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Polyphenols and immunity

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Flavonoids are biologically-active polyphenolic compounds with antioxidative, antineoplasic, cardiovascular protective and anti-inflammatory properties. Pharmacological therapy is essential in inflammatory bowel disease but has many adverse effects and does not cure the disease. Flavonoids are excellent candidates because of their anti-inflammatory properties and their low toxicity. Several flavonoids have been shown to exert intestinal anti-inflammatory activity *in vivo*, including (mg/kg) quercitrin 1–5[1], rutin 10–25[2], morin 25[3,4], hesperidin and diosmin 10–25[5]. However, the mechanism of action is unclear. Since inflammation is associated by significant oxidative stress, this mechanism may be relevant. Indeed, flavonoid treatment counters colitis-induced glutathione depletion. On the other hand, quercitrin treatment reduces macrophage infiltration in the dextran sulfate sodium colitis model[6]. The effects of flavonoids on primary macrophages have been studied and their structure–activity relationship characterized[7]. A number of flavonoids inhibit macrophage proliferation (but not cell viability) and some additionally reduce TNF and inducible NO synthase (iNOS) expression, probably interfering with the NF-κB pathway. The structural determinants of activity include the C-2═C-3 double bond, the catechol group in the B ring and the 2-position of the B ring.

Most of these flavonoids are glycosides, which are known to be hydrolysed by bacterial enzymes in the gut. Since luteolin and quercetin are not active *in vivo* and aglycone flavonoids are absorbed in the small intestine it is likely that glycosides act as prodrugs, releasing the biologically-active aglycone in the lumen and preventing their premature absorption, which has been proven in the case of quercitrin[8]. In particular, a faecal homogenate was shown to mediate quercetin release from quercitrin *in vitro*, and the resulting aglycone retained TNF, iNOS and IL-1β inhibitory activity in murine bone marrow-derived macrophages. This principle probably applies to the other heterosides with known intestinal anti-inflammatory activity.

In conclusion, flavonoids have intestinal anti-inflammatory activity that is associated with macrophage inhibition and antioxidative effects. Further investigation of the mechanistic aspects of flavonoid pharmacological action is underway.

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