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DOXORUBICIN COMBINED TO AN ANTIMETABOLITE IMPROVES EXPERIMENTAL EARLY MULTI-ORGAN CARCINOGENESIS

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Background: The chemo-preventive potential of the association of doxorubicin (Dox, an anthracycline antibiotic with anticancer effects through DNA intercalation and topoisomerase II inhibition) combined to an antimetabolite (ATM, with antioxidant properties) in early stage of colon carcinogenesis using a short-term multi-organ carcinogenesis bioassay.

Methods: Early phase of carcinogenesis was induced chemically in female mice (10/group). After a period of 7 weeks of induction, the mices were given NaCl (control), 3mg/kg Dox once a week for 3 weeks by subcutaneous injection, 20 mg/kg ATM once a day for 4 constitutive weeks by gavage or the combination of the two treatments. After mice sacrifice, blood and colon was harvested and analysed.

Results: Dox and ATM had no significant effect on body and organ weight, food and water consumption. The early steps of carcinogenesis resulted in aberrant crypt foci (ACF) formation and inflammatory cells infiltrate in colon mucosa at week 12. The lipid peroxides (malondialdehyde, MDA) level and myeloperoxidase (MPO) activity were enhanced by 248% ($p < 0.001$) and 67% ($p < 0.05$), respectively, while glutathione level (GSH) was decreased by 40% ($p < 0.01$) in induced group, indicating a neutrophil dependent oxidative stress.

Dox, ATM and Dox+ATM markedly improved the integrity of colon mucosa and restored gland structure and decreased inflammatory cells infiltrate. They also improve systemic oxidative stress by lowering MDA levels by 62%, 63% ($p < 0.001$) and 34% ($p < 0.01$) respectively, and improved antioxidant pool by restoring GSH level 181%, 218% and 223% ($p < 0.001$) respectively.

Conclusion: Thus, a dual therapy associating Dox with ATM would be a therapeutic approach for the treatment of multiorgan carcinogenesis. Cellular mechanisms are being studied.

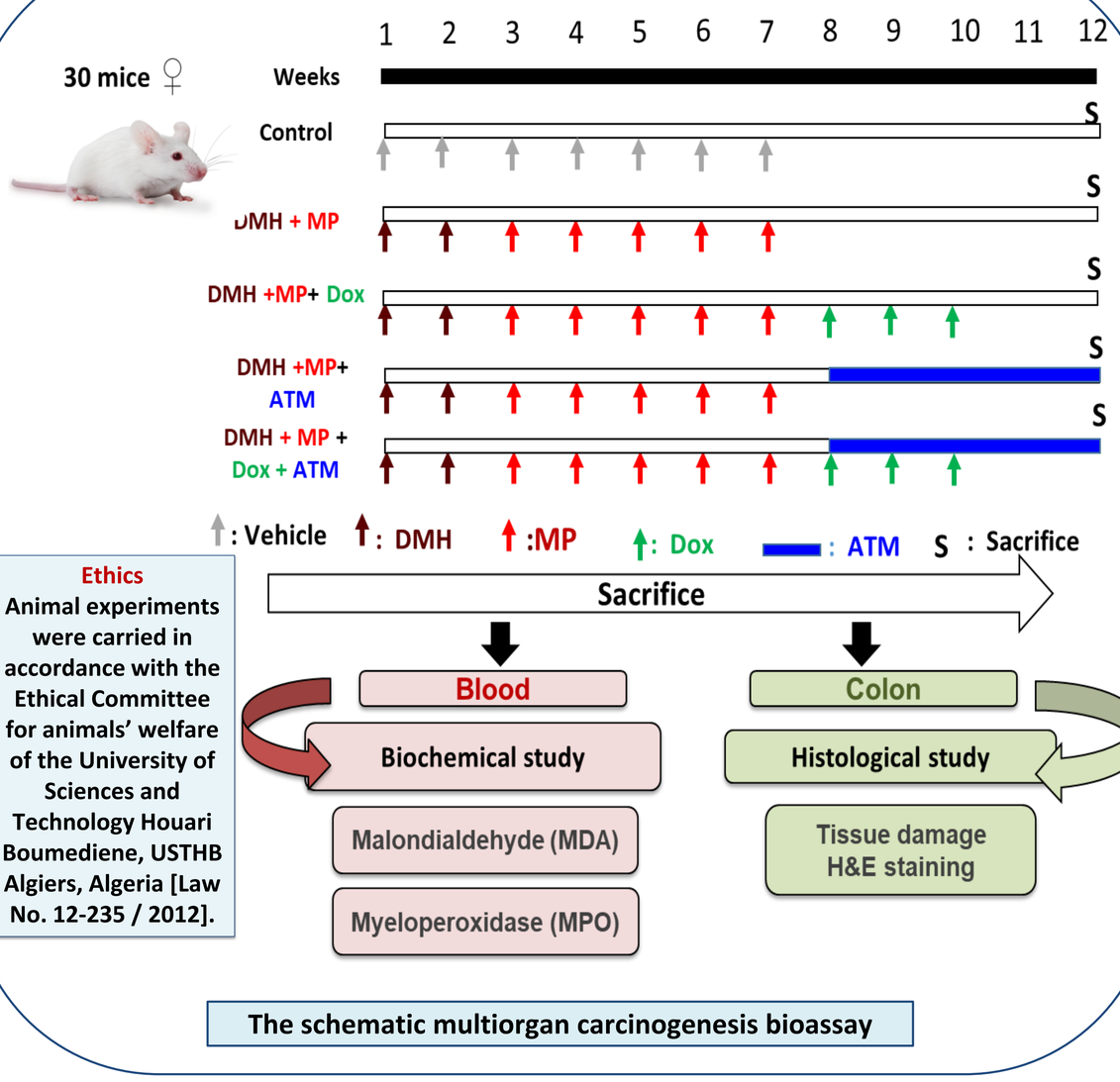
Key words: Doxorubicin; antimetabolite; oxidative stress; multi-organ carcinogenesis.

I- Introduction:

- **Early diagnosis** of cancer allows for more effective treatment, with improved survivalness. A considerable research effort is thus directed to the identification and elimination of precancerous lesions.
- The **short-term multi-organ carcinogenesis bioassay** is a suitable model to induce preneoplastic lesions over a short period. It allows faster screening of **chemopreventive pharmacological molecules** agents on several organs at the same time.
- **Doxorubicin (Dox),** an anthracycline isolated from *Streptomyces peucetius* var. *caesius*, induces **DNA damage** and increases the expression of tumor suppressors, which up-regulates the transcription of numerous **proapoptotic genes**, resulting in cancer cells **apoptosis**.
- In order to overcome the side effects of Dox treatment, the use of a dual therapy combining our anticancer treatment with an **antimetabolite (ATM).**

→ *This study examined the effect of Dox combined to an ATM in early stage of colon carcinogenesis using 1,2 dimetthyl hydrazine (DMH, a colon carcinogen) combined with polluting metal (MP), in a mouse model of chemically- multi organ carcinogenesis*

II- Material and Methods:



Ethics
Animal experiments were carried in accordance with the Ethical Committee for animals' welfare of the University of Sciences and Technology Houari Boumediene, USTHB Algiers, Algeria [Law No. 12-235 / 2012].

The schematic multiorgan carcinogenesis bioassay

III- Results and discussion:

A- Histological analysis

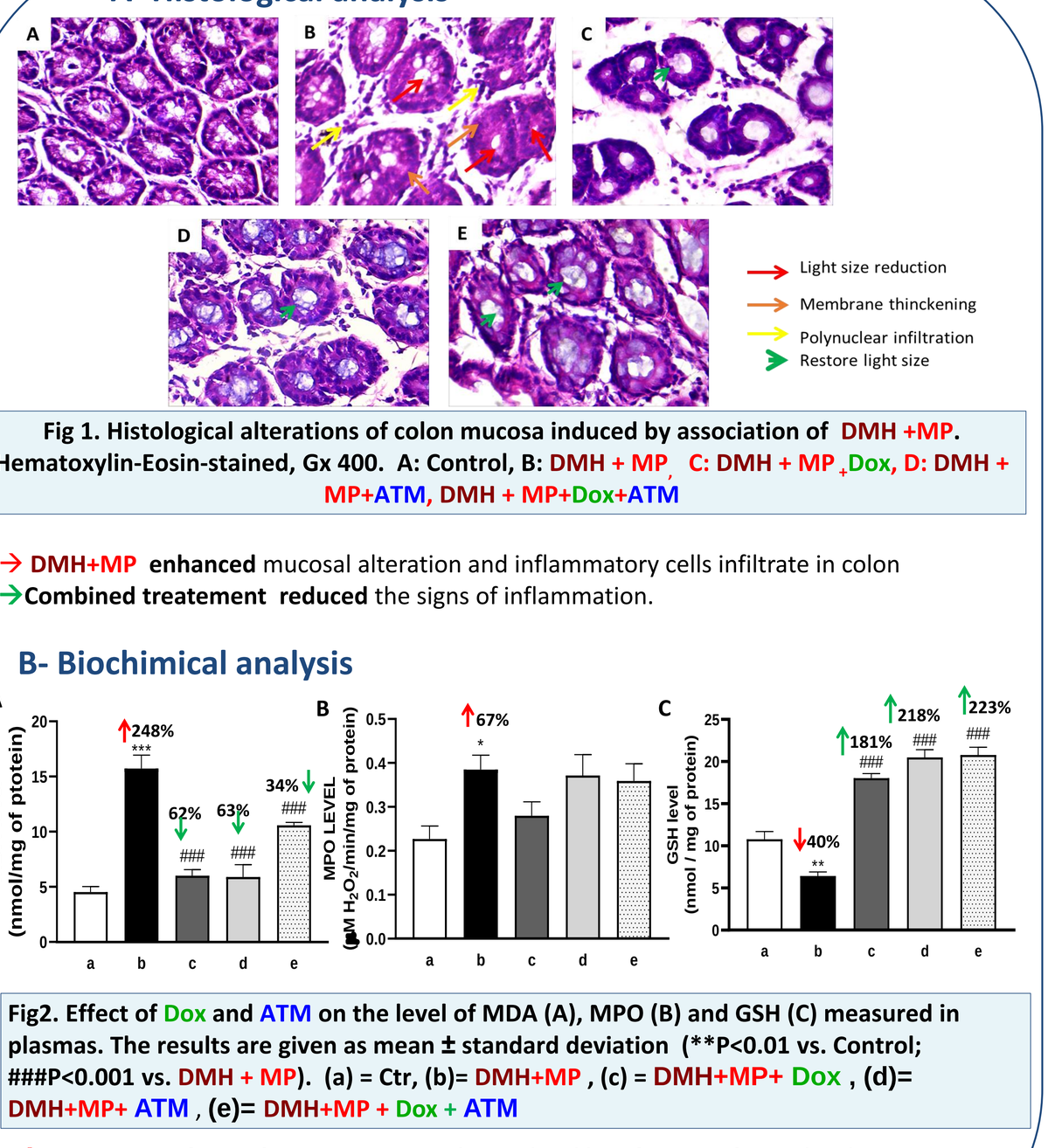


Fig 1. Histological alterations of colon mucosa induced by association of DMH +MP. Hematoxylin-Eosin-stained, Gx 400. A: Control, B: DMH + MP, C: DMH + MP +Dox, D: DMH + MP+ATM, DMH + MP+Dox+ATM

→ **DMH+MP enhanced** mucosal alteration and inflammatory cells infiltrate in colon
→ **Combined treatement reduced** the signs of inflammation.

B- Biochimical analysis

Fig2. Effect of Dox and ATM on the level of MDA (A), MPO (B) and GSH (C) measured in plasmas. The results are given as mean ± standard deviation (**P<0.01 vs. Control; ###P<0.001 vs. DMH + MP). (a) = Ctr, (b)= DMH+MP , (c) = DMH+MP+ Dox , (d)= DMH+MP+ ATM , (e)= DMH+MP + Dox + ATM

→ **DMH+MP enhanced** MPO activity and MDA level but **decreased** GSH level.
→Combined treatement of Dox and ATM **reduced** MDA level and increased GSH level while MPO activity was not affected in each groups.

VI- Conclusion:

→ *According to these results, a dual therapy associating Dox with ATM seems to be a good approach to consider in the treatment of colon cancer*
→ *We are pursuing our studies to determine pathways that Dox and ATM uses for its chemotherapeutic effect in colorectal and other cancer*