A011 Effects of an antirheumatic Turkish folk remedy on *in vitro* cytokine production

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Daphne oleoides Schreber ssp. *oleoides* (Thymelaeaceae) is used for the treatment of various inflammatory disorders, i.e., rheumatic pain, lumbago and fever in Turkish folk medicine (1). Liposoluble fractions (i.e. hexane and chloroform fractions) of MeOH extract were shown to possess potent *in vitro* inhibitory effects on interleukin-1α (IL-1α) and tumor necrosis factor-α (TNFα) (2). Seventeen compounds were isolated from the ethylacetate subfraction of the plant through activity-guided fractionation technique and tested for their effects on macrophage-derived cytokines, IL-1α, IL–1β and TNFα. Diterpenoids genkwadaphnin and 1,2-dehydrodaphnetoxin as well as a coumarine derivative, daphnetin, were shown to possess potent inhibitory activity.
Apart from the above-mentioned compounds; seven of the isolated compounds were selected and tested for their effects on various other interleukins; IL-2, IL-4, IL-8 and interferon-γ (IFN-γ). Diterpenoids; gnidilatin, genkwadaphnin-20-palmitate, gnidicin-20-palmitate and a lignan derivative (matairesinol) of the plant were shown to possess potent IL-2 releasing activity. Gnidilatin, the most potent compound, was further investigated by using *in vitro* models for its effects on IL-1α, IL-1β, IL-1ra, IL-5, IL-6, IL-10, TNFα, GM-CSF, M-CSF, LD78. For the *in vivo* toxicity assessment, effect of gnidilatin on body weight and organ weights (liver, spleen and kidney) as well as on liver enzymes (GOT and GPT) and in erythrocyte and leukocyte numbers were investigated in rats and was found safety up to 10 g/100 g b.w. concentration.

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A012 Inhibition of interleukin-8 production by structurally different sesquiterpene lactones

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Sesquiterpene lactones (SLs) are known to possess potent anti-inflammatory activities. In previous studies we have shown that they exert this effect in part by inhibiting activation of NF-κB, a central mediator of the immune response (1). This protein regulates the transcription of various pro-inflammatory and immunoregulatory cytokines such as IL-1, IL-2, IL-6, IL-8 and TNF-α as well as genes encoding for enzymes like COX-2 and iNOS (2). Recent data demonstrated that SLs not only inhibit activation of NF-κB, they also suppress the production of pro-inflammatory cytokine production (3).
In this study we focuse on Interleukin-8 (IL-8), that has been implicated in a variety of inflammatory diseases like rheumatoid arthritis, psoriasis and various cancer diseases. IL-8 is secreted by a wide variety of normal and tumorigenic human cell types and can be induced by various stimuli, such as LPS, IL-1 and TNF-α. It is an important activator and chemoattractant for neutrophils and induces e.g. their degranulation followed by the release of β-glucuronidase or elastase (4). Previously, parthenolide and isohelenin have been reported to inhibit IL-8 synthesis (3). To gain further insight into their structure activity relationships, we investigated several SLs from the eudesmanolide, guaianolide, pseudoguaianolide and germacranolide type for their effect on IL-8 production by enzyme-linked immunosorbent assay. We show that SLs inhibit the release of IL-8 in a dose-dependent manner at micromolar concentrations (IC_{50} values in the range of 0.5-30 µM). SLs with an α-methylene-γ–lactone function and a conjugated carbonyl group were most active. Inhibitory concentrations correlated well with those necessary for inhibition of the transcription factor NF-κB.

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