IOCXe 2026 Conference

The 1st International Online Conference on Xenobiotics

22–23 June 2026 | Online

MDPI

Impact of Dietary Xenobiotics on the Intestinal Activity of Sodin 5: Implications for RIP-Based Nanotherapeutic

F. Ferretti[1], C. Perrone[1], M. Bortolotti[1], F. Biscotti[1], S. Ragucci[2], N. Landi[2], A. Di Maro[2], A. Bolognesi[1], L. Polito[1]

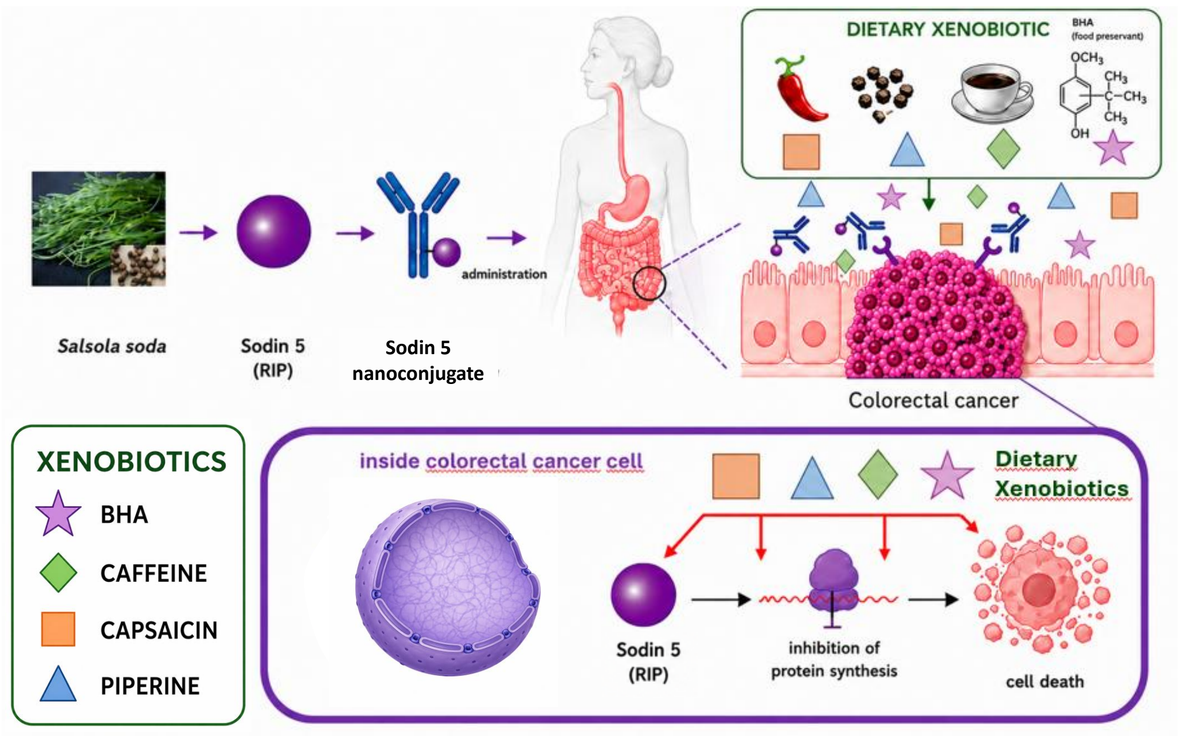
1 Department of Medical and Surgical Sciences (DIMEC), Alma Mater Studiorum, University of Bologna, Italy

2 Department of Environmental, Biological and Pharmaceutical Sciences and Technologies (DiSTABiF), University of Campania 'Luigi Vanvitelli', Italy

INTRODUCTION & AIM

Ribosome-Inactivating proteins (RIPs) are potent plant derived enzymes able to irreversibly inhibit protein synthesis and induce cell death. Due to their high cytotoxic activity, RIPs are widely investigated as toxic payloads for targeted nanoconjugates in experimental cancer therapy [1]. Among them, Sodin 5, a type 1 RIP isolated from the edible plant *Salsola soda* (agretti), has shown cytotoxic activity in colorectal cancer (CRC) derived cell models [2, 3]. However, in a potential RIP-based therapy for CRC, the influence of the tumor chemical environment should be taken into account. CRC cells are exposed not only to the RIP payload released by the nanoconjugates, but also to a wide range of dietary xenobiotics present in the intestinal lumen. These compounds may enhance or attenuate the cytotoxic activity of the RIP payload within target cell, potentially affecting therapeutic efficacy. Despite their potential relevance, dietary xenobiotics remain a completely overlooked variable in the evaluation of RIP based nanotherapeutic strategies.

The objective of this study was to determine whether selected dietary xenobiotics modulate Sodin 5 cytotoxicity in a Caco 2 intestinal cancer model, providing the first assessment of dietary xenobiotic mediated modulation of a RIP-based cytotoxic payload in an intestinal cancer setting.

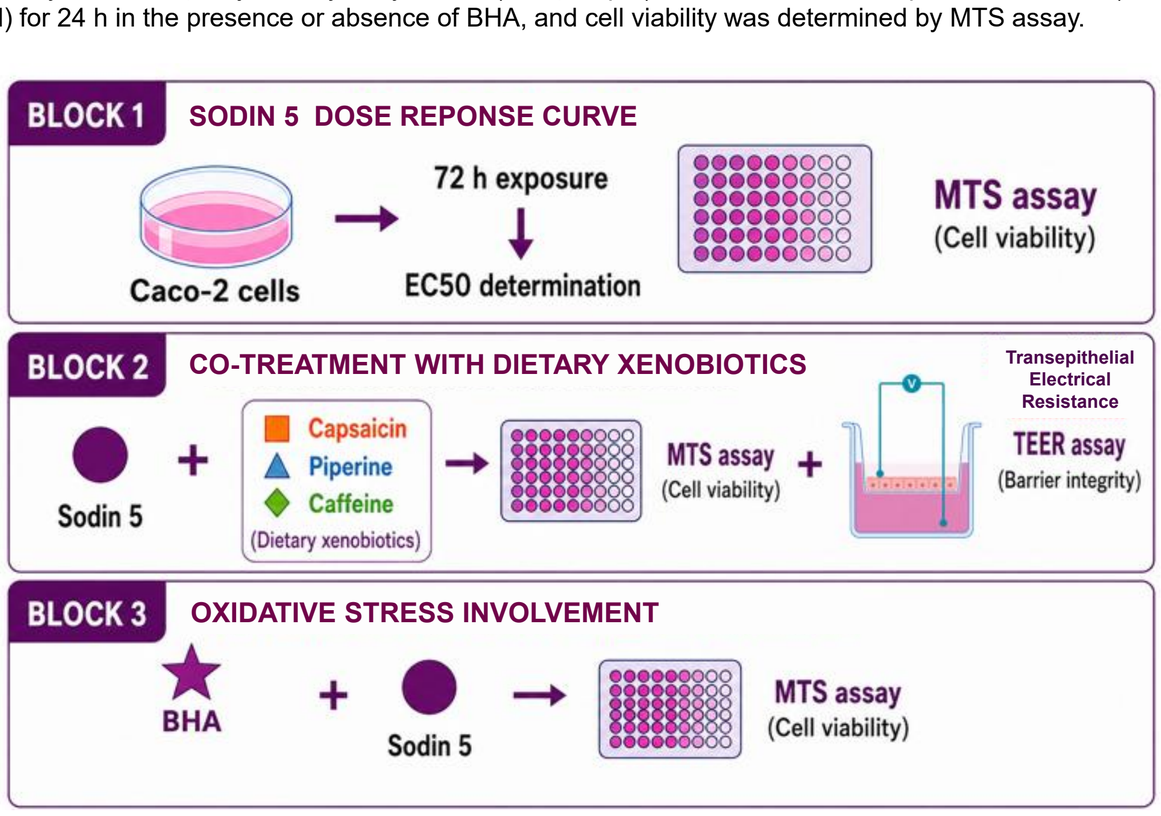


METHODS

In this pivotal study, capsaicin, piperine, and caffeine were selected as common dietary xenobiotics with established biological activity and reasonable intestinal exposure following food consumption.

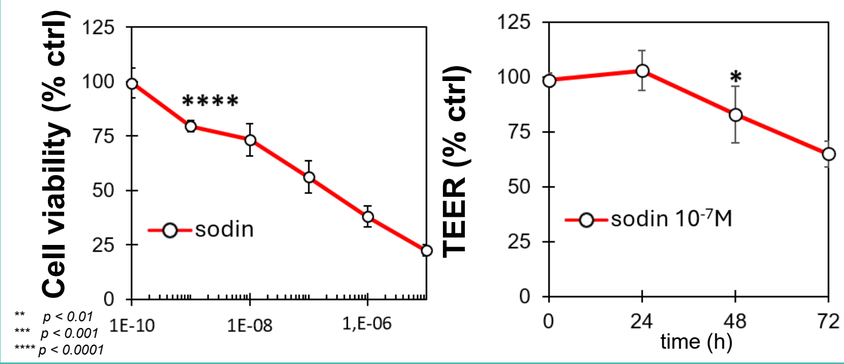
The cytotoxic activity of Sodin 5 was evaluated in Caco 2 cells through dose response experiments. Cell viability was determined by an MTS assay after 72 h exposure to scalar concentrations of Sodin 5. The effects of dietary xenobiotics on Sodin 5 activity was assessed through co-treatment experiments using Sodin 5 at EC_{50} (10^{-7} M) in combination with capsaicin (200 µM), piperine (200 µM), or caffeine (2.5 mM). These concentrations were selected within plausible intestinal exposure ranges and to allow detection of modulatory effects on Sodin 5 activity. The effects on epithelial barrier integrity was monitored in Caco 2 monolayers by transepithelial electrical resistance (TEER) measurements at 0, 24, 48, and 72 h following treatment with Sodin 5 alone or in combination with dietary xenobiotics.

Oxidative stress contribution was functionally evaluated using the food preservatives, and antioxidant dietary xenobiotic, butylated hydroxyanisole (BHA, 30 µM). Caco 2 cells were exposed to Sodin 5 (10^{-6} M) for 24 h in the presence or absence of BHA, and cell viability was determined by MTS assay.



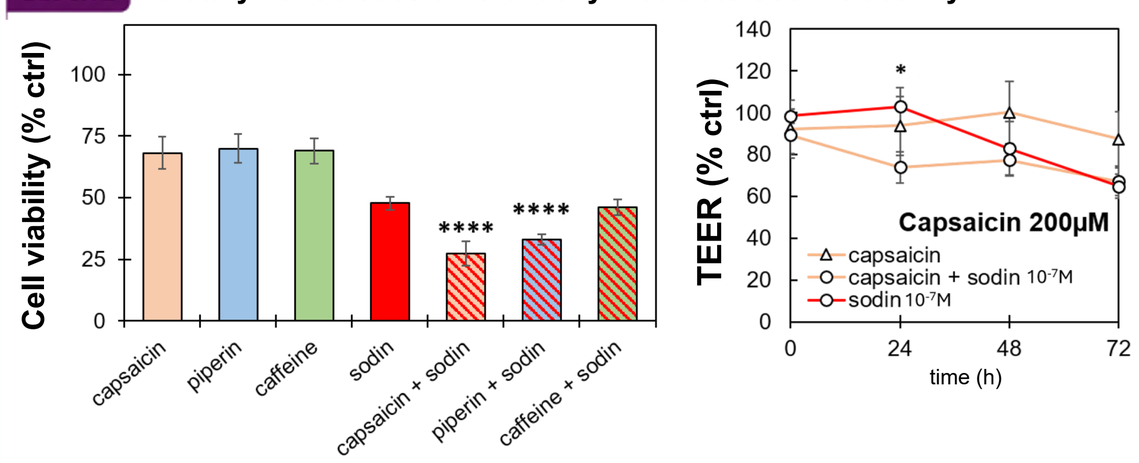
RESULTS & DISCUSSION

BLOCK 1 Sodin 5 activity in Caco 2 cells



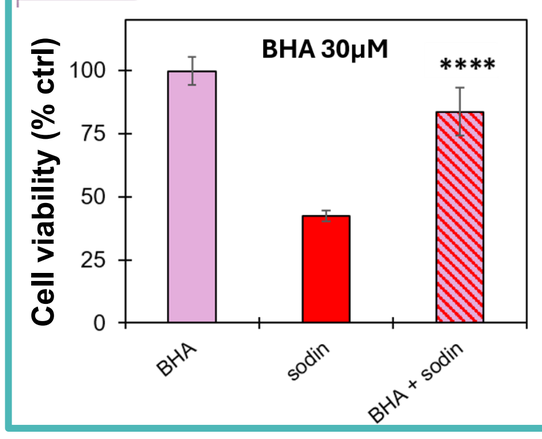
Sodin 5 reduced Caco 2 cell viability after 72 h exposure. A significant reduction was already evident at 10^{-9} M. The EC_{50} was about 10^{-7} M and was selected for subsequent experiments. TEER measurements further demonstrated that Sodin 5 progressively impaired Caco 2 epithelial barrier integrity.

BLOCK 2 Dietary xenobiotics differentially modulate Sodin 5 activity



Co-treatment with dietary xenobiotics produced distinct modulatory effects on Sodin 5 cytotoxicity. Capsaicin (200 µM) and piperine (200 µM) significantly enhanced the reduction in Caco 2 cell viability induced by Sodin 5, with capsaicin showing the strongest effect. Instead, caffeine (2.5 mM) did not significantly affect Sodin 5 cytotoxicity. At 24 h, TEER measurements further showed that co-treatment with capsaicin and Sodin 5 reduced epithelial barrier integrity compared with either compound alone, indicating that enhanced cytotoxicity was accompanied by increased epithelial dysfunction.

BLOCK 3 BHA protects against Sodin 5 induced cytotoxicity



Caco 2 cells were exposed to 10^{-6} M Sodin 5 for 24h, conditions that in previous works induced oxidative stress. The antioxidant dietary xenobiotic BHA strongly protected Caco 2 cells from Sodin 5 cytotoxicity, with a residual viability of 85% compared with 40% for Sodin 5 alone. This supports oxidative stress as a key component of Sodin 5 cytotoxicity and indicates that ROS scavenging can markedly attenuate RIP activity.

CONCLUSION

1. Sodin 5 reduced Caco 2 cell viability and impaired epithelial barrier integrity, supporting its value as potential candidate for RIP-based nanotherapeutic strategies in CRC therapy.
2. Dietary xenobiotics can influence Sodin 5 activity. In this context, capsaicin and piperine (200 µM) enhanced Sodin 5 cytotoxicity, whereas caffeine (2.5 mM) showed no significant effect.
3. BHA reduced Sodin 5 citotoxicty, suggesting that dietary antioxidant xenobiotics may attenuate the cytotoxic potential of sodin-based therapeutics.

Overall, our results suggest that diet derived xenobiotics represent a relevant but overlooked variable in the preclinical evaluation of RIPs as payloads for targeted nanoconjugates. These findings support further investigation of dietary xenobiotic interactions with RIP-based nanoconjugates and may also provide a framework for evaluating their impact on other therapeutic strategies for CRC.

FUTURE WORK / REFERENCES

1. Bolognesi, A., Bortolotti, M., Maiello, S., Battelli, M., & Polito, L. (2016). Ribosome-Inactivating Proteins from Plants: A Historical Overview. Molecules, 21(12), 1627. https://doi.org/10.3390/molecules21121627
2. Biscotti, F., Ragucci, S., Bortolotti, M., Falà, F., Perrone, C., Landi, N., Bolognesi, A., Di Maro, A., & Polito, L. (2026). Ribosome-Inactivating Proteins from Salsola soda L. and Saponaria officinalis L. Are Promising Candidates for Targeted Therapy of Colon Cancer. Biomedicines, 14(5), 981. https://doi.org/10.3390/biomedicines14050981
3. Landi, N., Ragucci, S., Citores, L., Clemente, A., Hussain, H. Z. F., Iglesias, R., Ferreras, J. M., & Di Maro, A. (2022). Isolation, Characterization and Biological Action of Type-1 Ribosome-Inactivating Proteins from Tissues of Salsola soda L. Toxins, 14(8), 566. https://doi.org/10.3390/toxins14080566