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LETTER TO THE EDITOR

Quercetin
A potential treatment for keloids

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Dear Editor,

Plant secondary metabolites are chemically diverse compounds, some of which have been largely exploited as pharmaceuticals, food additives and flavours. Flavonoids and other phenolic compounds constitute one of the main classes of secondary metabolites.[1,2] As one of the most abundant form of flavonoids, quercetin (3,3′, 4′, 5,7-pentahydroxyflavone) has been receiving much attention owing to its potential antioxidant, anti-allergic, anti-inflammatory, anti-cancer, anti-diabetic, anti-microbial and cardio-protective properties.[1]

Keloids are exuberant overgrowths of scar with excessive fibroblast proliferation and matrix deposition, which has the ability to spread beyond the original boundary of the wound.[3] Despite existence of a wide array of therapies available for keloids, no treatment is yet considered completely effective. Corticosteroids, surgical excision, silicone sheeting, cryosurgery, radiotherapy, laser therapy and photodynamic therapy have been extensively applied to treat keloids.[4] Other promising approaches such as mesenchymal stem cell therapy, fat grafting, electrical stimulation, and deployment of RNA interference seem to be beneficial for the treatment of keloids.[5] Over the past years, studies found compelling evidence that indicate the advantageous properties of quercetin as a potential candidate for adjuvant therapy of keloids.[3,4]

According to Si *et al*.'s recent study, keloid fibroblasts treated with quercetin showed augmented sensitisation to radiation compared to untreated cells.[3] The main mechanism underlying the suppression of radio-resistance by quercetin is down-regulation of hypoxia-inducible factor 1, a prognostic factor used in clinical practice after radiation therapy, through the phosphoinositide 3-kinase/Akt pathway.[3] An *in vitro* study by Mathangi Ramakrishnan *et al*. revealed a dose-dependent action of quercetin and vitamin D3 on isolated keloid fibroblasts.[4] In this context, both agents alone were capable of reducing either collagen I synthesis or *B-cell lymphoma 2* gene expression and increasing caspase-3 levels in fibroblast cells, resulting in higher number of apoptotic fibroblasts.[4] Cho *et al*. found that quercetin and onion extract diminished the proliferation rate of fibroblasts in a concentrate-dependent manner by up-regulation of matrix metalloproteinase-1 expression levels *in vitro* and *in vivo*.[2] However, contrary to expectations, expression levels of type I collagen were not markedly changed. Khonkarn *et al*. attempted to develop a quercetin-incorporated microemulsion-based gel formulation for topical delivery against keloids and concluded that the developed gel may be a promising vehicle for topical drug delivery.[6]

Doersch and Newell-Rogers found that quercetin diminishes fibrosis at wound sites in quercetin-treated mice by altering cell interactions with the extracellular matrix (ECM) through increasing αV- and decreasing β1-integrin expression levels.[1] This would enhance cell migration with less ECM requirement to facilitate wound closure. Gopalakrishnan *et al*. showed beneficial properties of 0.1% quercetin ointment in accelerating cutaneous wound healing in rats by increasing the expression levels of vascular endothelial growth factor, transforming growth factor-β1 and interleukin-10 as well as reducing tumour necrosis factor-α levels in rats.[7] In addition, quercetin-treated rats exhibited less inflammatory cells, more regular collagen deposition and better re-epithelialisation compared to the control group.[7]

Multiple approaches can be propounded to improve therapeutic efficacy of quercetin for ideal skin delivery. The conjugation of quercetin with nanoparticles or fatty acids and designing quercetin-based hydrogels are novel strategies for combating keloids. Furthermore, the use of quercetin as an adjuvant therapy with other anti-keloid treatments may result in lower keloid recurrence rates. In patients with keloids and hypertrophic scars, onion extract gel which is a rich source of quercetin, has been shown to be beneficial when combined with other therapeutic strategies such as silicone gel sheet and corticosteroids.[8,9] In terms of sensitiveness, pain, itching and elevation, intralesional triamcinolone acetonide plus onion extract gel was superior to triamcinolone acetonide alone.[8] Hosnuter *et al*.'s comparative prospective study combined onion extract gel and silicone gel sheet, which significantly reduced scar height; the combination was found to be more effective than onion extract gel alone.[9]

Quercetin can be formulated in different dermatological preparations such as micro-emulsion gels, liposomes and a nanostructured lipid carrier. These formulations can be used topically for both prevention and treatment of keloid scars. Overall, the propitious role of quercetin as an immunomodulatory, anti-fibrotic agent will hopefully increase the treatment options available for patients who are afflicted with keloids, hypertrophic scars and wounds.

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