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Anti-Tumour Treatment

Cancer chemoprevention revisited: Cytochrome P450 family 1B1 as a target in the tumor and the microenvironment

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ABSTRACT

Cancer chemoprevention is the use of synthetic, natural or biological agents to prevent or delay the development or progression of malignancies. Intriguingly, many phytochemicals with anti-inflammatory and anti-angiogenic effects, recently proposed as chemoprevention strategies, are inhibitors of Cytochrome P450 family 1B1 (CYP1B1), an enzyme overexpressed in a wide variety of tumors and associated with angiogenesis. In turn, pro-inflammatory cytokines were reported to boost CYP1B1 expression, suggesting a key role of CYP1B1 in a positive loop of inflammatory angiogenesis. Other well-known pro-tumorigenic activities of CYP1B1 rely on metabolic bioactivation of xenobiotics and steroid hormones into their carcinogenic derivatives. In contrast to initial *in vitro* observations, *in vivo* studies demonstrated a protecting role against cancer for the other CYP1 family members (CYP1A1 and CYP1A2), suggesting that the specificity of CYP1 family inhibitors should be carefully taken into account for developing potential chemoprevention strategies. Recent studies also proposed a role of CYP1B1 in multiple cell types found within the tumor microenvironment, including fibroblasts, endothelial and immune cells. Overall, our review of the current literature suggests a positive loop between inflammatory cytokines and CYP1B1, which in turn may play a key role in cancer angiogenesis, acting on both cancer cells and the tumor microenvironment. Strategies aiming at specific CYP1B1 inhibition in multiple cell types may translate into clinical chemoprevention and angioprevention approaches.

Introduction to chemopreventive strategies

The administration of synthetic, natural or biological agents to reduce or delay the occurrence or progression of malignancies is a very promising strategy for cancer prevention, known as "chemoprevention" [1,2]. Apart from conventional chemo-/radio-therapy, there is a growing interest in preventing tumor onset by acting both on cancer cells and the supporting environment. Chemoprevention approaches based on suppression of the host hallmarks of cancer, such as inflammation or angiogenesis, have been suggested [3–6]. Inflammation and angiogenesis have an early and permissive role in carcinogenesis [7]. Chronic inflammation is linked to the development of 30% of all cancers and affects all stages of tumor development as well as therapy [8], and chronic inflammatory processes promote angiogenesis [9]. The concept of angioprevention applies chemoprevention by angiogenesis inhibition [10,11]. The goal of angioprevention is to influence the pre-tumor and tumor microenvironment so that host defense systems are fortified to suppress the development of clinically detectable tumors. Blocking chronic inflammation can prevent immune cell pro-tumor polarization and contribute to angioprevention. Compared with classic chemoprevention directed at cancer cells, the inhibition of angiogenesis and inflammation improves host defense mechanisms and provides protection against a broad spectrum of neoplasms [10].

The emerging role of CYP1B1 in inflammation and angiogenesis

Anti-inflammatory and anti-angiogenic activities exerted by natural CYP1B1 inhibitors

During the last decades, the role of compounds of dietary origin ("phytochemicals") on cancer prevention has attracted substantial attention because of their low toxicity and high tolerability over long-term administration without substantial significant side effects [12]. Several phytochemicals are receiving increasing attention as agents for cancer prevention and therapy for their anti-oxidant, anti-angiogenic and anti-inflammatory activities, in

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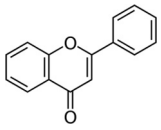
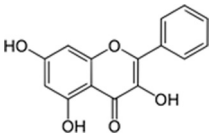
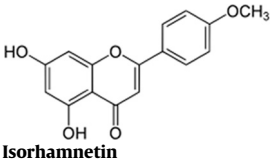
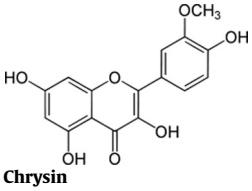
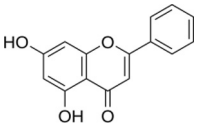
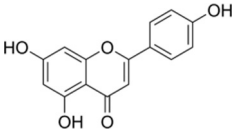
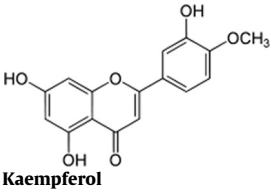
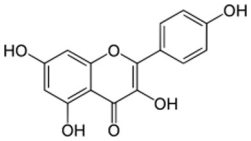
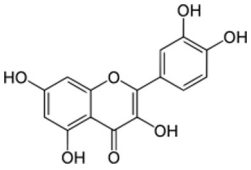
Table 1
Phytochemicals showing preferential CYP1B1 inhibition associated with anti-inflammatory and anti-angiogenic effects.

Compound category	Compound	Inhibition of enzymatic activity of CYP1 family members (nM)	Inhibition of enzymatic activity of other CYP enzymes (nM)	Anti-inflammatory effects	Anti-angiogenic effects
Flavonoids 	**Galangin** (3,5,7-trihydroxyflavone) 	**CYP1B1** IC_{50} = 3-25 [17,19] **CYP1A2** IC_{50} = 11–40 [17,19] **CYP1A1** IC_{50} = 73–77 [17,19]	**CYP2C9** IC_{50} = 200–7500 [19,237] **CYP3A4** IC_{50} = 2300–3000 [19,237]	[28]	[44]
	Acacetin (4′-methoxy-5,7-dihydroxy- flavone) 	**CYP1B1** IC_{50} = 7–14 [17,19,21] K_i = 7 [18] **CYP1A1** IC_{50} = 80–100 [17,19,21] K_i = 45 [18] **CYP1A2** IC_{50} = 80–360] [17,19,21]	**CYP2C9** IC_{50} = 650–4200 [19,237] **CYP3A4** IC_{50} = 1200–6500 [19,237]	[38]	[43,52]
	Isorhamnetin (5,7,3′,4′-tetrahydroxy-3-methoxyflavone) 	**CYP1B1** IC_{50} = 17 [17] **CYP1A1** IC_{50} = 56 [17] **CYP1A2** IC_{50} = 1261 [17]	**CYP2C9** IC_{50} = 15800 [237] **CYP3A4** IC_{50} = 16600 [237]	[30–32]	[238,239]
	Chrysin (5,7-dihydroxyflavone) 	**CYP1B1** IC_{50} = 24–270 [17,19] K_i = 16 [18] **CYP1A2** IC_{50} = 60–84 [17,19] **CYP1A1** IC_{50} = 153–170 [17,19] K_i = 42 [18]	**CYP2C9** IC_{50} = 800–6500 [19,237] **CYP3A4** IC_{50} = 900–7400 [19,237]	[27,37,39,40]	[39,40]
	Apigenin (4′,5,7-trihydroxyflavone) 	**CYP1B1** IC_{50} = 25 [17] K_i = 64 [18] **CYP1A1** IC_{50} = 427 [17] K_i = 390 [18] **CYP1A2** IC_{50} = 795 [17]	**CYP4F2** IC_{50} = 4600 [240] **CYP2C9** IC_{50} = 6400 [237] **CYP3A4** IC_{50} = 400 [237]	[37,105]	[36,41,50]
	Diosmetin (2S)-(5,7,3′-trihydroxy-4′-methoxyflavone) 	**CYP1B1** IC_{50} = 29 [17] K_i = 16 [18] **CYP1A1** IC_{50} = 140 [17] K_i = 89 [18] **CYP1A2** IC_{50} = 440–2437 [17,21]		[105]	[48]
	Kaempferol (3,4′,5,7-tetrahydroxyflavone) 	**CYP1B1** IC_{50} = 47 [17] K_i = 43 [18] **CYP1A1** IC_{50} = 632 [17] K_i = 750 [18] **CYP1A2** IC_{50} = 716 [17]	**CYP3A4** IC_{50} = 8800 [237] **CYP2C9** IC_{50} = 12600 [237]	[29,30]	[45,241]
	Quercetin (3,3′,4′,5,7-pentahydroxyflavon) 	**CYP1B1** IC_{50} = 77 [17] K_i = 23 [18] **CYP1A1** IC_{50} = 1191 [17] K_i = 660 [18] **CYP1A2** IC_{50} = 4097 [17]	**CYP2C19** K_i = 1740 [242] **CYP2D6** K_i = 18720 [242] **CYP3A4** IC_{50} = 22100 [237] **CYP2C9** IC_{50} = 26100 [237]	[29,243]	[42,53,244]