

Beneficial regulation of matrixmetalloproteinases and their inhibitors, fibrillar collagens and transforming growth factor-beta by *Polypodium leucotomos*, directly or in dermal fibroblasts, ultraviolet radiated fibroblasts, and melanoma cells.

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Abstract

The extracellular matrix (ECM) that gives tissue its structural integrity is remodeled in skin aging/photoaging and cancer via the increased expression/activities of matrixmetalloproteinases (MMP), inhibition of the tissue inhibitors of matrix metalloproteinases (TIMP), or inhibition of collagen synthesis. Transforming growth factor-beta (TGF-beta), a predominant regulator of the ECM, is inhibited in aging/photoaging and stimulated in carcinogenesis. *P. leucotomos* (fern) extract has potential to counteract these alterations via its antioxidant, anti-inflammatory and photoprotective properties. The goal of this research was to determine the efficacy of *P. leucotomos* to (a) directly inhibit MMP-1, 2, 3, and 9 activities, (b) inhibit MMP-2, and stimulate TIMPs, fibrillar collagens and TGF-beta in non-irradiated or ultraviolet (UV) radiated fibroblasts, and (c) inhibit MMPs and TGF-beta, and stimulate TIMPs in melanoma cells. To this purpose, we examined the direct effect of *P. leucotomos* (0-1%) on MMPs' activities, and its effects on the expression (protein and/or transcription levels) of (1) MMPs and TIMPs in dermal fibroblasts, and melanoma cells, (2) TGF-beta in non-irradiated, UVA (2.5 J/cm²) or UVB (2.5 mJ/cm²) irradiated fibroblasts, and melanoma cells, and (3) types I, III, and V collagen in non-irradiated or UV irradiated fibroblasts. *P. leucotomos* directly inhibited the activities of MMPs as well as the expression of MMPs in fibroblasts, and melanoma cells while stimulating the expression of TIMPs in these cells. *P. leucotomos* stimulated types I, III, and V collagen in non-irradiated fibroblasts, and types I and V collagen in UV radiated fibroblasts. *P. leucotomos* had predominant stimulatory effects on TGF-beta expression in non-irradiated or UV radiated fibroblasts, and inhibited TGF-beta expression in melanoma cells. The effects of *P. leucotomos* were largely similar to that of ascorbic acid. *P. leucotomos* demonstrated dual protective effects on the ECM via its inhibition of the ECM proteolytic enzymes and the stimulation of the structural ECM collagens. The effects of *P. leucotomos* on fibroblasts and melanoma cells may be partly via its cell-specific regulation of TGF-beta expression and partly via its antioxidant property. The intake or topical application of *P. leucotomos* may be beneficial to skin health, in aging and cancer prevention or treatment.

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