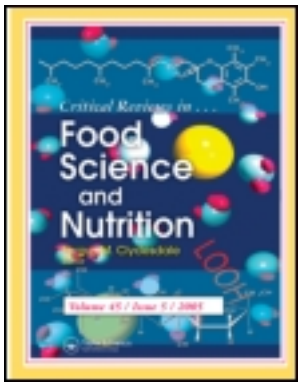

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R. González [a], I. Ballester [c], R. López-Posadas [a], M. D. Suárez [b], A. Zarzuelo [b], O. Martínez-Augustin [b] & F. Sánchez De Medina [a]

[a] Departments of Pharmacology, CIBERehd, School of Pharmacy, University of Granada

[b] Biochemistry and Molecular Biology II, CIBERehd, School of Pharmacy, University of Granada

[c] Massachusetts General Hospital, Gastrointestinal Unit GRJ716, 55 Fruit Street, Boston, MA, 02114, USA

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Effects of Flavonoids and other Polyphenols on Inflammation

R. GONZÁLEZ,[1] I. BALLESTER,[3] R. LÓPEZ-POSADAS,[1] M.D. SUÁREZ,[2] A. ZARZUELO,[2] O. MARTÍNEZ-AUGUSTIN,[2] and F. SÁNCHEZ DE MEDINA[1]

[1]Departments of Pharmacology, CIBERehd, School of Pharmacy, University of Granada
[2]Biochemistry and Molecular Biology II, CIBERehd, School of Pharmacy, University of Granada
[3]Massachusetts General Hospital, Gastrointestinal Unit GRJ716, 55 Fruit Street, Boston, MA 02114, USA

Flavonoids are a family of polyphenolic compounds which are widespread in nature (vegetables) and are consumed as part of the human diet in significant amounts. There are other types of polyphenols, including, for example, tannins and resveratrol. Flavonoids and related polyphenolic compounds have significant antiinflammatory activity, among others. This short review summarizes the current knowledge on the effects of flavonoids and related polyphenolic compounds on inflammation, with a focus on structural requirements, the mechanisms involved, and pharmacokinetic considerations. Different molecular (cyclooxygenase, lipoxygenase) and cellular targets (macrophages, lymphocytes, epithelial cells, endothelium) have been identified. In addition, many flavonoids display significant antioxidant/radical scavenging properties. There is substantial structural variation in these compounds, which is bound to have an impact on their biological profile, and specifically on their effects on inflammatory conditions. However, in general terms there is substantial consistency in the effects of these compounds despite considerable structural variations. The mechanisms have been studied mainly in myeloid cells, where the predominant effect is an inhibition of NF-κB signaling and the downregulation of the expression of proinflammatory markers. At present there is a gap in knowledge of in vitro and in vivo effects, although the pharmacokinetics of flavonoids has advanced considerably in the last decade. Many flavonoids have been studied for their intestinal antiinflammatory activity which is only logical, since the gastrointestinal tract is naturally exposed to them. However, their potential therapeutic application in inflammation is not restricted to this organ and extends to other sites and conditions, including arthritis, asthma, encephalomyelitis, and atherosclerosis, among others.

Keywords asthma, inflammatory bowel disease, arthritis, pharmacokinetics, atherosclerosis, mechanism of action

INTRODUCTION

Polyphenols, including flavonoids, are bioactive compounds that display a number of biological activities which have been reviewed before (Middleton et al., 2000). In particular, flavonoids are renowned for their antioxidant/antiradicalary properties, and the SAR has been extensively characterized (Amic et al., 2007). We will focus on the antiinflammatory/immunomodulatory actions of flavonoids. While antioxidant defense undoubtedly plays a role in many of flavonoid actions, they will be considered here only from a mechanistic point of view. In general, though, structural requirements differ for antioxidant and antiinflammatory activities (Loke et al., 2008b).

Address correspondence to Fermín Sánchez de Medina, Department of Pharmacology, CIBERehd, School of Pharmacy, Campus de Cartuja s/n, 18071 Granada, Spain. Tel.: 34 958 241747. Fax: 34 958 248964. E-mail: fsanchez@ugr.es

The canonical structure of flavonoids is made up of a 3-ring core as depicted in Fig. 1. Positioning of the B ring in 3 instead of 2 gives rise to isoflavones, of which genistein is the most known compound. Depending on the presence of a 3-OH group and a double bond at 2, the flavone, flavanol, and flavanone families are generated. Anthocyanidins have a fully aromatized C ring and as a result they are positively charged. Tannins are also related to flavonoids but are usually present as high molecular weight polymers. Chalcones are related aryl ketonic compounds in which the C ring does not exist. There are enormous structural variations as different substitutions come into play into this scheme. It should be noted that flavonoids are found in nature predominantly in glycosylated form, which in itself is another source of structural variation and has a profound impact in pharmacokinetic and pharmacodynamic properties of these compounds. Resveratrol is comparable to a chalcone but has a 2-carbon bridge and no ketone group. Curcumin is only loosely related to flavonoids in that it is a polyphenolic

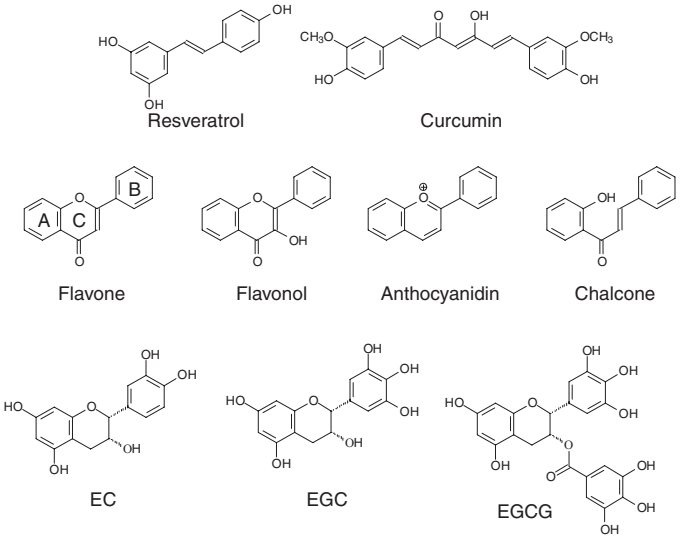

Figure 1 Chemical structure of some of the flavonoids and related polyphenolic compounds featured in this review. The flavonoid structure is composed of 3 rings, giving rise to the core flavone. The ring nomenclature is depicted in the flavone structure. Flavonols have an additional 3-OH, while anthocyanidins lack the 4-keto group and are fully aromatized and chalcones have an "open" C ring. Flavanones (not shown) are devoid of a 2–3 double bond. Catechins, including EC, ECG, and EGCG, lack both the keto group and the double bond. Considerable variation is introduced by distinct chemical substitutions, specially hydroxylation and glycosylation. Resveratrol resembles the flavonoid structure to a certain extent, but curcumin is only loosely related to the flavonoids.

aromatic compound found in vegetables. We will deal with sensu strictu flavonoids as well as related compounds, because of their interest and overall relation.

This minireview will focus on recent advances in the properties of these agents that are relevant to the treatment of inflammatory diseases. In vivo experiments will be presented classified by disease targeted, while in vitro studies will be presented separated by cell type. A consideration on pharmacokinetic issues will be presented first.

PHARMACOKINETICS

A substantial body of evidence has accumulated in the last few years regarding the pharmacokinetic profile of flavonoids. In vitro experiments using the standard Caco-2 cell model have revealed that aglycones, such as baicalein, wogonin, oroxylin-A, liquiritigenin, or isoliquiritigenin can be absorbed easily, while the glycosides have much lower permeability (Dai et al., 2008). In addition, some glycosides are extruded by P-glycoprotein (multidrug resistance-associated protein-1 or MDR1, gene symbol ABCB1), multidrug resistance-associated proteins (MRPs, ABCCs), or breast cancer resistance protein (BCRP, ABCG2) (Walgren et al., 2000a; Brand et al., 2008). However, it should be remembered that the epithelium produces the efficient glucuronidation and/or sulfation of these compounds, greatly reducing bioavailability (Steinert et al., 2008; Dai et al., 2008; Brand et al., 2008). Enzymatic cleavage by luminal bacteria also compromises flavonoid absorption, although deglycosylation seems to precede this (Hein et al., 2008).

Quercetin glycosides are substrates of the intestinal glucose transporter (SGLT-1) in the rat, which facilitates their absorption in the small intestine (Gee et al., 1998). This may account for the higher absorption of various quercetin glycosydes over quercetin (or rutin) in humans (Hollman et al., 1995). Similarly, the bioavailability of daidzein-7-O-beta-d-glucoside may be favored in glycosylated form (Rufer et al., 2008). In general rhamnosides are believed to be absorbed to a lesser extent than other glycosides. However, in the oocyte heterologous expression system, none of the 27 glycosylated and unglycosylated flavonoids were found to be absorbed via human SGLT1. However, the transporter was inhibited competitively by many of them (Kottra and Daniel, 2007). To further complicate matters, Walgren et al. (2000a; 2000b) reported effective absorption of quercetin 4′-beta-glucoside by SGLT1 in Caco-2 cells (i.e., by the human isoform), although this is greatly offset by apical MRP2 (Multidrug Resistance Associated Protein 2, also known as ABCC2) extrusion.

Flavanones such as hesperetin, naringenin, and eriodictyol are absorbed from the gastrointestinal tract (Kanaze et al., 2007; Gardana et al., 2007; Miyake et al., 2000) and it has been claimed that they are taken up by epithelial cells via a H^+-linked transporter and by transcellular passive diffusion (Kobayashi and Konishi, 2008), which is probably operative for all unglycosylated flavonoids.

Oral absorption of quercetin was reported quite a few years ago (Ueno et al., 1983), approaching 20%. It has since been confirmed in humans (Egert et al., 2008; Moon et al., 2008), rats (Santos et al., 2008), and pigs (Bieger et al., 2008). Other orally absorbed flavonoids are luteolin in the rat (Ying et al., 2008), narirutin and hesperidin (Brett et al., 2009), genistein in rats (Zhou et al., 2008b), flavan-3-ols ((-)-epigallocatechin –EGC– and (-)-epicatechin –EC–) (Auger et al., 2008), curcumin (Vareed et al., 2008), and the synthetic flavonoid NV-52 (Howes et al., 2008) in humans, and resveratrol in rats (Wenzel et al., 2005). Flavonoids bind to serum albumin with an affinity that depends on the B ring hydroxylation (Xiao et al., 2008).

Therefore, flavonoids are generally absorbed by the oral route, but intraluminal and first-pass metabolism, together with active extrusion mechanisms, reduce bioavailability substantially, and the main fraction of bioavailable flavonoid is in metabolized form. The rule of thumb is that in vitro actions should never be extrapolated to in vivo effects. In some cases metabolites may be as active as the parent compound, or even more, but this is relatively exceptional. In general, when antiinflammatory effects are studied in vivo, the route of administration is either oral/intragastric or parenteral, but no direct comparison is available. For example, for the assessment of antiarthritic activity in rodents, resveratrol, nobiletin, genistein (Verdrengh et al., 2003), procyanidins, and (-)-epigallocatechin-gallate (EGCG) (Imada et al., 2008) are administered by injection, while hesperidin and quercitin are active by the oral route (Mamani-Matsuda et al., 2006).

Table 1 Effects of polyphenols on different diseases

Flavonoid	RA	IBD	EAE	Res	Ath	IR	Br	Mtb	Sk	TS
apigenin				•						•
baicalein			•				•			•
catechin	•					•				
chrysin				•						
curcumin		•								
ECG					•					
EGCG	•	•				•			•	•
fisetin					•					
flavopiridol	•									
genistein	•	•	•							
hesperidin	•									
hesperidin		•								•
kaempferol					•					
luteolin	•	•*		•						
morin		•			•					
myricetin		•			•					
nobiletin	•			•						
quercetin	•			•	•		•	•		
quercitrin		•								
resveratrol	•	•	•	•**	•	•	•	•	•	•
rutin	•	•		•						•
silibinin			•							

Therapeutic effect in the different disease models is shown. *Depending on model. RA: rheumatoid arthritis; IBD: inflammatory bowel disease; EAE: Res: asthma except **COPD; Ath: atherosclerosis; IR: ischaemia-reperfusion; Br: brain inflammation; Mtb: metabolic syndrome; Sk: skin inflammation; TS: toxic shock. Some actions are based mostly on in vitro effects.

IN VIVO STUDIES

There have been quite a few studies performed in vivo with natural polyphenols (see Table 1 for a summary).

Rheumatoid Arthritis

A number of flavonoids and related polyphenols are active in rheumatoid arthritis models, i.e., collagen- and adjuvant-induced arthritis, including rutin, quercetin, resveratrol, nobiletin, hesperidin, alpha-glucosylhesperidin, catechin, the chalcone derivative 1-(2,4-dichlorophenyl)-3-(3-(6,7-dimethoxy-2-chloroquinolinyl))-2-propen-1-one (known as CIDQ), EGCG (and green tea polyphenols), flavopiridol, genistein, and others (Li et al., 2008; Tang et al., 2007; De Leon et al., 2003; Kawaguchi et al., 2006; Kometani et al., 2008; Verdrengh et al., 2003; Murakami et al., 2007; Imada et al., 2008; Kauss et al., 2008a; Wang et al., 2008a; Morinobu et al., 2008; Elmali et al., 2007; Mamani-Matsuda 2006). The mechanisms are ill defined, but include inhibition of osteoclast/macrophage differentiation and function (Murakami et al., 2007; Kauss et al., 2008a), estrogen modulation (Wang et al., 2008a), downregulation of NFAT (Morinobu et al., 2008), inhibition of ADAMTS (A Disintegrin-like and Metalloprotease (reprolysin type) with ThromboSpondin type 1 motif) 2/5 and protease expression in synovial fibroblasts and chondrocytes (Imada et al., 2008; Lin et al., 2003; Ishiwa et al., 2000), antiproliferative (Sekine et al., 2008) or proapoptotic (Byun et al., 2008) actions on synovial fibroblasts, and general immune depression (Li et al., 2008). Nobiletin counteracts osteoporosis when given parenterally to ovariectomized rats, also suggesting estrogen-related effects (Murakami et al., 2007). A recent small clinical trial with a hesperidin derivative with improved solubility yielded promising results (Kometani et al., 2008).

Experimental Allergic Encephalomyelitis

Experimental allergic encephalomyelitis is a widely used model of multiple sclerosis. It is induced in mice by injection of Freund's adjuvant and a myelin glycoprotein, producing a Th1/Th17 immunological reaction that results in brain derangement. Some flavonoids have been tested in this model, including resveratrol, baicalin, genistein, and silibinin (Zeng et al., 2007; Singh et al., 2007a; Min et al., 2007a; De Paula et al., 2008). Resveratrol induces apoptosis of preferentially activated but also quiescent T cells via actions on the estrogen and aryl hydrocarbon receptors (Singh et al., 2007a). In the other cases the mechanism was largely undetermined.

Inflammatory Bowel Disease

Since flavonoids are naturally ingested as part of the normal diet, it is logical that they have been studied frequently as possible modulators of intestinal inflammation. Various dietary polyphenols have been shown to exert intestinal antiinflammatory activity (reviewed in (Shapiro et al., 2007; Ballester et al., 2006)). These include rutin and quercitrin, glycosides of quercetin (Galvez et al., 1997; Sanchez de Medina et al., 1996; Kwon et al., 2005b), resveratrol (Martin et al., 2004; Martin et al., 2006), EGCG (Abboud et al., 2008; Lin et al., 2007; Ran et al., 2008), a green tea polyphenol extract (Mazzon et al., 2005; Oz et al., 2005; Varilek et al., 2001), curcumin (Nones et al., 2009a; Camacho-Barquero et al., 2007; Jian et al., 2005; Ukil et al., 2003; Sugimoto et al., 2002; Zhang et al., 2006; Jiang et al., 2006; Salh et al., 2003), theaflavin-3,3′-digallate (Ukil et al., 2006), 2′,4′,6′-tris(methoxymethoxy) chalcone (Lee et al., 2007c), piceannetol (3,5,3′,4′-tetrahydroxy-trans-stilbene) (Kim et al., 2008a), genistein (Seibel et al., 2008), morin (Galvez et al., 2001), hesperidin (Xu et al., 2009; Crespo et al., 1999), and diosmin (Crespo et al., 1999). The flavonoid synthetic derivatives NV-52 (an inhibitor of thromboxane synthase) and DA-6034 (Howes et al., 2007; Nam et al., 2008) are also active. Resveratrol is effective also in the animal model of necrotizing enterocolitis, a disease that affects predominantly formula-fed premature newborns and is associated with significant mortality (Ergun et al., 2007). There is one single study on small intestinal inflammation, showing lack of clinical efficacy of quercetin despite the demonstrated immunomodulatory effects at the epithelial level (Ruiz et al., 2007a). One intriguing study showed that orally administered luteolin actually worsens dextrane

sulfate sodium (DSS) colitis in mice, while ameliorating colitis in IL-10 KO mice (Karrasch et al., 2007a). By using transgenic mice expressing green fluorescent protein under the control of the NF-κB promoter, this group formulated the hypothesis that in DSS colitis luteolin blocked epithelial protective NF-κB proteins, while subepithelial actions predominated in IL-10 KO mice. The basis of this hypothesis is that DSS elicits colitis primarily by disruption of the epithelial layer, while IL-10 mice develop colonic inflammation in a more progressive and subtle fashion originating from immunological imbalance. There are various inflammatory bowel disease models which are used for preclinical drug testing that differ in their immune and pathological characteristics, raising the possibility of this type of analysis, although this approach is not regularly applied, probably because of the problems implied. For instance, dietary rutin supplementation failed to ameliorate colitis in MDR1A knockout mice (Nones et al., 2009b), while it is beneficial in acetic acid, trinitrobenzenesulfonic acid (TNBS), and DSS induced colitis (Galvez et al., 1997; Kwon et al., 2005b), but the implications of this discrepancy, if any, are difficult to ascertain.

The intestinal antiinflammatory activity of curcumin has been associated with a reduction in the activation of p38 MAPK but not JNK in vivo (Camacho-Barquero et al., 2007). In virtually all studies, however, a mechanism of action was not defined, owing to the broad impact of the flavonoids on inflammatory parameters measured in these studies, which typically include morphological parameters, myeloperoxidase activity, glutathione, and cytokines (TNF, IL-1β, IL-6). Rutin and quercitrin have been proposed to act as quercetin prodrugs, preventing premature absorption of the aglycone in the small intestine and releasing it in the colon (Fig. 2) (Kwon et al., 2005b; Comalada et al., 2005). This is based on the inability of quercetin to ameliorate DSS colitis and in the demonstrated release of quercetin from glycosydes by bacteria. This further suggests a local action of the flavonoid. Nevertheless, a number of other flavonoids are active when given in the unglycosylated form (see above).

One interesting article studied the deleterious effect of in utero and postnatal exposure to isoflavones on adult life colitis, an unexpected result (Seibel et al., 2008). This raises the possibility that phytoestrogen dietary enrichment or supplementation may have deleterious effects on the offspring, certainly an important issue that will require further experimentation.

Asthma

The antiallergic potential of flavonoids has been reviewed (Kawai et al., 2007). Typical parameters examined in drug testing in asthma models such as the ovalbumin sensitization model include functional performance (bronchoconstriction and bronchial hyperreactivity), anti-IgE, eosinophil infiltration, and cytokines (IL-4, IL-5, IFN-γ). Luteolin has been found to reduce ovalbumin-specific IgE levels in serum, to increase IFN-γ and to decrease IL-4 and IL-5 levels in the bronchoalveolar fluid at doses as low as 0.1 mg/kg (Das et al., 2003). Luteolin, which was given orally, was effective both pre- and post-induction, and it also alleviated bronchoconstriction and hyperreactivity. In the same model diets enriched in apigenin or chrysin lower total IgE, IL-4, and cytokine production (IL-4 and IL-13) by splenocytes ex vivo (Yano et al., 2007). In fact, dietary apigenin reduces IgE as well as RANTES in normal mice as well (Yano et al., 2006). Thus 3 different flavones are active in experimental asthma. On the other hand, the flavonol quercetin and its glycoside rutin have been tested in a guinea pig variant of the ovalbumin model, where they both lower airway resistance and reduce histamine, phospholipase A_2 and eosinophil peroxidase levels, and neutrophil/eosinophil infiltration (Jung et al., 2007). However, they were not as effective as dexamethasone. The beneficial effect of quercetin was confirmed in a separate study, showing diminished eosinophil but not neutrophil infiltration and no effect on IL-5 (Rogerio et al., 2007a). Isoquercitrin, another quercetin glycoside, had a somewhat higher effect, since it additionally lowered neutrophils and IL-5 (Rogerio et al., 2007a). Other quercetin derivatives are also active, including 3-O-methylquercetin 5,7,3′,4′-O-tetraacetate and quercetin 3-O-methyl ether (selected for their improved potency as inhibitors of phosphodiesterase 3/4), with an extended therapeutic impact that includes protection against induced bronchoconstriction, reduction of eosinophil infiltration and a decrease in IL-2, IL-4, IL-5, IFN-γ, and TNF (Jiang et al., 2007). It should be noted that the i.p. route was used in this study, although the doses were quite small. Narirutin, a flavanone glycoside, is also active in this model, reducing eosinophil counts in the peripheral blood and bronchoalveolar lavage fluid, IL-4 and IgE (Funaguchi et al., 2007). Nobiletin, a polymethoxylathed flavone, is also effective given intraperitoneally but it is less potent (Wu et al., 2006a). Resveratrol has been tested successfully in a chronic obstructive pulmonary disease model (Zhou et al., 2008a). Taken together, these data indicate that various different flavonoid derivatives have the capacity to modulate Th2 driven inflammation, although the mechanism is again imprecise. Possible cell targets include airway epithelial, macrophage, and lymphocytes, among others (see below).

Atherosclerosis

Polyphenols have received a great deal of attention in the prevention of cardiovascular disease, stemming from the so-called French paradox, which has been justified tentatively in terms of the antioxidant protection afforded by polyphenols present in wine and vegetables. Clearly, a high flavonoid diet appears to be of benefit, but whether polyphenols themselves account for this effect or may exert it on their own remains an unsolved question. Perhaps the compound most avidly studied in this regard is resveratrol. For instance, resveratrol has been shown to exert protective effects in the ApoE deficient mice model (Do et al., 2008), acting on blood lipid levels and also at the atherosclerotic plaque. The mechanism appears to be at least in part antiinflammatory, because the levels of ICAM-1 and VCAM-1

in atherosclerotic blood vessels were reduced. Resveratrol did not affect lipid levels, however, in dietary hipercolesterolemic rabbits (Wilson et al., 1996) or in normal rats (Turrens et al., 1997), although it ameliorates blood lipids in Zucker rats, a model of obesity that in advanced age is associated with some alterations similar to those observed in type II diabetes (Rivera et al., 2009). In fact, one study showed an extension of atherosclerosic lesions by resveratrol, with no other significant effect on lipids or LDL oxidation (Wilson et al., 1996). Thus resveratrol is unlikely to have cardiovascular protective effects via changes in the lipidic profile. Resveratrol may inhibit the production of oxidative species secondary to oxLDL uptake by macrophages (Vivancos and Moreno, 2008). Apart from the immunomodulatory actions described below, resveratrol inhibits vascular smooth cell proliferation in vitro, via upregulation of protein kinase G/guanylate cyclase and downstream inhibition of oxidative stress or endothelin 1 activated ERK (El-Mowafy et al., 2008a; 2008b). Resveratrol also reduces cellular infiltration, fibrosis, and expression of inflammatory cytokines in a model of autoimmune myocarditis (Yoshida et al., 2007).

Other relevant mechanisms are the antioxidant protection of LDL and the downregulation of CD36, the macrophage scavenger receptor, as shown for a number of polyphenols, including morin, myricetin, and fisetin (Lian et al., 2008). Both actions are expected to reduce foam cell formation and therefore are considered protective against atherosclerosis. One way flavonoids can inhibit LDL oxidation is by neutrophil myeloperoxidase blockade (see below), an effect that is preserved in at least some flavonoid metabolites (Loke et al., 2008a), which as a rule are less bioactive than the intact aglycone precursors (Loke et al., 2008b). It should be noted also that macrophages located in atherosclerotic plaques can uptake quercetin conjugates and convert them back to active quercetin (Kawai et al., 2008a).

A similar LDL protection/downregulation of CD36 mechanism has been described for ECG which, interestingly, appears to exert it in atherosclerotic lesions specifically (Kawai et al., 2008b), as do kaempferol and rhamnocitrin (Tu et al., 2007), quercetin (Terao et al., 2008), and even quercetin-3-glucuronide (Kawai et al., 2008a). Other protective mechanisms include activation of the ABCA1 (ATP-binding cassette, sub-family A (ABC1), member 1) transporter (possibly augmenting HDL) (Gao et al., 2008); downregulation of NADPHox (Romero et al., 2009; Steffen et al., 2008); antiatherothrombotic actions (Jin et al., 2008; Pasten et al., 2007); lowering of MCP-1 (Nagarajan et al., 2008); inhibition of C reactive protein (Kaur et al., 2007); and downregulation of heat shock proteins (Rosier Olimpio Pereira and Saes Parra Abdalla 2006). Of course, polyphenols exert purely vascular effects which will not be covered here (Grassi et al., 2009). Other than that, the bulk of the evidence points at an antiinflammatory (rather than antioxidant) mechanism for flavonoid antiatherosclerotic/cardiovascular benefit. In general, these effects have been ascribed to different polyphenols without trying to establish structural requirements. However, a SAR study related to inhibition of LDL oxidation by resveratrol and derivatives has been published (Cheng et al., 2006).

Ischaemia-Reperfusion

Polyphenols combat tissue damage originated by ischaemia-reperfusion episodes. Examples include resveratrol (Kaplan

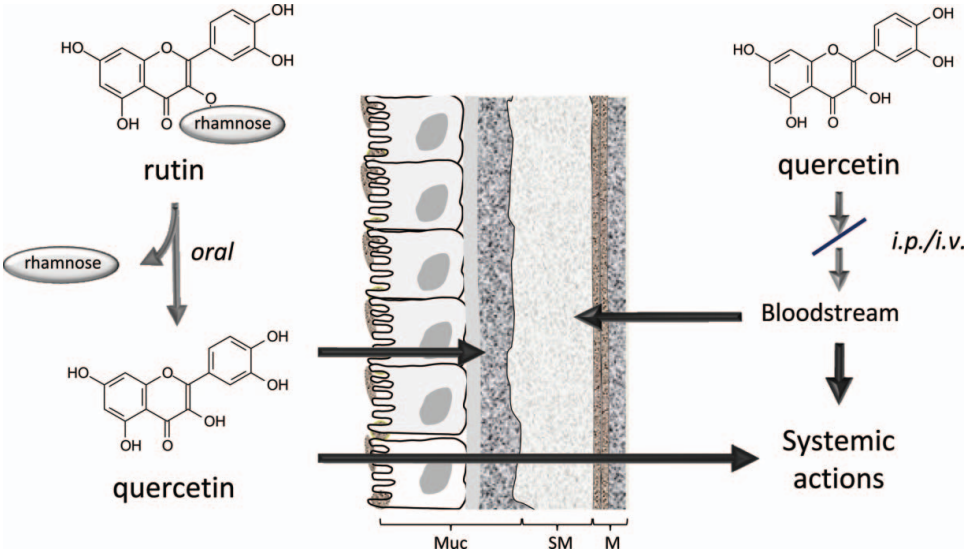

Figure 2 Possibilities of flavonoid inmunomodulation, depicted for rutin/quercetin and the intestine. Rutin is antiinflammatory when given by the oral route, an effect that may be due to local actions on the intestinal mucosa, to systemic actions, or both. Absorption and mucosal effects are believed to occur after glycoside hydrolysis in the gut lumen, releasing quercetin. The aglycone could also be administered by the parenteral route, which is expected to favor systemic over local (mucosal) actions. Even within the mucosa, multiple cell types can be theoretically modulated by flavonoids. However, many unglycosylated flavonoids are active orally in the gut and other organs. Muc: mucosa; SM: submucosa; M: muscular layer and serosa.

et al., 2005), theaflavin (Cai et al., 2006), 3-methoxypuerarin (Zhao et al., 2007), catechin (Rao and Vijayakumar, 2007) and EGCG (Giakoustidis et al., 2008). Tea catechins protect against postischemic myocardial remodeling via antiinflammatory actions (Suzuki et al., 2007). The structure-activity relationship (SAR) for phosphatidylinositol 3-kinase (PI3K) inhibition in ischaemia-reperfusion injury has been defined (Palanki et al., 2007). Again, the protection in this setting is conferred by antiinflammatory properties.

Metabolic Syndrome

Some groups have extended the study of cardiovascular protection by polyphenols to metabolic syndrome. Not surprisingly, several polyphenols have been established to limit the inflammatory component of obesity in animal models. Thus oral treatment of Zucker rats with quercetin improves the overall status, including control of hypertension, dyslipemia, and hyperinsulinemia and lower TNF and iNOS expression in visceral fat (Rivera et al., 2008). Resveratrol has similar but even more substantial beneficial effects in this model, ameliorating the dyslipemia and hypertension, reducing hyperinsulinemia, decreasing the hepatic lipid content, and acting on the visceral fat inflammatory component by lowering TNF and increasing adiponectin and eNOS (Rivera et al., 2009). The effects on the liver are associated with activation of AMP-activated protein kinase (AMPK) and acetyl-CoA carboxylase. It should be noted that resveratrol did not prevent obesity itself, although it seems that it might have antiobesity effects at high doses.

Gravinol, a proanthocyanidin, has similar effects, including an attenuation of the inflammatory component at the hepatic level (Yokozawa et al., 2008). NF-κB is blocked in adipocytes by both curcumin and resveratrol (Gonzales and Orlando 2008; Zhu et al., 2008; Ahn et al., 2007). Part of the effect of resveratrol in the control of insulin resistance may derive from PPAR-γ activation, as observed in cultured adipocytes (Kennedy et al., 2009). Quercetin, kaempferol, naringenin, and hesperetin are partial PPAR-γ agonists in fat cells, but it has been argued that the antagonist component may be the predominant one in vivo (Fang et al., 2008c; Liu et al., 2008a). Interestingly, naringenin chalcone has been shown to reduce the production of inflammatory cytokines in an in vitro co-culture model of obesity-related inflammation, in which 3T3-L1 adipocytes and Raw264 macrophages exhibit potentiation of TNF, MCP-1, and NO production (Hirai et al., 2007). Last, curcumin has been shown to inhibit diabetes related increases in IL-1β, vascular endothelial growth factor (VEGF), and NF-κB in the retina independently of glycemia (Kowluru and Kanwar, 2007).

Brain Inflammation

The effect of flavonoids has been studied in different types of brain inflammation in experimental animals. In a model of traumatic brain damage in the rat baicalein exerts protective effects via antiinflammatory mechanisms (Chen et al., 2008b). In ischemic brain injury resveratrol has therapeutic properties (Liu et al., 2007b; Tsai et al., 2007), an effect shared by theaflavin (Cai et al., 2006). Neuronal cell death induced by microglial activation is prevented by resveratrol and quercetin by reducing apoptosis, acting probably on the microglia component (Bureau et al., 2008). In addition, resveratrol has well known neuroprotective effects, which are due to AMPK activation (Dasgupta and Milbrandt 2007). As we will show below, myeloid cells are well characterized targets of the antiinflammatory actions of polyphenols. In this particular cell population (microglia) luteolin (Jang et al., 2008a; Kim et al., 2006), biochanin A (Chen et al., 2007c), and the already mentioned quercetin (Chen et al., 2005) and resveratrol are reported to downregulate cell activation. Quercetin, however, might be toxic to neurons in micromolar concentrations in basal conditions (Jakubowicz-Gil et al., 2008).

Skin Inflammation

Resveratrol (Kundu et al., 2006), 5-O-demethylnobiletin (Bas et al., 2006), sylimarin (Han et al., 2007), 5-hydroxy-3,6,7,8,3′,4′-hexamethoxyflavone (Lai et al., 2007) and black tea theaflavin derivatives (Huang et al., 2006) are active in acute skin inflammatory models, while ginkgetin, a biflavone, is active in chronic skin inflammation (Lim et al., 2006). EGCG reduces the severity of atopic dermatitis in mice (Noh et al., 2008) and it also prevents UV damage when administered topically (Sevin et al., 2007). Similarly, eupatilin, and jaceosidin diminish the response of skin cells to IgE-antigen complexes (Lee et al., 2007a). Myricitrin has antiallodynic properties via antiinflammatory actions (Meotti et al., 2006). Of course, the utility of tannins in skin dermatitis is well established (Folster-Holst and Latussek, 2007).

Miscellaneous In Vivo Antiinflammatory Activities

Many flavonoids possess substantial anticancer activity by direct mechanisms, which will not be covered here. However, they may also contribute to antineoplastic defense by modulation of the immune response. Thus oral genistein has been shown to protect against carcinogenesis via immunostimulation, lowering Treg and enhancing T cell cytotoxicity and NK cell function (Guo et al., 2007a). In ovariectomized cats, genistein reduces circulating CD8+ cells, while enhancing respiratory burst in neutrophils when given at a "minimum estrogenic" dose (Cave et al., 2007). Genistein also has protective effects against cisplatin nephrotoxicity by antiinflammatory actions (Sung et al., 2008) and prevents gastric mucosal inflammation and ulceration (Takekawa et al., 2006), an action shared by other flavonoids such as catechin (Rao and Vijayakumar, 2007), and DA-6034 protects against gastric ulcer (Choi et al., 2007).

A number of flavonoids protect against LPS-induced shock or immune stimulation in experimental animal models, including rutin (Guruvayoorappan and Kuttan 2007b), baicalein (Liu et al., 2008), apigenin (Nicholas et al., 2007a), hesperidin (Yeh et al., 2007a), resveratrol (Sebai et al., 2009), quercetin 3-O-beta-(2(")-galloyl)-rhamnopyranoside (Jo et al., 2008), and EGCG (Li et al., 2007b;Wheeler et al., 2007). These effects derive most likely from inhibition of monocyte function. An interesting study says that quercetin but not luteolin protects against *Salmonella typhimurium*-aroA shock in mice (Sugiyama et al., 2008). At any rate, quercetin does not affect LPS induced fever (Kanashiro et al., 2008). In addition, quercitrin protects against anaphylactic shock (Cruz et al., 2008).

Resveratrol (Szabolcs et al., 2006; Wang et al., 2008b) and baicalin (Xue et al., 2006; Zhang et al., 2008) protect in experimental pancreatitis, while ellagic acid is useful in chronic pancreatitis (Suzuki et al., 2009). Demethylnobiletin reduces delayed hipersensitivity, with lower T cell proliferation, lower cytokine synthesis, and higher IL-10 (Bas et al., 2007).

Resveratrol (Chavez et al., 2008) and baicalin (Park et al., 2008) have protective effects against CCl_4 induced hepatic damage. Additionally baicalin is active in the model of hepatic injury induced by LPS/D-galactosamine, acting in part by HO-1 upregulation (Wan et al., 2008), as well as in concanavalin A induced hepatitis (Liu et al., 2007a). Resveratrol ameliorates liver injury in a traumatic hemorrhage model, acting by estrogen like actions (Yu et al., 2008).

ACTIONS ON INDIVIDUAL CELL TYPES

There is an impressive number of in vitro studies published that are related to the antiinflammatory/immunomodulatory actions of flavonoids, even when restricting the focus to the last few years. These experiments are somewhat simpler and more straightforward to perform than in vivo work, explaining the imbalance between the amount of evidence presented in the first and second part of this review. We will present mostly observations for cell types for which a substantial number of studies have been put forward, and we will focus on mechanistic issues and any relevant extrapolation to actual in vivo effects (see Table 2 for a summary).

Effects of Polyphenols on Macrophages and Glial Cells

Biological Effects

Many flavonoids have been shown to inhibit the activity of myeloid cells, including macrophages but also dendritic cells, glial cells, and osteoblasts. The general effect of polyphenols is a downregulation of myeloid cell (mostly macrophage) activity, which translates into a lower expression of iNOS, COX2, the proinflammatory cytokines IL-1β, TNF, IL-6, and other markers.

Among flavonols, fisetin, quercetin, and kaempferol inhibit NO production and iNOS/COX-2 induction in a concentration dependent fashion in Raw264.7 cells by $\sim$70% at 10 μM via interference with the NF-κB pathway (Wang et al., 2006a). Myricetin and morin had feeble effects in this study, suggesting that 2′-OH is deleterious for activity. None of the flavonoids studied is toxic at this relatively low concentration, a common observation. A variety of other flavonols, such as ermanin, santin, centaureidin, and 5,3′-dihydroxy-4′-methoxy-7-methoxycarbonylflavonol have similar properties in Raw 264.7 cells (Guerra et al., 2006). In these cells quercetin appears to inhibit NF-κB transcriptional activity but also specifically NF-κB dependent iNOS promoter activity (Kim et al., 2007b). Quercetin, but not kaempferol, has marked inhibitory effects on bone marrow derived macrophages, a more physiological cellular model (Comalada et al., 2006), where the activation of Akt has also been involved as a target of flavonoid action (Kaneko et al., 2008a). Quercetin may increase IL-10 at low concentrations (Comalada et al., 2006). The effect of quercetin has been related also to inhibition of the p38, ERK, and JNK MAP kinases in rat peritoneal macrophages (Lee et al., 2008b). In the THP-1 human monocytic cell line quercetin (and catechin) virtually suppresses IL-1β and TNF production stimulated by advanced glycation endproducts (Huang et al., 2008b). Other cell products inhibited include β_2-integrin and PECAM-1, and to a lesser extent MCP-1 and IP-10. Consistent with a predominant NF-κB blockade mode of action, COX1 is not affected. Interestingly, quercetin may act in part by modulation of monoclonal non-specific suppressor factor beta (MNSFbeta), which is a regulator of ERK in Raw264 cells (Nakamura and Omura 2008). 3-O-methylquercetin retains the NO/iNOS inhibitory activity (Jiang et al., 2006). Quercetin (and luteolin) also exerts significant antiinflammatory effects on IL-1β activated human astrocytes, reducing cytokines and chemokines and oxidative stress (Sharma et al., 2007b). Taken together, these data suggest that the 3′- and 5-OH are not determinant for activity and that methylation in 3 and 4′ is probably of little importance. However, there are discrepancies regarding the role of 3′-OH.

Flavones are also reportedly active. Thus chrysin inhibits COX2 enzymatic activity but not expression, while luteolin exerts both actions (Harris et al., 2006). Luteolin appears to inhibit prostaglandin E synthase also (Wang et al., 2007b), theoretically potentiating the inhibitory effect on prostaglandin synthesis, and it additionally affects iNOS/NO, IL-6, and TNF, exhibiting a broader effect as in the case of flavonols (Chen et al., 2007a). In this study luteolin (5–25 μM) acted via NF-κB inhibition at different levels (IκB-α phosphorylation, translocation, DNA binding), plus actions on Akt and AP-1. IL-10 was not affected either way. However, in bone marrow derived macrophages luteolin has been shown to augment IL-10 mRNA, but only at low ($<$50 μM) concentrations (Comalada et al., 2006). Apigenin, on the other hand, similarly blocks monocyte iNOS, COX2, and endothelial adherence (Lee et al., 2007a). p38 and Jnk but not Erk may mediate this effect (Ha et al., 2008). MCP-1 is also inhibited at least at the transcriptional level by

Table 2 Effect of flavonoids on specific cell types

Flavonoid	M	OB	GC	DC	LY	MC	PMN	IEC	AEC	EC	KC	FB
apigenin	↓			↓	↓			↓		↓		
baicalein	↓					↓				*		
biochanin A	↓	↓			↑						↓	
cardamonin	↓											
catechin	↓											
chrysin	↓							↓		↓		
curcumin	↓	↓			↓	↓		↓	↓	↓		↓
cyanidin	↓									—		
daidzein	↓				↓					↓		
delphinidin	↓											
diosmetin	↓				↓							
ECG	↓								↓			↓
EGCG	↓	↓	↓	↓	↓	↓		↓	↓	↓	↓	↓
fisetin	↓				↓	↓			↓			
flavopiridol	↓											
genistein	↓			↓	↑↓			↑↓		↓		↓
hesperidin	↓					↓			↓	↓		
isorhamnetin	↓	↓			↓					↓		
kaempferol	↓	↓			↓		↓			↓		
luteolin	↓	↓	↓		↓	↓		↓		↓		↓
morin	↓			↓	↓							
myricetin		↓			↓		↓		↓			
naringenin	↓	↓			↓					—		
nobiletin												↓
pelargonidin	↓											
quercetin	↓	↓	↓		↓	↓	↓	↓—	↓	↓		↓
quercitrin	↓											
resveratrol	↓		↓		↑↓	↓	↓	↑	↓	↓		↓
rutin	↓	↓			↑↓					—		
silibinin				↓	↓				↓			
wogonin	↓								↓		↓	

*The most important flavonoids are included. The predominant effect is shown as increased (↑) or decreased (↓) immune activation (this is a qualitative estimation); – denotes lack of effect, whereas ↑↓ indicates disparity of results. Where conflicting reports exist, the trend deemed dominant is depicted whenever possible. *Promotes adhesion but reduces cell migration. M: macrophages; OB: osteoblasts; GC: glial cells; DC: dendritic cells; LY: lymphocytes; MC: mastocytes; PMN: neutrophils; IEC and AEC: intestinal and airway epithelial cells, respectively; EC: endothelial cells; KC: keratinocytes; FB: fibroblasts.

apigenin in J774.2 cells, a monocyte/macrophage cell line derived from Balb-c mice (Kowalski et al., 2006). The transcription factor C/EBP-β has been involved in the comparable effect of baicalein (Woo et al., 2006b). JNK blockade has been involved in the inhibition of NO synthesis exerted by wogonin (but not nor-wogonin) (Huang et al., 2007b). The 5 and 7-OH appear to be essential to this activity. There is a confirmatory study by Pan et al., (2006a), but also a contradicting study showing wogonin to activate leukocytes (Tang et al., 2006). Biflavones such as biapigenin and taiwaniaflavone have similar inhibitory effects (Woo et al., 2006a; Pokharel et al., 2006; Park et al., 2006). Artocarpesin, which features a 3-methyl-2-butenyl in 6, inhibits COX2 and iNOS in Raw264.7 cells (Fang et al., 2008a). Isovitexin, a 6-glycoflavone, also reduces oxidative stress and iNOS/NO in these cells via inhibition of IKK (IκB kinase), NF-κB translocation, and transcription (Lin et al., 2005), and it also affects COX2 and TNF (Huang et al., 2005). Acacetin (5,7-dihydroxy-4′-methoxyflavone), i.e., the flavone equivalent of ermanin, inhibits the transcriptional activation of iNOS and COX-2 in Raw264.7 cells activated by LPS via interference with Akt and IκB-α phosphorylation, as well as ERK but not p38 (Pan et al., 2006b). The semisynthetic flavone flavopiridol also inhibits IκB-α phosphorylation, AP1, Erk, p38, Jnk, and Akt, and it is proapoptotic in myeloid cells (Takada et al., 2008). Also worth noting is the ability of nobiletin to inhibit tissue factor production by THP-1 cells, possibly reducing coagulability (Hirata et al., 2008). In a SAR study carried out by our group the basic requirements were equivalent in flavones and flavonols, i.e., four hydroxylations at positions 5, 7, 3′, and 4′, together with the double bond at C2–C3 and the position of the B ring at 2 (Comalada et al., 2006). Accordingly, chrysin showed little activity in this study. The data presented further suggest that 6-substitution is of little consequence and that biflavones retain activity. In a study performed on Raw264.7 cells the SAR for NO inhibition was found to comprise a 4′-OH and a C2-C3 double bond, so that flavones are more potent inhibitors than flavanones (Shanmugam et al., 2008).

Isoflavones, especially biochanin A and genistein, have been described to inhibit NO generation in Raw264.7 cells, although at somewhat high concentrations ($\sim$50 μM). Arachidonic acid release is also inhibited (Jun et al., 2005). Nakaya et al. (2005) reported quite the opposite—activation of iNOS, via estrogen

receptor stimulation. Genistein has been additionally reported to block TNF but not IL-6 expression in monocytes from hemodialysis patients (Asmis et al., 2006), and it also reduces TNF secretion in bone marrow derived macrophages, possibly by mechanisms unrelated to IκB-α phosphorylation (Comalada et al., 2006). Daidzein seems to be inactive. Soy isoflavones inhibit monocyte adhesion to CD54 bearing endothelium via modulation of CD11a affinity (Nagarajan et al., 2006). Irigenin (3–30 μM) inhibits iNOS and COX2 expression via interference with NF-κB translocation and binding in Raw264.7 cells (Ahn et al., 2006). Thus genistein and irigenin but not daidzein appear to exert a more limited antiinflammatory activity on macrophages than flavones and flavonols and via not so straightforward mechanisms.

(+)-Catechin inhibits the production of NO and TNF in LPS-stimulated primary macrophages (Guruvayoorappan and Kuttan, 2008). EGCG inhibits NO and iNOS in Raw264.7 cells, and this effect has been ascribed to apoptosis (Hashimoto and Sakagami, 2008) and to NF-κB inhibition (Olmos et al., 2008). This is quite unique to EGCG, as flavonoids are generally found to be nontoxic for macrophages. Curiously, EGCG has been described to exert stimulatory actions on bacteria-infected macrophages, stopping *Legionella pneumophila* growth at 1 μM, together with an increase in IL-12, IFN-γ, and TNF and a reduction in IL-10 but with no change in IL-6 (Matsunaga et al., 2001). It also reportedly increases IL-1α in human peripheral blood mononuclear cells (hPBMC) (Sakagami et al., 1995). In addition, EGCG inhibits IL-6, IL-8, VEGF, and COX2/PGE_2 in human astrocytoma U373MG cells treated with IL-1β and beta-amyloid (25–35) fragment via NF-κB and p38/Jnk and the induction of mitogen-activated protein kinase phosphatase-1 (Kim et al., 2007a). EGC lowers NO in LPS stimulated Raw264.7 cells (Lyu and Park, 2005). Thus the effect of catechins may depend on the experimental conditions.

The flavanones hesperitin and hesperidin both block LPS-induced COX2 expression in Raw264.7 cells (Hirata et al., 2005), and the aglycone reduces TNF secretion in bone marrow derived macrophages (Comalada et al., 2006), while naringenin inhibits IL-6, IL-8, TNF, and IL-1β in macrophages activated by LPS (Bodet et al., 2008).

In a study dealing with five anthocyanidins (which lack the 4-keto group and are positively charged, Fig. 1), delphinidin and cyanidin, which are the equivalent of myricetin and quercetin respectively, inhibit LPS-induced COX2 expression in Raw264.7 cells, whereas pelargonidin (equivalent to kaempferol), peonidin (isorhamnetin), and malvidin do not (Hou et al., 2005). Thus the ortho-dihydroxyphenyl structure on the B-ring appears to be related with the inhibitory actions. There is some similarity to the requirements found in flavonols, suggesting that the keto group is of limited importance for activity. The mechanism is described as related to MAPK, NF-κB, AP-1, and (C/EBP)delta inhibition. The proanthocyanidin prodelphinidine B-4 3′-O-gallate also inhibits COX2 via NF-κB interference at several levels, as well as TAK-1 (Hou et al., 2007).

Cardamonin (a chalcone) has been described to inhibit iNOS and COX2 via NF-κB/Akt and p38 (Lee et al., 2006). In another study cardamonin only downregulated iNOS but not COX2 in macrophages, by a direct blockade of NF-κB driven transcription, since it did not affect the phosphorylation of the MAP kinases, the degradation of IκB-α, or the phosphorylation of NF-κB (Hatziieremia et al., 2006). These results are quite different from those of Israf et al. (2007), which show classical NF-κB inhibition by blockade of IκB-α phosphorylation, affecting both COX2 and iNOS. Thus cardamonin clearly inhibits macrophage function but the specific details require clarification. The SAR of chalcones for NO/iNOS inhibition was studied by Kim et al. (2007c), finding that the activity was favored by a methoxyl substitution in the A-ring at an adjacent position to the carbonyl moiety and a 3-halogen substitution in the B-ring.

Resveratrol inhibits iNOS and COX2 in C6 astroglioma cells via NF-κB interference (Kim et al., 2007b). In Raw264.7 cells, however, NO and PGE_2 levels were lowered by resveratrol and other related stilbenoids, arachidin-1 and piceatannol, but COX2 and iNOS were not affected, despite the fact that NF-κB and C/EBP were in fact inhibited (Djoko et al., 2007). In primary rat glial cells, resveratrol was found again not to affect COX2, but instead reduced prostaglandin E synthase expression and blocked prostaglandin synthesis (Candelario-Jalil et al., 2007). Resveratrol inhibits TNF, IL-1β and NO, as well as NF-κB, in peritoneal macrophages (Ma et al., 2006). The effects generally extend to a resveratrol tetramer, vaticanol B (Tabata et al., 2007), a prenylated derivative (Patel et al., 2005), and the resveratrol analogue RV09 (5-[2-(4-bromothiophen-2-yl)vinyl]benzene-1,3-diol) (Meng et al., 2008b). Resveratrol reportedly inhibits TNF but not IL-1β in J774.2 macrophages, while quercetin and kaempferol inhibit both (Kowalski et al., 2005). Resveratrol (and curcumin) inhibits the release of cytokines by peritoneal macrophages and stimulates IL-10 expression at 20 μM (Sharma et al., 2007a). These changes are accompanied by a reduction in CD80/86. Resveratrol also affects bacterial phagocytic capacity in a negative fashion, opposite to the effects of EGCG described above (Iyori et al., 2008). This action is related to general inhibition of cell immune function and specifically with downregulation of phagocytic receptors such as macrophage scavenger receptor-1, CD36, DC-SIGN, and dectin-1. Resveratrol inhibits monocyte CCR2 binding activity in an NO-, MAPK-, and PI3K-dependent manner, whereas it inhibits CCR2 mRNA in an NO- and MAPK-independent, PI3K-dependent manner (Cullen et al., 2007). Resveratrol downregulates EMMPRIN (Extracellular Matrix MetalloPRoteinase Inducer) and matrix metallopeptidase (MMP)-9, through PPAR-γ activation (Ge et al., 2007). This study also shows that resveratrol inhibits NF-κB but independently of PPAR-γ. ERK and p38 have been also shown to be involved in the effect on EMMPRIN (Huang et al., 2008c). Taken together these data indicate that resveratrol and some structural analogues exert a predominantly inhibitory effect on myeloid cells acting on MAP kinases and NF-κB as well as PPAR-γ, although the specific consequences vary depending on the experimental conditions.

In general, flavonoids do not cause changes in proliferation or viability of macrophages, and those studies that do show such effects indicate only a minor impact. However resveratrol inhibits proliferation and viability (9–29 μM) in Raw264.7 cells (Billack et al., 2008; Radkar et al., 2007); this effect is reduced under activation.

One important aspect to consider is that of glycosylation, which in general appears to lower the effect of flavonoids (Rao et al., 2008). However, glycosides may retain significant activity in some cases. For instance, rutin has been reported to inhibit TNF and NO production in primary peritoneal macrophages obtained from arthritic rats, in which rutin is effective as well in vivo (Kauss et al., 2008b). Similarly, quercetin, but also rutin and quercitrin, inhibits NO, TNF, and IL-6 production in peritoneal macrophages (Fang et al., 2008b). Metabolization is also associated as a rule with a loss of activity, although there are also exceptions—methyl derivatives of quercetin are still effective (Kim et al., 2008a), while demethylation enhances the inhibitory effects of nobiletin on macrophages (Li et al., 2007a).

Other Effects of Flavonoids on Macrophages

In addition to their effects on gene expression, some polyphenols inhibit enzyme function. For instance, cardamonin inhibits COX1 and COX2 (Ahmad et al., 2006). Resveratrol is also a nonselective COX inhibitor (Likhitwitayawuid et al., 2002). The flavonols spinacetin, axillarin, penduletin, and the flavones jaceosidin, axillarin, penduletin, tricin, and chrysoeriol all inhibit PGE_2 synthesis, and some additionally block phospholipase A_2 (Moscatelli et al., 2006). In a SAR study for inhibitory activity on PGE_2 production in peritoneal macrophages (Takano-Ishikawa et al., 2006) a number of flavonoids showed a potency comparable to that of aspirin, including quercetin, resveratrol, apigenin, genistein, or kaempferol but curiously not luteolin, fisetin, or morin, so that no obvious SAR is apparent.

Flavonoids are also inhibitors of the lipoxygenases, and the SAR for 5-LO inhibition has been reviewed (Werz, 2007). The catechol moiety is an important (but not essential) determinant of activity, while methoxylation, the 3-OH, and the 2,3 double bond have little impact and glycosylation normally lowers efficacy. Another SAR study concluded that catechol was relevant for other lipoxygenases (12- and 15-LO) (Vasquez-Martinez et al., 2007). The human 15-LO-2 isoform is generally not affected by flavonoids. In general, flavonoids such as quercetin are more potent for LOX than for COX-2 inhibition (Deng et al., 2007). As mentioned above, the effect is in either case potentiated in some instances by additional phospholipase A_2 blockade, as with quercetin, kaempferol, galangin, fisetin, and morin (Lattig et al., 2007). Thus flavonols appear to exert the highest activity.

Catechins are also able to inhibit gelatinase (MMP9) expression and activity, although the structural requirements differ (Dell'agli et al., 2005). Thus OH groups diminish transcriptional inhibition, while maximal hydroxylation favors enzyme blockade (always in the low μM range). Curcumin shows a notable effect, as it restores the corticoid sensitivity of oxidant treated monocytes, which is typically lost in chronic obstructive pulmonary disease; this is achieved by augmenting histone deacetylase-2 activity at low (30–200 nM) concentrations (Meja et al., 2008).

Mechanism of Inhibition

As anticipated above, the effects of flavonoids on myeloid cells have been largely connected with actions on the NF-κB pathway. For instance, Hamalainen et al. (2007) studied the correlation between NO/iNOS production and NF-κB inhibition, finding that all active flavonoids that reduced iNOS also were active on NF-κB: flavone, the isoflavones daidzein and genistein, the flavonols isorhamnetin, kaempferol, and quercetin, the flavanone naringenin, and the anthocyanin pelargonidin. In this study genistein, kaempferol, quercetin, and daidzein also inhibited the activation of the signal transducer and activator of transcription 1 (STAT-1), another important transcription factor for iNOS. An important question then is how exactly NF-κB is inhibited. Apigenin has been shown to inhibit IKK-γ (IKK regulatory subunit) indirectly, resulting in lower p65 phosphorylation at Ser536 (Nicholas et al., 2007b), reportedly without affecting other targets. Because apigenin has been regularly found to inhibit IκB-α phosphorylation instead in the so-called canonical NF-κB pathway, the authors stated that this was an artifact of the use of cell lines rather than primary cultures. However, our group found apigenin, together with quercetin, luteolin, and diosmetin, to inhibit the NF-κB pathway at this very step, although at relatively high concentrations (Comalada et al., 2006). Thus it remains possible that this is a secondary target of apigenin in primary cell cultures.

Other flavonoids have been shown to inhibit IKK-β (considered the main kinase IKK subunit in the canonical or classical NF-κB pathway, directly upstream of IκB-α, see Fig. 3), such as EGCG (Youn et al., 2006), butein, a tetrahydroxychalcone (Pandey et al., 2007), morin (Manna et al., 2007), fisetin (Sung et al., 2007), or gossypin (Kunnumakkara et al., 2007). In fact, the most common approach for the assessment of the status of the NF-κB pathway is to evaluate changes in IκB-α phosphorylation or total IκB-α levels (since phosphorylation targets IκB-α for proteasoma digestion), and virtually all flavonoids are inhibitory at concentrations similar to those causing the final effects, for instance with quercetin (Cho et al., 2003), resveratrol (Ge et al., 2007), liquiritigenin (a flavanone, (Kim et al., 2008b)), fisetin (Zheng et al., 2008), poncirin (a flavanone glycoside, (Kim et al., 2007b)), or luteolin (Chen et al., 2007a). In some cases, like that of quercetin 3-O-beta-(2"-galloyl)-glucopyranoside, the target lies downstream of IκB-α phosphorylation (Kim et al., 2007a). Other popular assays are reporter systems and electrophoretic mobility shift assays, although they look at endpoints rather than intermediate steps, for instance with kaempferol and quercetin (Wang et al., 2006b), naringin (Kanno et al., 2006), or jaceosidin (Kim et al., 2008c). Because of the experimental approach applied in most studies, it is likely that upstream targets of flavonoids have not been

identified yet. For example, quercetin and luteolin suppress the accumulation of lipid rafts that occurs as a first step in TNF and TLR4 signaling in bone marrow derived macrophages but also in other cell types (Kaneko et al., 2008b). Because activation by phorbol ester is not inhibited, this may be a very important and hitherto unrecognized target of flavonoids. Similarly, resveratrol has been reported to inhibit MyD88-independent but not Myd88-dependent signaling downstream of TLR3 and TLR4 ligation in Raw264.7 cells (Youn et al., 2005). In this study resveratrol inhibits NF-κB acting on TANK binding kinase 1 (TBK1). ECGC has a similar effect (Youn et al., 2006).

On the other hand, NF-κB is also modulated by other signaling pathways. This is the case of the p38, ERK, and JNK MAP kinases. Flavonoids inhibit these kinases, although not all compounds have the same profile. For instance, in THP-1 cells stimulated with S100B protein (RAGE agonist) quercetin inhibits ERK and JNK, while catechin inhibits p38 and JNK (Huang et al., 2006). In macrophages the activation of NF-κB requires the phosphorylation of IKK-α and IKK-β by Akt. Although this pathway has not received much attention, several flavonoids have been shown to inhibit it directly or indirectly, by actions on PI3K, located upstream of Akt, which is blocked by a number of flavonoids (in fact, the prototypic inhibitor LY294002 is a partially saturated flavone) (Chen et al., 2007b; Lee et al., 2006).

Heme oxygenase 1 (HO-1) is a relevant factor for flavonoid inhibition of macrophage function, as demonstrated for chalcones (Abuarqoub et al., 2006; Sawle et al., 2008), EGC (Ogborne et al., 2008), baicalein (Lin et al., 2007), and corilagin (a tannin, (Zhao et al., 2008)). For chalcones, HO-1 induction is favored by methoxylation in the 3,4,5- and 3′,4′,5′-positions and depends on the PI3K pathway (Sawle et al., 2008). HO-1 overexpression may protect against oxidant-evoked apoptosis (Lin et al., 2007).

It should be noted also that a recent study reports a complete lack of effect of luteolin on IκB-α degradation or NF-κB binding in BV-2 microglial cells (Jang et al., 2008b). In turn, luteolin inhibited JNK phosphorylation and AP-1 activation in this study. The reason for this descrepancy is unknown.

Of course, there are other relatively unexplored pathways. Thus cyanidin-3-O-beta-glucoside may inhibit NF-κB by activation of LXR-α (independently of PPAR-γ) (Wang et al., 2008). Luteolin inhibits AP-1 (Chen et al., 2007b).

Effects of Polyphenols on Dendritic Cells

Apigenin inhibits the phenotypical and functional maturation of dendritic cells and inhibits LPS-evoked IL-12 but also CD80, CD86, and MHCI/II expression in bone marrow dendritic cells (BMDC), resulting in an impairment of the Th1 response but not of the cell-mediated immune response (Yoon et al., 2006). This was associated with inhibition of the effects of LPS on ERK1/2, JNK, and p38 MAPK as well as the nuclear translocation of the NF-κB p65 subunit. EGCG inhibits LPS-induced IL-12 production but also increases TNF in BMDC, just as it does in infected macrophages in vitro, as stated above (Rogers et al., 2005). In human monocyte-derived dendritic cells EGCG was in another study found to induce apoptosis, to downregulate CD83, CD80, CD11c, and MHC class II expression, to inhibit endocytosis and to impair allogenic T cell stimulation, i.e., it was unequivocally immunosuppresive (Yoneyama et al., 2008). The flavanol silibinin also reduces CD80, CD86, MHC class I/II, LPS-induced IL-12 production, and T cell stimulation by BMDC, through the blockade of the MAPK/NF-κB pathways (Lee et al., 2007b). Similar findings have been reported with morin (Li et al., 2006). Genistein inhibits IL-6 release in monocyte derived dendritic cells acting on NF-κB but seemingly operating through an upregulation of p53 rather than by modulating the canonical pathway (Dijsselbloem et al., 2007). Thus the limited evidence available points to an inhibition of dendritic cell function.

Effect of Polyphenols on Osteoblasts/Osteoclasts

Biochanin A has differentiating and antiinflammatory effects on osteoblasts (MC3T3-E1 cells), augmenting cell growth, alkaline phosphatase activity, collagen content, and osteocalcin secretion and reducing H_2O_2 evoked TNF, IL-6, and NO production, at least in part via estrogenic actions (Lee and Choi, 2005). Luteolin also appears to enhance osteoblast differentiation and to diminish inflammatory markers (TNF, IL-6, PGE_2, NO), in a strogen-dependent fashion (Choi, 2007). Myricetin is antiapoptotic and induces differentiation in the MG-63 osteoblast cell line, suggesting a possible role combating osteoporosis (Kuo, 2005). Whether this effect is mediated by estrogenic mechanisms is unknown. Naringenin can inhibit human osteoclastogenesis from primary osteoclast precursor cells activated by receptor activator of nuclear factor-kappaB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF); it also inhibits osteoclastic bone resorption and reduces inflammatory markers (IL-23, IL-1α, MCP-1), showing no cell toxicity. It thus holds promise as a therapeutic or preventive agent for bone-related diseases such as periodontitis (La et al., 2009).

Rutin also inhibits osteoclastogenesis (from bone marrow-derived macrophages) by NF-κB inhibition (Kyung et al., 2008). Quercetin at low concentrations (0.01–1 μM), myricetin, kaempferol, isorhamnetin, and curcumin also inhibit osteoclastogenesis (Yamaguchi et al., 2007). This is not surprising, given that many of the factors that promote osteoclast formation do so by activating this transcription factor. There may be also complementariety of cellular targets in vivo. Thus baicalin inhibits RANKL expression in human periodontal ligament cells, perhaps via reduction of PGE_2 levels (Wang et al., 2006).

In an osteomyelitis model, osteoblasts were infected with *Staphylococcus aureus* and EGCG was found to inhibit IL-6 and RANKL production (Ishida et al., 2007). EGCG promotes osteoclast apoptosis by caspase 3 activation (Nakagawa et al., 2002). Further, EGCG inhibits endothelin 1 evoked IL-6

production in the osteoblast-like MC3T3-E1 cells via ERK and Raf1 (Tokuda et al., 2007). Icariin, a prenylated flavonol glycoside, inhibits osteoclastogenesis and bone resorption in vitro (Chen et al., 2007). Taken together, these studies indicate that flavonoids exert antiosteoporotic effects due to anti-NF-κB and/or estrogenic actions.

Effects of Polyphenols on Lymphocytes

There is comparatively little information on the effects of flavonoids on lymphocytes, and most of the studies focus on cancer cell lines rather than on immune modulation. Only the latter will be considered here.

Rutin has been found to be antiproliferative and proapoptotic when splenocytes or thymocytes are stimulated with pokeweed mitogen or concanavalin A, but antiapoptotic and augmenting IL-10 under LPS treatment (Roseghini et al., 2007). This suggests differential effects on T- and B-lymphocytes, but the results are too preliminary to reach further conclusions. This study is remarkable because it is one of the few examples of in vitro activity of a flavonoid glycoside. Apigenin inhibits NFAT DNA binding, resulting in lower IL-4 release, in EL4 T thymoma cells and in primary lymph node cells (Park et al., 2006b). Conversely, biochanin A, genistein, and the metabolite p-ethylphenol enhance IL-4 production via modulation of NFAT and PKC-p38-AP1 (Park et al., 2006a). This suggests that flavones and isoflavones may exert opposite actions on Th2 driven immune responses. In addition, the flavonols fisetin, kaempferol, and morin, the flavones apigenin and luteolin, and the chalcone butein all inhibit IL-4 effects via JAK3/STAT6 in hematopoietic cell lines (Cortes et al., 2007).

The flavones cirsilineol, 6-methoxytricin, and apigenin significantly inhibit T cell proliferation and activation (Yin et al., 2008). Apigenin reportedly exerts antiproliferative actions on mouse primary T cells without toxicity and it also opposes corticoid evoked apoptosis (Liang et al., 2008). Similarly, baicalin (another glycoside) inhibits cytokine synthesis in splenocytes in the micromolar range (Liu et al., 2007b). Morin reduces splenocyte activation by concanavalin A and reduces CD69 expression (Zang et al., 2007). Conversely centaureidin, a 3-methylated flavonol, enhances IFN-γ expression via NFAT and NF-κB in Jurkat cells at 2.5 μM (Chang et al., 2007). (-)-epicatechin inhibits CD25 and IL-2 expression by activated EL4.BU.OU6 cells, which have a T lymphocyte phenotype (Ramiro et al., 2005). EGCG may induce an anergic state of alloreactive T cells by either weakening of antigen signaling or blockade of costimulatory signals (Kim et al., 2007).

Resveratrol and curcumin have both been shown (Sharma et al., 2007a) to inhibit splenocyte proliferation in the micromolar range, with lower secretion of cytokines, although with little selectivity. These changes have been related to modulation in the expression of CD28 (curcumin only) and CTLA-4. Treg cells are not altered in either case. Neither compound seems to be cytotoxic based on 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) assays. However, another study showed that resveratrol is toxic to T cells in the low micromolar range (Radkar et al., 2007). In fact, resveratrol has been found to trigger high levels of apoptosis in activated T cells and to a lesser extent in unactivated T cells, mediated through activation of aryl hydrocarbon receptor (AhR) and estrogen receptor (ER) (Singh et al., 2007b). Resveratrol may additionally hamper lymphocyte migration to inflammatory sites by inhibiting phosphatidylinositol 4-kinase and limiting matrix adhesion (Srivastava et al., 2005). Yet another study reported that resveratrol is predominantly immunostimulant, since it inhibits Treg in vitro and in vivo in splenocytes and enhances IFN-γ expressing CD8+ lymph node cells obtained from tumor bearing mice (Yang et al., 2008). Therefore, there is not a clear image of the real effect of this compound.

Astilbin (3,3′,4′,5,7-pentahydroxyflavanone, a flavanol) inhibits cytokine production by activated but not quiescent Jurkat cells via apoptosis (Yan and Xu, 2001). Astilbin, and a number of derivatives, also inhibit the single-mixed lymphocyte reaction and enhances splenocyte apoptosis (Yang et al., 2006). This activity is affected by the position at which the sugar is linked to the flavone, the presence of carbonyl on C-4 and of the phenol hydroxyl group in A or B ring, with the presence of a B ring being unfavorable and the double bond at C2─C3 irrelevant. Another flavanol, silibinin (constituent of sylimarin), inhibits cytokine production by splenocytes (Min et al., 2007b).

Finally, to our knowledge there is only one SAR study, carried out by our group on rat splenocytes (Lopez-Posadas et al., 2008) and which confirmed the antiproliferative effect of flavonoids (at 50 μM). In addition, apigenin, luteolin, genistein, and quercetin had substantial cytotoxic/proapoptotic effects. These effects are greatly diminished at 1 μM, and the quercetin metabolite isorhamnetin was generally less active, suggesting that biotransformation accounts for the far less dramatic effects observed after in vivo administration even by the parenteral route. Interestingly, unconjugated genistein but not genistin has been reported to produce thymic atrophy and lymphocytopenia in rats at doses of 2.0 or 20 mg/kg, i.e., within the "therapeutic" range. Evidently, there is a shortage of information on the lymphocyte actions of flavonoids, although the available evidence suggests that they have significant effects on activation and even cell viability in vitro, which probably do not occur in vivo, or do so in a greatly attenuated fashion.

Effects of Polyphenols on Mast Cells

Quercetin inhibits IL-1 induced IL-6 production in HMC-1 (human leukemic mast cells) and human umbilical cord blood-derived cultured mast cells via p38 and PKC-ζ (Kandere-Grzybowska et al., 2006). Luteolin inhibits mast cell activity dramatically (Theoharides et al., 2007). Baicalein inhibits the production of cytokines, such as IL-6, IL-8, and MCP-1, by HMC-1 cells stimulated with IL-1β or TNF, via blockade of IκB-α phosphorylation (Hsieh et al., 2007a). Ginkgetin

(a biflavone) and ochnaflavone inhibit both COX2 and 5-LO as well as cell degranulation in bone marrow-derived mast cells (Son et al., 2005; 2006). Hesperidin also inhibits cytokines, as well as hypoxia inducible factor (HIF)-1α expression and the subsequent production of VEGF, acting at least in part via ERK (Choi et al., 2007). Quercetin has similar effects, operating via p38 and NF-κB (Min et al., 2007c).

In the HMC-1 cell line EGCG has been found to reduce the expression of two integrins (α5 and β3) and a chemokine (MCP-1), resulting in a lower adhesion of mast cells to extracellular matrix and reduced monocyte recruitment, without cell toxicity (Melgarejo et al., 2007). EGCG (100 μM) inhibits the production of TNF, IL-6, and IL-8 elicited by PMA+A23187 in HMC-1 cells (Shin et al., 2007). The mechanism involves the lowering of the intracellular Ca^{2+} level, and of ERK1/2 and NF-κB activation. Fisetin has very similar effects, although JNK and p38 appear to be also implicated (Park et al., 2007). Resveratrol inhibits mast cell degranulation, apparently via PLC-γ1 and ERK (Koo et al., 2006). Therefore, structurally unrelated flavonoids have profound depressing effects on mast cell function, working chiefly via interference with the MAP kinases and NF-κB pathways.

Effects of Polyphenols on Natural Killer Cells

Curcumin reverts the capacity of tumors to downregulate natural killer (NK) cell activity via exosome secretion (Zhang et al., 2007). There is some evidence that flavonoids may activate NK cells in vivo (Guruvayoorappan and Kuttan 2007a; Guo et al., 2007b; Beaumont et al., 2008).

Effects of Polyphenols on Eosinophils

Nobiletin promotes eosinophil apoptosis via upregulation of Fas, a mechanism related to the antiasthmatic effect of the flavonoid in rats (Wu et al., 2006b). Resveratrol, conversely, does not evoke apoptosis in human eosinophils but inhibits the production of eosinophil peroxidase, LTC_4, and CD11b, CD62L shedding, and chemotaxis, actions that correlate with p38 and ERK inhibition (Tan and Lim, 2008). Genistein inhibits LTC_4 synthesis via p38 modulation (Rogerio et al., 2007b). Hence the effect on eosinophils seems to be also inhibitory.

Effects of Polyphenols on Basophils

Quercetin, fisetin, apigenin, and flavone plus chalcone and a number of polymethoxyflavones, but not taxifolin, hesperetin, or flavonoid glycosides, inhibit basophil degranulation (Itoh et al., 2008; Middleton and Drzewiecki, 1984). The flavonoid related compounds thunberginol A and B inhibit cytokine production in a basophil cell line, and their impact on the gene expression profile was comparable to that of luteolin (Matsuda et al., 2008).

Effects of Polyphenols on Neutrophils

Moreira et al. (2007) attempted to approach the SAR of flavonoids for inhibition of oxidative metabolism in polymorphonuclear leukocytes (PMN) by studying quercetin, kaempferol, myricetin, and galangin. The activity appeared to depend mostly on lipophilicity, and cell viability and phagocytosis were not affected. Quercetin is the most active of the four toward neutrophil degranulation and inhibition of elastase secretion (Kanashiro et al., 2007). Quercetin (40 μM) also inhibits IL-6 secretion (Liu et al., 2005a), counteracts the antiapoptotic effect of LPS, reverts the downregulation of CD62L, and reduces CD11b/CD18 expression and superoxide generation in stimulated neutrophils (Liu et al., 2005b). Quercetin-3-glucuronid, but not quercetin or quercetin-3′-sulfate, reduces the intracellular Ca^{2+} increase that is observed under neutrophil stimulation (Suri et al., 2008). CD62L was not affected in this study, contradicting the previous one mentioned above. Baicalin inhibits IL-8 evoked MMP-8 secretion by human primary neutrophils (Zhu et al., 2007). Resveratrol inhibits PMN by radical scavenging and direct myeloperoxidase inhibition (Kohnen et al., 2007). In fact, several flavonoids cause irreversible inactivation of this enzyme (responsible for the generation of the strong oxidant HClO) as they are oxidized by it, the activity being favored by the number of hydroxyl groups in the B ring of the flavonoids, the C2—C3 double bond and the presence of a free hydroxyl m-phenol group in the A ring, as well as general hydrophobicity (Meotti et al., 2008; Shiba et al., 2008). This does not necessarily translate into a reduction of HOCl output, however. Curcumin and quercetin also inhibit crystal activated PMN (Jackson et al., 2006b). Thus, PMN are a well established cellular target of flavonoids, although the mechanims are ill defined.

Effects of Polyphenols on Epithelial Cells

Intestinal Epithelial Cells

Flavonoids have been shown to be uptaken by Caco-2 as long as they are not glycosylated (with the exception of myricetin), conferring antioxidant protection (Yokomizo and Moriwaki, 2006). Isoflavones have been independently shown to exert similar protective effects (Wijeratne and Cuppett, 2007). Interestingly, flavonoids have been described to modulate bacterial growth in a coculture with Caco-2 cells, suggesting a potential in vivo effect on intestinal microbiota (Parkar et al., 2008).

Quercetin ($\sim$40 μM) but not its metabolites has been reported to inhibit IP-10 and MIP-2 expression in intestinal epithelial cells (Mode K cells) by Akt and atypical NF-κB modulation, i.e., by inhibition of phospho-RelA (p65) recruitment to the IP-10 and MIP-2 gene promoters and of histone acetyl transferase activity (Ruiz et al., 2007b). Apigenin, luteolin, genistein, 3′-hydroxy-flavone, and flavone have been compared in the same cell line (Ruiz and Haller, 2006). All inhibited IP-10 similarly, except flavone, but via different mechanisms. Thus

3′-hydroxy-flavone acts via classical NF-κB inhibition, while apigenin, luteolin, and 3′-hydroxy-flavone all block Akt, and genistein inhibits IP-10 via NF-κB, IRF, and Akt independent mechanisms. It should be remembered that Akt stimulates the NF-κB signaling pathway at various levels including IKK-β activity, NF-κB DNA binding activity, and NF-κB transcriptional activity.

In Caco-2 cells chrysin (50 μM) blocks NF-κB by inhibiting IκB-α phosphorylation, while genistein and resveratrol have the opposite effect (Romier et al., 2008). However, there is a bad correlation between IκB-α phosphorylation or IL-8 secretion or other endpoints, indicating unidentified signaling intermediates. For example, chrysin, which had the most marked NF-κB inhibitory activity, barely affected IL-8, while genistein was a very effective blocker of cytokine secretion. None of the compounds tested affected proliferation or viability substantially. Remarkably, quercetin was without effect. No SAR could be ventured. In IEC18 cells, a nontumor cell line, luteolin blocks ICAM1 expression by inhibiting IKK-β directly (Kim and Jobin 2005). Luteolin also sensitizes colonic epithelial HT29 cells to TNF-induced apoptosis, caspase 3 activation and DNA fragmentation, and it additionally reduces TNF-induced C-IAP1 (inhibitor of apoptosis), C-IAP2, and COX-2 gene expression via NF-κB (Karrasch et al., 2007b).

One interesting target for flavonoids in intestinal epithelial cells is hypoxia-inducible factor-1 (HIF-1). Quercetin activates HIF-1 in HCT116 and SW620 cells, resulting in upregulation of VEGF and angiogenesis (Jeon et al., 2007). Although not tested in epithelial cells, baicalein, luteolin, and fisetin, but not kaempferol, taxifolin, or rutin, can induce HIF-1 as well (Triantafyllou et al., 2008).

2′,4′,6′-tris(methoxymethoxy) chalcone (TMMC) inhibits IL-8 and MPP-7 production in HT29 cells (Lee et al., 2007d). The mechanism seems to be related to the induction of HO-1, subsequent to stimulation of ERK/p38 and NRF2 (nuclear respiratory factor-2). TMMC also inhibits TNF-induced NF-κB activation directly (IκB-α phosphorylation) and indirectly (via HO-1). EGCG (6–50 μM) blocks IL-8, MIP-3α, and PGE_2 release in activated T84 and HT29 cells, and it reduces the mRNA levels of IL-8, TNF, MIP-3α, MIP-2, GRO-α, GRO-γ, and COX-2 by 40–85% in both cell lines in basal conditions (Porath et al., 2005).

Delphinidin, an anthocyanidin, exerts classical NF-κB inhibitory effects in HCT116 cells (resulting in cycle arrest and apoptosis) (Yun et al., 2009). Resveratrol produces apoptosis in HT29 cells, perhaps via endoplasmic reticulum stress (Park et al., 2007). Quercetin does not produce apoptosis in Caco-2 cells; instead claudin 4 is upregulated, resulting in higher epithelial resistance (Amasheh et al., 2008). In Caco-2 cells, hexameric procyanidin, but not the dimer B2 or (−)-epicatechin, inhibits the TNF response with accompanying inhibition of NF-κB, an effect that might be due to interference with receptor binding (Erlejman et al., 2008). In HCT116 cells curcumin acts on NOD2, inhibiting signal transduction by preventing oligomerization (Huang et al., 2008). Butein inhibits IL-8 and MMP-7 production in HT29 cells by blockade of p38 and Akt-osteopontin-IκB-α (Lee et al., 2007b).

While flavonoids appear to generally inhibit the immune function of intestinal epithelial cells, there are some conflicting reports that suggest that the scenario may differ significantly from this simple picture. Signaling pathways are also more complex and diverse than those observed for immune cells.

Airway Epithelial Cells

In the airway epithelium quercetin inhibits Akt, PI3K, NF-κB, IL-8, and chemokine secretion, involving transcriptional and post-transcriptional mechanisms (Nanua et al., 2006). Quercetin-3′-sulfate (25 μM), and also resveratrol (>50 μM), inhibit IL-6 and IL-8 in A549 lung alveolar type II pneumocyte cells (Gauliard et al., 2008). Both quercetin and resveratrol inhibit iNOS, GM-CSF, and IL-8 in human primary airway epithelial cells independently of acetylation of core histones, possibly via NF-κB, AP-1 and the cAMP response element (Donnelly et al., 2004; Rahman et al., 2006). Several flavonoids (myricetin, flavone, tricetin, gossypetin, delphinidin, quercetin, and fisetin) have been identified as significant inhibitors of PARP1; thus quercetin, flavone, fisetin, and tricetin reduce poly(ADP-ribose) polymers and thereby lower IL-8 in airway epithelial cells (Geraets et al., 2007a; 2007b). Baicalin and wogonin, but, remarkably, not baicalein, inhibit ATP-evoked mucin production in primary hamster tracheal surface epithelial cells, an effect that conceivably might help clear the airway in asthma (Heo et al., 2007). Luteolin inhibits NF-κB but activates the c-Jun N-terminal kinase (JNK) to increase apoptosis induced by TNF in human airway epithelial cells, by inhibition of superoxide dismutase and early oxidative stress (Ju et al., 2007). This is a rare occurrence of flavonoid-evoked MAPK activation and its significance is unclear. Wogonin inhibits COX-2 expression in A549 cells via lowered c-Jun expression and AP-1 activation (Chen et al., 2008a). Hesperidin inhibits IL-8, ICAM-1, and VCAM-1 expression in A549 cells via NF-κB and AP-1 (Yeh et al., 2007b). Similarly, EGCG, ECG and to a lower extent EGC and EC, but not catechin, block IL-8 production in these cells (Kim et al., 2006c). EGCG also modulates prostaglandin synthesis via EGR-1/Erk, resulting in upregulation of COX-2 and prostaglandin E synthase (Moon et al., 2007). This is therefore an atypical effect as well.

Silibinin inhibits multiple pathways (STAT1/3, Erk, p38, AP-1, and NF-κB) leading to iNOS upregulation in A549 cells, independently of Akt and actually downregulating HIF-1α (Chittezhath et al., 2008). Resveratrol augments TGF-β_2 in airway epithelial cells, resulting in Smad autocrine regulation, a possible antiinflammatory mechanism in this cell type (Suenaga et al., 2008). (+)-Vitisin A (a resveratrol tetramer) is more effective than resveratrol itself for inhibition of influenza virus infection-evoked RANTES secretion in A549 cells, acting on Akt and STAT1 (Huang et al., 2008a). It is of interest for chronic obstructive pulmonary disease that resveratrol helps airway cells

to combat cigarette smoke oxidative stress by rescuing Nrf2 from the cytoplasma (where it is confined by the effect of smoke components) to the nucleus, leading to greater antioxidant defense (Kode et al., 2008). In normal human nasal epithelial cells EGCG inhibits MUC5AC synthesis and secretion, via suppression of the phosphorylation of ERK MAP kinase, MSK1, and the transcription factor cAMP response element-binding protein (Kim et al., 2008). This may be helpful in allergic rhinitis. Curcumin inhibits NF-κB, IL-8 release, COX-2, and HO-1 expression in vitro in the airway epithelium (Biswas et al., 2005; Shishodia et al., 2003). Therefore the overall effect of flavonoids is to inhibit proinflammatory cytokines, NO, and prostaglandins in airway epithelial cells, mostly by MAPK and NF-κB interference. In addition, there is some evidence that mucus production may be lightened by flavonoids.

Other Epithelial Cells

Some flavonoids have been tested in other epithelial cell types, although in a much less extensive way. In addition, many studies focus on antitumoral rather than antiinflammatory activity. As a result, it is difficult to extract general conclusions. For instance, in normal prostate epithelial cells curcumin and resveratrol inhibit COX-2, IL-6 and IL-8 production by activation of mitogen-activated protein kinase phosphatase-5 (MKP5) and the downstream inhibition of p38 (Nonn et al., 2007). In human metastatic prostate PC3-M cells apigenin markedly decreases HIF-1α expression under both normoxic and hypoxic conditions (HIF-1α is upregulated by hypoxia) and the downstream induction of VEGF, via inhibition of the I3K/Akt/GSK-3 pathway (Mirzoeva et al., 2008). This finding, of course, has implications for the possible modulation of inflammatory mediators, but the aim of this study was actually to characterize the chemopreventive effect of the flavonoid.

In HepG2 hepatoblastoma cells isoorientin (luteolin 6-C-beta-D-glucoside) enhances Nrf2 via PI3K and thereby protects against oxidative stress (Lim et al., 2007), while in Chang hepatic cells quercetin, kaempferol, taxifolin, and, to a lower extent, apigenin, protect against cytokine-induced oxidative stress (Crespo et al., 2008a).

In human lens epithelial (HLE-B3) cells genistein inhibits aldose reductase and TGF-β production, resulting in less lens opacity under hyperglycemic conditions (Kim et al., 2008b). EGCG enhances the resistance of human lens epithelial cells against UV damage (Heo et al., 2008). Similarly, quercetin reverts the lowering of collagen I expression induced by oxidative stress and UV light acting on Jnk, an action considered protective against cataracts (Jiang et al., 2008). EGCG also protects against oxidative stress in HLEB-3 cells, probably by actions on ERK, p38 MAPK, and Akt (Yao et al., 2008). Quercetin protects against dimethyl sulfoxide oxidative stress at low (0.1 μM) concentrations, while it is proapoptotic at very high levels (Cao et al., 2007).

In epidermal epithelial JB6 P+ cells myricetin inhibits COX2 via multiple pathways (Jung et al., 2008). Resveratrol appears to block NF-κB classical activation pathway in mouse epidermis (Cichocki et al., 2008). Similarly, procyanidin B2 inhibits COX2 expression by AP1, NF-κB, MEK, and Erk blockade (Kang et al., 2008b). Quercetin (Lee et al., 2008a), EGCG (Kundu and Surh 2007), and myricetin (Lee et al., 2007) have similar actions. However, these effects were studied in the context of chemoprevention using stimuli such as phorbol esters. Such studies abound specially with mammary epithelial cells (Lin et al., 2008; Na et al., 2008).

Effect of Polyphenols on Endothelial Cells

Many studies have focused on the effects of flavonoids on endothelial cells in vitro, especially measuring adhesion molecules and cellular adhesion. This is a relevant target because all leukocytes ultimately access the inflammatory sites by adhesion mechanisms and thus it is a proximal step for intervention. In this regard, quercetin and resveratrol suppress ICAM1 expression in endothelial cells, acting on Rac dependent pathways via inhibition of STAT3 Tyr^{705} phosphorylation and upregulation of eNOS derived NO (Wung et al., 2005). Kaempferol, and to a lesser extent quercetin, inhibit cytokine induced ICAM1, VCAM1, and E-selectin production, while iNOS and COX2 are more sensitive to quercetin (Crespo et al., 2008b). These effects are due to an inhibition of NF-κB and AP-1. In another study quercetin was reported to inhibit VCAM-1, ICAM-1, and MCP-1 expression in endothelial cells in what were referred to as "physiological" concentrations (2–10 μM), while quercetin metabolites (quercetin 3′-sulfate, quercetin 3-glucuronide, and 3′-methylquercetin 3-glucuronide) had a much lower effect (Tribolo et al., 2008). Using homocysteine to produce endothelial injury, quercetin (starting at 6.25 μM) was found to exert significant protection and to reduce NF-κB activation and endothelin release (Lin et al., 2007).

In another study dealing with flavonoid modulation of THP-1 adherence to oxLDL activated human umbilical vein endothelial cells (HUVEC), luteolin and apigenin (25 μM) but surprisingly not quercetin were found to be active inhibitors (Jeong et al., 2007). Other inactive flavonoids include EGCG, (+)catechin, rutin, naringin, naringenin, hesperidin, and hesperetin. The mechanism involves the downregulation of VCAM1 and E-selectin. However, in the same study quercetin and luteolin did inhibit the endothelial uptake of oxLDL, via downregulation of its receptor LOX1 (Jeong et al., 2007). Whether the failure of quercetin to affect cell adhesion is inducer specific or due to some other factor is unknown. Another beneficial activity of quercetin appears to be the increase on t-PA expression via p38/Sp1 (Pan et al., 2008). The aforementioned effect of apigenin on VCAM1 and E-selectin, and also on ICAM1, in HUVEC was confirmed by Lee et al. (2007a). Other flavone derivatives also interfere with adhesion of THP-1 monocytic cells to HUVEC (Kwon et al., 2005a); thus methoxyflavone (3′,4′-dimethoxy-7-hydroxyflavone, $\geq$25 μM) blocks VCAM-1 (but not E-selectin) expression in activated HUVEC, while 2′,3′,

7-trihydroxyflavone (hydroxyflavone) has a minimal effect. 6,8-di-C-glucosylapigenin and 6,8-di-C-glucosyldiosmetin also inhibit ICAM1 expression in these cells (Miyake et al., 2007). The proinflammatory effect of hyperglycemia includes an induction of ICAM1 and MCP-1 and increased cell adhesion; these actions are counteracted by low concentrations (0.1–1 μM) of the flavone scutellarin in human endothelial cells (ECV304 cells) via NF-κB (Luo et al., 2008). Baicalein has a somewhat different effect on rat heart endothelial cells, in which it enhances rather than inhibits adhesion, but it also reduces cell migration, possibly by up-regulation of the integrins ($\alpha_5\beta_1$ and $\alpha_v\beta_3$) and vinculin and by promotion of actin reorganization and focal adhesion contact formation (Hsieh et al., 2007b).

Lotito and Frei (2006) investigated the structural requirements for inhibition of adhesion molecules in human aortic endothelial cells (under TNF stimulation). The 5,7-dihydroxyl substitution of the flavonoid A-ring and the 2,3-double bond and the 4-keto group of the C-ring were the main structural requirements for inhibition of adhesion molecule expression. Hence the ideal structure differs again from that for antioxidant activity. Apigenin, chrysin, galangin, kaempferol, and quercetin were active in this study, reducing E-selectin and ICAM-1 but not VCAM-1, whereas flavone, chromone, naringenin, and (-)-epicatechin were ineffective. Furthermore, in vitro modeled first pass metabolism diminished all activities greatly, suggesting that the efficacy in vivo may be severely limited by this factor. Nevertheless, the quercetin metabolite isorhamnetin is able to prevent oxLDL evoked endothelial damage in EA.hy926 cells via inhibition of lectin-like ox-LDL receptor-1 upregulation, interference with ox-LDL-mediated intracellular signaling pathways (p38 activation, NF-κB nuclear translocation, eNOS expression), and it is the antioxidant activity (Bao and Lou, 2006). Interestingly icariin, a flavonol, stimulates eNOS and NO production via NF-κB activation in these same cells (Xu and Huang, 2007).

Isoflavones exert distinct actions on the endothelium due to their hormonal properties. Thus daidzein and genistein modulate PGI_2 production and upregulate COX2 via activation of the estrogen receptor (Hermenegildo et al., 2005). In addition, genistein but not daidzein protects against oxidative injury by activation of Nrf1 and the downstream induction of glutathione peroxidase (Hernandez-Montes et al., 2006). Nrf2 was also activated in this study but it is not related with the protective effect. In line with these studies, in brain microvascular endothelial cells genistein reduces cytokine-induced production of TNF, IL-1β, MCP-1, IL-8, and ICAM-1, as well as leukocyte transmigration (Lee and Lee, 2008). Both genistein and daidzein inhibit LPS-induced upregulation of VCAM-1 and ICAM-1 in cultured human endothelial cells by stabilization (thereby inhibition) of NF-κB (Simoncini et al., 2008). In addition, genistein (1–10 μM) increases eNOS expression and NO production independently of the estrogen receptor in aorta and umbilical endothelial cells, an action similar to that described for icariin, quercetin, hesperetin, or resveratrol (Si and Liu, 2008).

Hesperidin and hesperidin methyl chalcone lower VCAM-1 levels and monocyte adhesion, but not ICAM-1 expression, in TNF-stimulated HUVEC, linked to inhibition of Akt phosphorylation but not of Erk (which is key for the regulation of ICAM-1) (Nizamutdinova et al., 2008). Hesperetin but not naringenin increases eNOS/NO although both activate estrogen receptors, perhaps because ERα may be more relevant for this particular effect (Liu et al., 2008b). Conversely, hesperidin inhibits endothelin 1 secretion and increases NO release under cyclic strain conditions by lowering Erk phosphorylation and enhancing Akt and eNOS activity (Chiou et al., 2008). Thus the effects of hesperetin/hesperidin seem to depend on the experimental conditions, although they are antiinflammatory.

Primary bovine aortic endothelial endothelial cells are protected from oxidative stress injury by resveratrol, which increases GSH decisively (Brito et al., 2006). Resveratrol ($\sim$1 μM or less) also reduces the endothelial response to TNF, including iNOS, IL-6, bone morphogenetic protein-2, ICAM-1, VCAM, and THP-1 adhesion, in human coronary arterial endothelial cells, via NF-κB inhibition (Csiszar et al., 2006). Resveratrol also reduces fraktalkine production in HUVEC as well as THP-1 adhesion, acting again via NF-κB and additionally Sp1 (Moon et al., 2006). By activation of PI3K/Akt resveratrol leads to reduced senescence and increased proliferation and migration of endothelial precursor cells (Xia et al., 2008; Wang et al., 2007a). Resveratrol protects the endothelium from smoke-evoked oxidative damage, inflammatory gene expression, NF-κB activation, and apoptosis via Sirt-1, i.e., the well known mediator of prolonged survival of this polyphenol (Csiszar et al., 2008). Resveratrol at nanomolar concentrations augments NO by enhancing the ERα-Cav-1-c-SRC interaction (Klinge et al., 2008). In fact, even low concentrations (0.1 μM) of either resveratrol or quercetin are capable of modulating gene expression in endothelial cells (Nicholson et al., 2008).

EGCG (but not other catechins) reduces HUVEC endothelial exocytosis, the initial step in leukocyte trafficking and vascular inflammation, by enhancing Akt and eNOS phosphorylation, leading to decreased adhesiveness (Yamakuchi et al., 2008). Activation of phosphatidylinositol 3-kinase, Akt, and eNOS leads to vasodilator effects (Kim et al., 2007a). In another study epicatechin also augments NO in HUVEC by scavenging superoxide, but it also inhibits NADPH oxidase indirectly, by way of its methylated metabolites (Steffen et al., 2007). However, EGCG has also been reported to lower rather than enhance Akt activation in TNF treated bovine coronary artery endothelial cells, resulting in decreased MCP-1 expression (Ahn et al., 2008). The former study was carried out in basal conditions, perhaps explaining this discrepancy. In human endothelial ECV304 cells EGCG also inhibits MCP-1 but acting via the p38 and NF-κB pathways (Hong et al., 2007). The effect of EGCG on adhesion molecule expression (VCAM1, ICAM1) extends to angiotensin II stimulation and takes place via inhibition of p38/Erk (Chae et al., 2007), although Erk appears to be relevant for ICAM-1 only. EGCG protects against hypoxic lesions (Yu et al., 2007) and reduces oxLDL-evoked oxidative stress and apoptosis in

endothelial cells, acting via Jak2/Jnk and p53, an effect shared by hesperetin (Choi et al., 2008). EGCG inhibits angiogenesis by blockade of PI3/Akt and Erk in HUVEC, augmenting FOXO activation (Shankar et al., 2008).

Isoliquiritigenin (4,2′,4′-trihydroxychalcone) inhibits neutrophil adhesion to human primary endothelial cells through actions on VCAM1, ICAM1, E-selectin, and oxidative stress in the endothelium, associated with inhibition of IκB-α phosphorylation (Kumar et al., 2007). Anthocyanin prevents the inflammatory response to CD40 by redistribution of membrane cholesterol, preventing TRAF2 translocation to lipid rafts and the downstream activation of NF-κB (Xia et al., 2007). Anthocyanidins (cyanidin-3-O-beta-glucoside (Cy-3-g) and peonidin-3-O-beta-glucoside (Pn-3-g)) inhibit p38/Jnk activation secondary to CD40 ligation, thus inhibiting HUVEC and producing apoptosis and reduced MMP-1 and MMP-9 secretion (Xia et al., 2009). Similarly, anthocyanins have been found to reduce NF-κB and ICAM1, VCAM1, and COX2 expression in vitro, protecting against ischaemia-reperfusion injury (Kim et al., 2006a). Licochalcone E is proapoptotic by inhibiting NF-κB and by shifting the Bax/Bcl-2 ratio (Chang et al., 2007). Cyanidin-3-O-beta-glucoside is another flavonoid that can increase eNOS and HO-1, although at high concentrations it also augments iNOS and oxidative stress (Sorrenti et al., 2007). Chalcone inhibits ICAM1 expression and monocyte adhesion acting by abrogation of activation of STAT3 and NF-κB; curcumin has similar effects. In contrast, quercetin and cyanidin were essentially ineffective in this study (Liu et al., 2007a).

Of note, flavonoids may be toxic to HUVEC, according to one study, in the order (LD50 in μM): myricetin (100) > quercetin (50) > kaempferol (20) > genistein (10) (Kim et al., 2006). However, most articles do not appreciate any significant toxicity of flavonoids toward endothelial cells. These flavonoids exhibited antiagiogenic properties under VEGF stimulation in the same study (Kim et al., 2006). On the other hand, the effect of chrysin on angiogenesis has been studied in the chicken chorioallantoic membrane model, where it was found to reduce LPS-induced VEGF and VEGFR-2 (KDR) but not VEGFR-1 (Flt-1) expression and to interfere with the IL-6 pathway, at low concentrations (Lin et al., 2006).

There is a SAR study of chalcones as VCAM1 inhibitors in endothelial cells (Meng et al., 2007) for possible application in asthma. Lipophilicity was found to be important, and the pharmacophore was identified as the chalcone alpha, beta-unsaturated ketone moiety; the maximum potency was in the high submicromolar range. Therefore, flavonoids clearly have a predominant inhibitory effect on adhesion molecules that impairs monocyte adhesion, and the prevailing mechanism appears to be interference with the NF-κB and MAPK pathways, just like in other cell types. In addition, at least some flavonoids favor eNOS function and NO production in basal conditions, actions that also inhibit cell adhesion and also may serve vasodilator effects.

Effect of Polyphenols on Keratinocytes

EGCG attenuates UV induced IL-6 secretion, apoptosis and NF-κB activation in keratinocytes (Xia et al., 2005). EGC also protects against UVB apoptosis and oxidative stress (Huang et al., 2007a). EGCG has in addition differentiating effects on keratinocytes via activation of the nPKC, Ras, MEKK1, MEK3, and the p38δ-ERK1/2 signaling cascade, which leads to increased AP-1 and C/EBP transcription factor expression and transcriptional activity (Balasubramanian and Eckert, 2007); apigenin and curcumin have opposite effects, and curcumin is additionally proapoptotic. Kaempferol modulates UV-B driven gene expression in a human keratinocyte cell line, HaCaT cells. The analysis shows that the transcription factors putatively involved are c-REL, SAP-1, Ahr-ARNT, Nrf-2, Elk-1, SPI-B, and NF-κB (Kang et al., 2008a). Wogonin induces HO-1 in keratinocytes and thereby inhibits CCL17 expression specifically (Lee et al., 2007). In keratinocytes stimulated with serum of Behcet's disease patients biochanin A is antiinflammatory, reducing IL-8 secretion (Kalayciyan et al., 2007). Anthocyanidins inhibit UV-B-induced COX2 expression and PGE_2 synthesis through an NF-κB dependent pathway and the regulation of the PI3 kinase/Akt pathway activated by UV-B in HaCaT cells (Tsoyi et al., 2008). Of note, T-flavanone (trans-3,4′-dimethyl-3-hydroxyflavanone, synthetic) inhibits TGF-β_2 activation (not synthesis) in keratinocytes, a mechanism of action for hair growing effects (Sasajima et al., 2008).

Effect of Polyphenols on Mesangial Cells

Sylimarin blocks NF-κB activation independently of its antioxidant properties in these cells (Chang et al., 2006). Conversely, resveratrol enhances cytokine activated NF-κB signaling both in these cells and in renal tubular LLCPK1 cells, although iNOS was inhibited (Uchida et al., 2005).

Effect of Polyphenols on Fibroblasts

In gingival fibroblasts quercetin, luteolin, genistein, and quercetagetin inhibit MAPK activation, IL-1β and COX2 expression and PGE_2 synthesis (Gutierrez-Venegas et al., 2007). Quercetin and curcumin inhibit synoviocyte proliferation (Jackson et al., 2006a). 5,6,3′,5′-tetramethoxy 7,4′-hydroxyflavone inhibits inflammatory mediators (ICAM-1, COX2, and iNOS) in fibroblasts (Yoon et al., 2008). In rheumatoid arthritis derived synovial fibroblasts EGCG has relevant antiinflammatory actions, inhibiting IL-1β-induced ENA-78, RANTES, GRO-α, and MCP-1 production, as well as MMP-2 activity, at 20 μM, acting via NF-κB (Ahmed et al., 2006). EGCG also inhibits MMP-1/3 production via MAPK and AP-1 in synovial fibroblasts (Yun et al., 2008). In a similar model nobiletin inhibits ADAMTS4/5 expression (Imada et al., 2008). Both EGCG

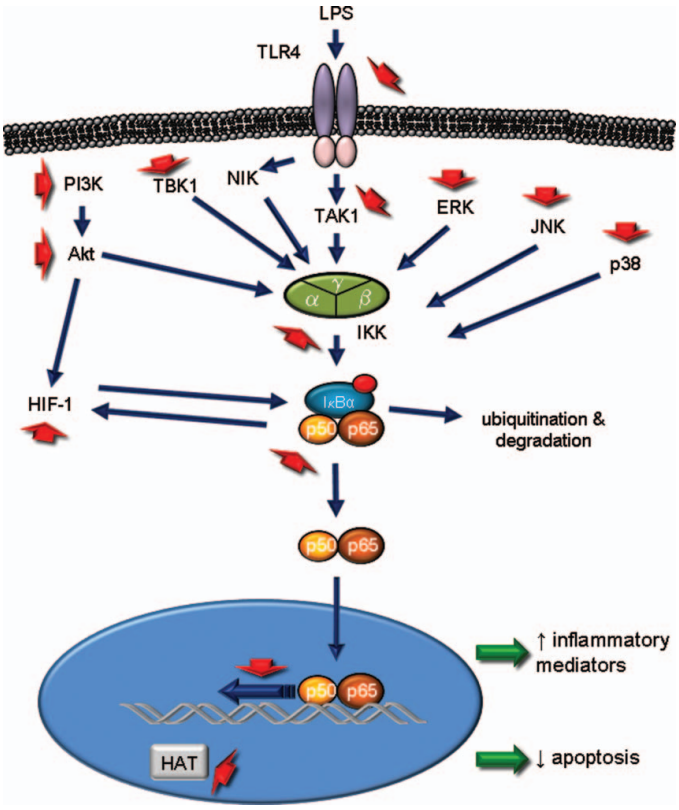

Figure 3 Targets of flavonoid action within the NF-κB pathway. Flavonoids have been described to affect a number of steps in the NF-κB pathway, primarily in the canonical pathway, represented here in the central axis. Thus flavonoids can modify the function of the IKK complex and thereby IκB-α phosphorylation, p65 phosphorylation, binding to gene promoters and histone acetylation. There is also evidence of receptor modulation. In addition, many other targets have been established (all designated by the arrow), which interact with the NF-κB pathway but also have other signaling routes (not shown). This scheme is a simplification of the multiple interactions that have been established.

and ECG, and to a lesser extent EGC and EC, but not catechin, inhibit IL-8 production by nasal mucosal fibroblasts (Kim et al., 2006b). In addition, EGCG exerts protective effects against oxidative stress in human fibroblasts (Meng et al., 2008a). In primary nasal polyp fibroblasts EGCG also lowers cobalt chloride induced HIF-α and VEGF levels, possibly counteracting polyp growth (Lin et al., 2008).

Synovial fibroblast proliferation is inhibited without cell toxicity by alvocidib (flavopiridol) (Sekine et al., 2008). Resveratrol produces apoptosis in rheumatoid arthritis derived fibroblast-like synoviocytes via caspase 8 (Byun et al., 2008). Licochalcone A inhibits PGE_2 production in skin fibroblasts at nanomolar concentrations, without affecting COX2 levels or cytokines (Furuhashi et al., 2005). Primary mouse cardiac fibroblasts exhibit glucose inducible IL-17 secretion, which stimulates collagen production, and this is inhibited by resveratrol via PI3K-, Akt-, and ERK-dependent actions (Venkatachalam et al., 2008).

Thus flavonoids seem to exert broad antiinflammatory and antiproliferative effects on fibroblasts and synoviocytes, and mechanistically these resemble those described above.

CONCLUSIONS

The amount of evidence gathered in the field of inflammatory/immunological modulation by flavonoids in the last few years is impressive, let alone considering the entire set of studies available. Despite the fact that there are thousands of flavonoid derivatives, the vast majority of the studies have centered, understandably, on the simplest and most abundant ones. This necessarily limits our understanding of the biological actions of these compounds in terms of structural requirements and pharmacological spectrum. For instance, using a model 293 reporter cell line resveratrol and structural analogues were found to inhibit NF-κB, but many other related compounds were found with more potency (Heynekamp et al., 2006). Moreover, there are relatively few direct structural comparisons, making it necessary to compare results obtained by different investigators in different studies. Considering this, the consistence of the results reported is the dominant note, to an extent that is somewhat surprising. The main conclusion of the in vitro studies is that flavonoids are almost without exception antiinflammatory on the different cell types studied, lowering the expression and/or function of a variety of inflammatory mediators including eicosanoids, NO, adhesion molecules, and cytokines. The impact of flavonoids is reported generally as a broad one rather than specific, and this is in keeping with the fact that NF-κB, a master regulator of these mediators, is a common target of flavonoids, although the specific details are more variable. This applies also to other signaling pathways, such as PI3K-Akt or the MAPK, which to a great extent converge on NF-κB activation or serve complementary functions (Fig. 3). There are other emerging signaling targets of flavonoids (HO-1, Nrf2, Sp1) that deserve further exploration.

If the above is true, then the effects of flavonoids must depend greatly on pharmacokinetics and cell access. Compared with the situation of 10–15 years ago we have now a much clearer picture of this aspect of flavonoid pharmacology, albeit one that leaves many questions unanswered. For instance, it is unclear why rutin and quercitrin are much more active than quercetin in experimental colitis, while other aglycones appear to be as efficacious as these glycosides. Another question is, if flavonoids have such prominent actions (in vitro), why their in vivo effects are not so evident? This applies specially to lymphocytes, on which flavonoids appear to be toxic. Also, in a given disease (model), which cells are responsible for the therapeutic effect of tested flavonoids? It may very well be that a combination of separate actions on different cell types accounts for the beneficial effect. For instance, the amelioration of asthma may be due to actions on macrophages, airway epithelial cells, basophils, mast cells, endothelium, and eosinophils.

For almost all the in vitro activities reported, flavonoids that display significant effects do so at relatively high concentrations, approximately 1–50 μM. Macrophages in atherosclerotic plaques have been described to uptake flavonoid glycosides and then to release the aglycone intracellularly, as explained above, but other than that, the distribution of flavonoids and

their metabolites appears to be quite extensive in the organism. Upon continued administration there may be some minor concentration in the liver and intestine. The present evidence does not suggest that flavonoids may produce a high magnitude effect at the concentrations that may be present in the serum or other body compartments. It is possible that accumulated low-grade inhibition of different cell types compensates for this. Clearly, our understanding would benefit from a more profound characterization of flavonoid pharmacokinetics and from a refinement of structure-activity molecular optimization.

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