**Prospects for the application of tryptanthrin and mostotrin alkaloids in therapy and control of inter-specie interactions in various symbiotic systems: A Review**

**ABSTRACT:** Tryptanthrin (TR) is one of the most widespread and well-known quinazolinone alkaloids with cytotoxic, antimicrobial and immunomodulatory efficiencies. This secondary metabolite exhibits a large area of biological activity, generating an increasing interest in the synthesis and evaluation of its derivatives and analogues. As main natural sources are known plant species like *Polygonum tinctorium* and other indigo plants. Currently, a lot of attention has been paid to the studies on the possible bio-regulatory role of TR. Mostotrin (MT) is a synthetic water-soluble analogue of TR which can expand the spectrum of pharmaceuticals for the treatment of inflammatory, antitumor, infectious diseases, and recent appearing epidemics like SARS-CoV-2. TR and MT derivatives even have capacity for use as important elements of signaling control in inter-species or inter-kingdom relationships of various multi-member microbiomes (community of microorganisms in e.g. the human body) with the host organisms and interactions of microorganisms in diverse marine or earth ecosystems. Recent published studies on the biological activity and probable molecular mechanisms underlying the therapeutic and regulatory actions of TR and MT became the subject of analysis in this mini-review.

Key words: tryptanthrin, mostotrin, antitumor, antimicrobial, anti-inflammatory agents, signaling control, QS

**1. Introduction**

Tryptanthrin (TR) is one of the most widespread and well-known quinazolinone alkaloid with cytotoxic, antimicrobial and immunomodulatory potencies. This secondary metabolite exhibits a wide spectrum of biological activity, generating increasing interest in the synthesis and evaluation of its derivatives and analogues [1-3, 30]. Currently, a lot of attention has been paid to the studies on the possible bio-regulatory role of TR [3].

TR was obtained from extracts of several indigo higher plants (genera *Couroupita*, *Isatis*, *Polygonum*, *Strobilanthes* and others), fungi (*Candida lipolitica, Schizophyllum commune, Leucopaxillus cerealis)*, marine bacteria, as well as yeasts of the genus *Malassezia*, known as part of the skin microflora [3, 4]. Recently, it was found that TR plays an important role in ensuring the proper functioning of a complex system of intercellular interactions of microorganism populations with the immune system and human microbiome. It also involved in the regulation of symbiotic relationships in the natural habitats of micro- and macroorganisms in marine and soil biocenoses (biological communities).

**2. Biological activity and molecular - actions of TR and MT mechanisms**

Secondary metabolites of the TR series are examples of natural bioregulators, which currently being intensively researched to clarify possibilities of the control of the microbiome of humans and animals, as well as for managing of plant and marine biocenoses [5, 6]. Recently, the high potential of TR for blockage of the virulence of *Acinetobacter baumannii* via disrupting of intercellular signaling communications was discovered. TR reduces the formation of biofilm and inhibits quorum sensing-related genes. Quorum Sensing or Quorum Signaling (QS) interactions are the systems for coordinating gene expression depending on bacterial population density [7]. Indole secondary metabolites of the yeast *Malassezia* spp. (including tryptanthrin, indirubin, indolocarbazoles), exerted a dramatic effect on antigen-presenting cells in the skin cells and the cutaneous mycobiota, directly related to the pathogenesis of seborrheic dermatitis and pityriasis versicolor, in common English “tinea versicolor” [8].

The both structural diversity of secondary metabolites of this series and their biological potency provide the promising prospects for drug development with different therapeutic applications, ranging from anti-inflammatory and anti-cancer agents to the action against resistant bacterial and fungal infections [9]. Given is the urgent need to develop new antimicrobial agents and strategies to combat antibiotic-resistant pathogens [10]. TR can be considered as one of the promising candidates for the development of new antimicrobial and anti-inflammatory remedies to treat cutaneous infections of humans and animals. As an example, the strong effect of TR on the opportunistic pathogen *Vibrio splendidus* might be mentioned, this bacterium is known to cause the skin ulcer syndrome and huge losses in the *Apostichopus japonicus* sea cucumber farming industry [6]. TR can be used as a bactericide against *V. splendidus* by inhibiting the growth of the bacterium itself, bacterial flagella, and the biosynthesis of extracellular proteases. Moreover, the sigma 54-dependent transcriptional regulators and, especially, LuxO1 the quorum-sensing regulatory protein, were identified as potential targets for the TR inhibitory effect on *V. splendidus* [11].

TR inhibits also the biofilm formation of *A. baumannii* by altering the QS system and reducing the level of virulence factors that disturb bacterial interactions [7]. It highly exhibits *in vitro* activity against mycobacteria by inhibiting enoyl-ACP reductase (ENR), one of the key enzymes involved in the synthesis of mycolic acid, an important component of the cell walls of *Mycobacterium spp*. ENR can be considered as a main target for the antimicrobial activity of TP (growth arrest) [12].

TR exhibits strong antifungal activity against yeasts and dermatophytes. The zoophilic dermatophyte *Trichophyton benhamiae* causes inflammatory cutaneous fungal infections in humans and animals. This alkaloid almost completely prevents *T. benhamiae*-induced damage to dermal fibroblasts and epidermal keratinocytes. Important evidence has been provided that it is not only a potent antifungal agent, but also modulator of the innate immune response [13].

Antiangiogenic (preventing the formation of new blood vessels) pathways are important for inhibiting tumor growth and migration. TR demonstrates anticancer and antiangiogenic properties *in vivo* [1, 2] and can inhibit tumor growth by down-regulating the expression of delta-like protein 4, which plays an important role in tumor vascular development [14]. Therefore, TR is a promising scaffold for developing anticancer agents aimed for the inhibition of tumor angiogenesis [2]. Oxidative stress, induced by TR in tumor cells of various origins is one of the proposed mechanisms for its cytotoxic effect, causing tumor cell death through apoptotic mechanisms [15].

Recently, tryptanthrin was shown to be a potent inducer of liver cancer cell senescence. Screening of senolytics (selectively eliminates senescent cells) *in vitro* and *in vivo* identified a key regulator of redox homeostasis, glutathione S-transferase P1 (GSTP1), as a target protein responsible for tumor cell aging. TR directly binds to GSTP1 and inhibits its enzymatic activity, mediating the accumulation of reactive oxygen species (ROS) followed by the DNA damage response (DDR). This promotes TP-induced of primary cellular senescence *via* the GSTP1/ROS/DDR/NF-κB/SASP axis, highlighting its potential application in liver cancer therapy [16].

TR also has the properties of a potent anti-inflammatory agent, as a specific inhibitor of a set of enzymes involved in the development of inflammatory processes. During inflammation in macrophages, synoviocytes (tissues in the lining of joints), fibroblasts, chondrocytes (cells of healthy cartilage) and endothelial cells after their induction by lipopolysaccharide, oxidative enzymes cyclooxygenase 2 (COX-2) and lipoxygenase 5 (LOX-5) begin to function actively. The inhibitory effects of TR on COX-2 (IC50 = 64 nM) and LOX-5 (IC50 = 150 nM) at the cellular level, as well as its suppression of the synthesis of pro-inflammatory prostaglandin PGE2, highlighted prospects for its possible use as an anti-inflammatory agent [17, 18]. TR also demonstrated significant beneficial effects on neutrophils (white blood cells of the immune system) by regulating the production of the pleiotropic cytokine oncostatin M (OSM), which belongs to the interleukin 6 group and acts through the PI3K, AKT, and NF-κB signaling pathways. Therefore, TR may have a positive potential for the treatment of OSM-mediated inflammatory diseases. In addition, TR inhibits the activation of JAK/STAT3 signaling and nuclear translocation of NF-κB p65, promotes nuclear expression of Nrf2 *in vitro* and *in vivo* by regulating the Keap1/Nrf2 signaling pathway, and suppresses the TLR4/MyD88/ROS/NF-κB signaling pathways, exerting a pronounced anti-inflammatory effect [19, 20].

TR can also inhibit the activation of inflammasomes (innate immune system receptors/sensors), important sentinels of innate immunity that play a key role in the development of inflammation and cancer progression. Several inflammasome sensor proteins interact with specific pathogen- and injury-associated molecular patterns (PAMPs and DAMPs, respectively), forming multiprotein complexes with the adaptor proteins ASC and caspase-1. During disease, cells are exposed to multiple PAMPs and DAMPs, that leads to the concerted activation of several inflammasomes. In a mouse model of inflammatory diseases, TR significantly reduces their progression [21]. According to the authors, targeting the adaptor basic protein ASC is a key stage in the mechanism of anti-inflammatory action of TR. Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease affecting joints and bones, which is partly mediated by proteases and cytokines influencing synovial macrophages and fibroblast-like synoviocytes. Evaluation of the therapeutic potential of TR and its oxime derivative (TR-Ox) *in vivo* on mouse arthritis models showed that both compounds significantly attenuated the development of collagen-induced arthritis and anti-collagen antibody-induced arthritis with comparable efficacy. TR and TR-Ox were equally effective in suppressing the clinical symptoms of RA and associated lesions and can be considered promising drug candidates for therapy of RA [22].

Current studies on the skin microbiome reveal the potential of using TR for the treatment of various skin diseases. Pre-clinical trials have demonstrated the efficacy of TR against psoriasis, a skin disease characterized by keratinocyte (primary cells in the epidermis) hyperproliferation and inflammation. The liposomal formulation of TR exhibited high therapeutic efficacy in an experimental model of psoriasis without signs of local or systemic toxicity [23]. Topical application of TR suppressed skin carcinogenesis. It attenuated inflammation, inhibited hair follicle (HF) cell proliferation, and suppressed the activation of β-catenin (multifunctional protein), the major HF cell proliferation factor. In addition, TR inhibited the activation of mitogen-activated protein kinases ERK1/2 and p38, which promote β-catenin activation, and appears to be an effective skin cancer suppressor [24].

Pressure ulcers (PUs), or ischemic necrosis caused by prolonged local pressure on tissue, remain to be a serious health problem today. Treatment with TR reduces inflammation by inducing macrophage polarization into the anti-inflammatory M2 phenotype. This type of macrophage polarization occurs by suppressing the activation of the cytosolic (cytoplasm fluid) DNA sensor cGAS and the stimulation of interferon genes (STING). The cGAS-STING signaling pathway plays an integral role in the host immune response, and abnormal activation of cGAS-STING is closely associated with various autoimmune diseases. Therefore, targeting the cGAS-STING-TBK1 axis now considered a promising strategy in the treatment of autoimmune diseases [25].

The drug candidate Kourochitin, developed on the basis of TR and chitosan, is a promising complex therapeutic agent. This drug has pronounced wound-healing efficiency against burn, flap and infected wounds, and can be widely used as a potential agent for healing wounds of various etiologies [26]. In the model of allergic contact dermatitis, Kourochitin demonstrates a therapeutic effect on pathophysiological, hematological and immunological parameters, increases the epidermal healing index and suppresses the production of major pro-inflammatory cytokines in the blood. In a mouse model of imiquimod-induced (drug to induce skin inflammation) psoriasis, the use of Kourochitin led to a decrease in the severity of psoriasis manifestations on the inflamed epidermis and in the treatment of atopic dermatitis in dogs, it almost completely eliminated signs of allergic symptoms [27]. The obtained data indicate that Kourochitin is the effective therapeutic agent for the treatment of various dermatological diseases.

In order to develop more active and less toxic leads, a number of new and/or poorly studied TR analogues have been synthesized and tested for biological activity. Our research strategy led to the synthesis of mostotrin (MT), a water-soluble analogue of TR, in which the CO group is replaced by an bioisosteric C=N group bearing a cationic center in the side chain. This modification resulted in significantly improved aqueous solubility of TR and enhanced its biological potency compared to TR [28, 29].

High solubility in water and significantly lower acute toxicity (LD50 = 375 for MT *vs* 75 mg/kg for TR) enable its use in aqueous drug formulations, both for *per os* and for parenteral routes of the administration. The mentioned advantages of MT could significantly improve bioavailability and therapeutic effectiveness in treating of cancer and infectious diseases. MT selectively inhibits tumor cell proliferation *in vitro*, exhibits antitumor efficacy *in vivo* and enhances the chemotherapeutic potency of doxorubicin in combination therapy. The obtained results form the foundation for further study of MT as a potential immunomodulatory, antitumor and antibacterial agent. The synthesis of MT paves the way to structural optimization of the TR scaffold that can increase the therapeutic potential of this class of compounds [28, 29].

Thereby, the of synthesis of MT as well as its derivatives and analogs can expand the arsenal of pharmaceuticals for the treatment of inflammatory, oncological and infectious diseases. TR and MT derivatives also have potential for use as important elements of signaling control in inter-species or inter-kingdom relationships in various multi-member microbiomes with the host organisms and interactions of microorganisms in diverse marine or terrestrial ecosystems. The molecular mechanisms underlying the regulatory action of TR and MT, as well as their involvement in signaling pathways for the implementation of QS, remain the subject of further research. Furthermore, TR revealed good results in the battle against SARS-CoV-2. The results from the molecular docking strongly imply that the prepared compounds, especially T8H-TSC, displayed potent inhibitory effects against the PLpro and Mpro proteases. Accordingly, T8H-TSC potently represses SARS-CoV-2 replication in Vero cells. The antiviral effect of PAA-TSC was significantly smaller. The obtained results suggest that the structural motif of thiosemicarbazone could represent a promising starting point for designing novel antiviral agents [30].

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