

## Effects of nitric oxide donation and nuclear factor-kappa B inhibition on schistosomiasis mansoni

*Schistosoma* chronically infects millions of people worldwide, and is considered an important cause of liver fibrosis; a reversible wound healing that reflects a balance between liver repair and scar formation, and is mainly maintained by chronic activation of the wound healing response and oxidative stress. Praziquantel (PZQ) is the drug of choice against human schistosomiasis, but it cannot halt or revert hepatic fibrosis and has an increasingly recognized resistance.

Pharmacological targeting of the scarring process might be a promising strategy to prevent progression to potentially fatal fibrosis. Recent views about the pharmacological control of inflammatory diseases have focused on targeting pro-inflammatory signals (e.g. nuclear factor-kappaB; NF- $\kappa$ B pathway that plays a central role in regulating liver homeostasis, inflammation, fibrosis, and carcinogenesis) or cytokines, as well as the regulation of nitric oxide (NO) synthesis. Hence, targeting the scarring process by anti-inflammatory agent/s or NO donation can pause or even reverse liver fibrosis.

This study investigated the anti-inflammatory effect of vinpocetine as a NF- $\kappa$ B inhibitor, and the vasodilator and the anti-oxidant effects of the NO donor; IS-5-MN, alone and in combination with the anti-schistosomal drug; PZQ in a liver fibrosis model of schistosomiasis mansoni.

The study included 110 Swiss albino female mice (CD-1 strain), divided into: **group I:** non-infected (control); **group II:** infected non-treated; **group III:** infected and treated with **PZQ** (6 weeks post infection; WPI at 500 mg/kg/day for two successive days); **group IV:** infected and treated with **vinpocetine** (4-10 WPI, at 11.76 mg/kg, 5 days/week); **group V:** infected and treated with **vinpocetine** (as in group IV), and **PZQ** (as in group III); **group VI:** infected and treated with **IS-5-MN** (4-10 WPI, at 10.08 mg/kg, 5 days/week); **group VII:** infected and treated with **IS-5-MN** (as in group VI), and **PZQ** (as in group III); **and group VIII:** infected and treated with **vinpocetine** (as in group IV), and **IS-5-MN** (as in group VI).

All mice were euthanized after 10 weeks. Blood was collected and sera were separated, then mice were autopsied and liver tissues were collected. Concentrations of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and total bilirubin in sera were measured using the commercially available kits. Liver homogenates were used to determine NO levels using a commercially available kit, and hydroxyproline as well as collagen contents following alkali digestion. In addition, NF- $\kappa$ B-p65 expression was evaluated using the standard avidin-biotin immunoperoxidase technique.

The best results were obtained in the mice group treated with PZQ combined with IS-5-MN; as detected by significant increase in hepatic NO level (by 289.47%), and significant reductions in hydroxyproline and collagen contents of the liver (by 33.90% and 33.79%, respectively), as well as NF- $\kappa$ B expression, compared with infected non-treated group.

Furthermore, mice received combined vinpocetine and IS-5-MN regimen showed statistically significant reductions in serum ALT and AST levels (by 51.13% and 57.07%, respectively), hydroxyproline and collagen

contents of the liver (by 28.81% and 27.59%, respectively), as well as NF- $\kappa$ B expression, compared with infected non-treated group.

Vinpocetine dosing protocol induced the lowest expression of NF- $\kappa$ B, compared to infected non-treated group. Addition of PZQ to vinpocetine did not decrease serum ALT and AST levels or NF- $\kappa$ B expression, while treatment with IS-5-MN caused significant reduction in NF- $\kappa$ B expression, compared with infected non-treated group.

In conclusion, the best results were obtained with PZQ and IS-5-MN combined therapeutic regimen. A careful interpretation of results from mouse studies might be helpful to clinical hepatology that can establish IS-5-MN being more superior to vinpocetine as potential drug candidate for patients with chronic hepatic schistosomiasis.

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## **Publication**

[Effectiveness of vinpocetine and isosorbide-5-mononitrate on experimental schistosomiasis mansoni: Biochemical and immunohistochemical study.](#)

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