new therapies[1,2]. Drug repurposing is a faster and more economical strategy than prospecting new molecules[3]. In this context, Mebendazole (MBZ), a member of the benzimidazoles, has anticancer activity and also inhibits growth, migration, and invasion in gastric cancer cell lines[4].

Aim and Methods

This study aimed to assess the effect of the modulation of the LHD enzyme by the drug Mebendazole and its role in metabolic regulation as a target in gastric carcinogenesis. For this purpose, the following methodology was used.

Figure 1. Representative scheme of *in silico* analyses.

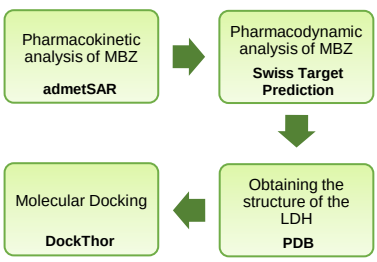
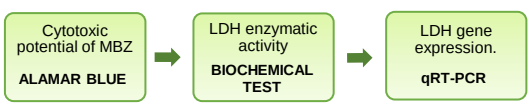


Figure 2. Representative scheme of *in vitro* analyses.



Results

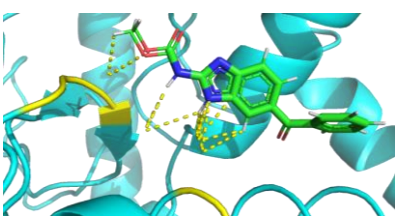
Table 1. Pharmacokinetic profile of MBZ absorption and metabolism.

ADMET Properties	Probability
Human Intestinal Absorption	99%
CYP3A4 (non-inhibitory)	83%
CYP2C9 (non-inhibitory)	91%
CYP2D6 (non-inhibitory)	92%
CYP2C19 (non-inhibitory)	90%

Table 2. Pharmacodynamic profile of MBZ.

Target	Probability	Class
ABL1	100%	Kinase
FLT1	100%	Kinase
FLT4	100%	Kinase
KDR	100%	Kinase
ABL2	100%	Kinase

Figure 3. Hydrogen bonds formed between the ligand and the amino acids. Bindings were observed with the amino acids Arg268, Val269, His270 and Asp257.



Results

Table 3. Cytotoxic activity of the drug Mebendazole after 72 hours of treatment in gastric lineages. AGP-01 and MNP-01 were treated with a concentration-response curve of the drug Mebendazole for 72 hours, then the compound Alamar Blue was added to obtain the IC50.

Lineage	Histological Type	MBZ IC_{50} (µM) (IC 95%)	Selectivity Index
AGP-01	Ascitic fluid from gastric adenocarcinoma	0.2 (0.1 - 0.39)	3.7
MNP-01	Normal stomach mucosa	0.74 (0.58 – 0.97)	-

Figure 4. The drug Mebendazole reduces the intrinsic activity of the LDH enzyme in the metastatic lineage AGP-01. The AGP-01 line was treated for 24 hours with the compounds Mebendazole (0.1 µM) and Rotenone (1 µM) and then the enzymatic activity was measured. NC= Negative Control. ***p<0.01, compared to untreated cells (NC) by 1-way ANOVA followed by Bonferroni test, with a significance level of 95% (p<0.05).

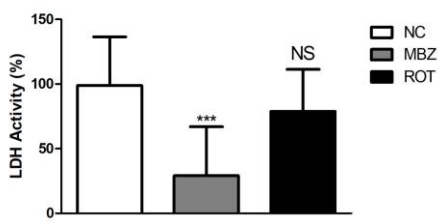
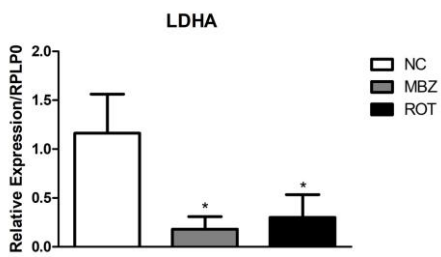


Figure 5. The drug Mebendazole alters *LDHA* expression *in vitro*. The bars represent the mean ± standard deviation of the mean of 3 independent experiments. NC= Negative control. *p<0.05 compared to untreated cells by 1-way ANOVA followed by Bonferroni test, with a significance level of 95% (p<0.05).



Conclusion

Based on the founds it is possible to infer the drug MBZ's potential as a tumoral metabolic modulator, being a potential new therapeutic compound for gastric cancer treatment. These findings create new possibilities for using artificial intelligence in the design of drugs based on the pharmacophoric groups of MBZ, making it possible to obtain more efficient drugs with a target base and with fewer side effects.

Acknowledgment

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