



Dr. Douwes informs!



4-Methylumbelliferone [4-MU] in cancer treatment

4-Methylumbelliferone (4-MU) was used in Germany for many years as a spasmolytic especially for bile problems. The brand name was "Cholespasmin". Since the request for this drug was so low, it was taken from the market last year. In the meantime we have evidence underlined by intensive research, that 4-MU could be active in cancer treatment.

What exactly does 4-MU?

It boosts the tumor microenvironment, remodeling the tumor vessels, and has the an antitumor effect especially if combined with Immunotherapy. More important is that it inhibits the hyaluronic acid. (Mariana Malvicini, Esteban Fiore, Valentina Ghiaccio, Flavia Piccioni, Miguel Rizzo, Lucila Olmedo Bonadeo, Mariana García, Marcelo Rodríguez, Juan Bayo, Estanislao Peixoto, Catalina Atorrasagasti, Laura Alaniz, Jorge Aquino, Pablo Matar and Guillermo Mazzolini)

Very important is the activity of 4-MU in prostate cancer.

Prevention and treatment of advanced prostate cancer (PCa) by a nontoxic agent can improve the longterm outcome, while maintaining quality of life.

4-Methylumbelliferone (4-MU)

- is a dietary supplement that inhibits hyaluronic acid (HA) synthesis.
- is an effective nontoxic, oral chemopreventive and therapeutic agent.

Hyaluronan (HA) is a prominent component of the extracellular matrix at many sites of chronic inflammation, including type 1 diabetes (T1D), multiple sclerosis, and numerous malignancies. Recent publications have demonstrated that when HA synthesis is inhibited using 4-methylumbelliferone (4-MU), beneficial effects are observed in several animal models of these diseases. Notably, 4-MU is an already approved drug in Europe and Asia called "hymecromone" where it is used to treat biliary spasm.

- decreased microvessel density and proliferative index ($P < .0001$).
- completely prevented/inhibited skeletal metastasis in the PC3-ML/Luc+ model and DU145-tumor growth (85–90% inhibition, $P = .002$).
- also statistically significantly downregulated HA receptors, PI-3K/CD44 complex and activity, Akt signaling, and β -catenin levels/activation, but upregulated GSK-3 function, E-cadherin, and apoptosis effectors ($P < .001$); HA addition or mAkt overexpression rescued these effects.
- is an effective nontoxic, oral chemopreventive, and therapeutic agent that targets PCa development, growth, and metastasis by abrogating HA signaling.

Prostate cancer is diagnosed largely on the basis of the levels of a protein in blood, the prostate specific antigen (PSA).

About 70 percent of the patients diagnosed with prostate cancer survive more than 10 years following curative treatments. Patients with low-risk/low-volume disease may opt for active-surveillance where surgery or radiation is delayed until the disease progresses. However, the disease recurs within two to eight years in about 30 percent of patients.

Once relapsed, the disease is highly aggressive and metastasizes to bone in the later stages, causing debilitating morbidity and mortality. The current treatments are only palliative for metastatic prostate cancer. However, since prostate cancer is a slow progressive disease, our hypothesis was that it should be amenable to preventive strategies using local transurethral hyperthermia in combination of dietary supplements which when started early may eradicate the disease and enhance survival while also improving patients' quality of life.

One of the drugs we prescribe our patients after transurethral hyperthermia is 4-MU. It has some anti-cancer properties against prostate cancer cells. Since it is non-toxic and readily consumed to improve liver health and gall bladder function, 4-MU is the best preventive agent on hand. 4-MU has been known to inhibit the synthesis of hyaluronic acid (HA), a sugar polymer. The HA family of molecules promotes prostate and bladder cancer cell growth, their invasive activities and induces angiogenesis (the growth of new blood vessels that feed the tumor). 4-MU shuts down these processes by inhibiting HA synthesis and is therefore an excellent drug for aftercare after transurethral hyperthermia and secondary prevention.

4-MU is available as a specific prescription from our compounding pharmacy.



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