

Tannins and Related Compounds: Killing of Amastigotes of *Leishmania donovani* and Release of Nitric Oxide and Tumour Necrosis Factor α in Macrophages *in vitro*

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The antileishmanial and immunomodulatory potencies of a series of 28 polyphenols were evaluated in terms of extra- and intracellular leishmanicidal activity and macrophage activation for release of nitric oxide (NO), tumour necrosis factor (TNF) and interferon (IFN)-like properties. For this, several functional bioassays were employed including an *in vitro* model for leishmaniasis in which murine bone marrow-derived macrophages (BMM Φ) were infected with the obligate intracellular parasite *Leishmania donovani*, an extracellular *Leishmania* proliferation assay, a fibroblast-lysis assay (TNF-activity), and a biochemical assay for NO. Except for gallic acid, its methyl ester, shikimic acid and catechin (EC₅₀ 25.8–67.9 nM) all polyphenols tested significantly inhibited the intracellular survival of *L. donovani* amastigotes (EC₅₀ 0.4–13.9 nM) when compared with the clinically used agent, sodium stibogluconate (EC₅₀ 10.6 nM). In contrast, none of the samples proved to be directly toxic for the extracellular promastigote form of the parasite. Noteworthy, the phenolic samples showed only moderate or no cytotoxicity against the murine host cells (EC₅₀ 10 to >144 nM). Although NO is an important effector molecule in macrophage microbicidal activity, the inducing potential of the test compounds for its release was found to be very moderate ranging from 7–54 μ M (IFN- γ /LPS 119 μ M). On the other hand, inhibition of NO production had no apparent effect on intracellular leishmanicidal activity of polyphenols. Their *in vitro* TNF-inducing potential producing 50% lysis in murine L929 cells increased in the order of simple phenols and flavanols (34–48 U/ml) < A-type proanthocyanidins (53–80 U/ml) < B-type proanthocyanidins (64–200 U/ml) < hydrolyzable tannins (287–350 U/ml) at the host cell subtoxic concentration of 50 μ g/ml. Furthermore, gallic acid and some hydrolyzable tannins showed appreciable IFN-like activities (14–23 U/ml) as reflected by inhibition of the cytopathic effect of encephalomyocarditis virus on fibroblast L 929 cells. The results provide a rational basis for the recorded anti-infectious efficacy of traditionally used herbal medicines containing tannins *in vivo*, in the light of both only moderate direct antimicrobial activities of distinct polyphenols *in vitro* and the limited knowledge on their uptake in humans.