Review paper

Immunotropic and anti-tumor effects of plant adaptogens. II. *Oenothera L.* (Evening primrose)

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Abstract

This paper describes some beneficial and also some unwanted effects of evening primrose oil (EPO) feeding on the cells of immune system. Evening primrose oil is a rich source of omega-6 essential fatty acids [γ-linolenic acid (GLA) and linoleic acid (LA)]. Some effects of EPO and essential fatty acids on tumor cells are also described.

Key words*: evening primrose oil, essential fatty acids, immunity, tumors.*

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Introduction

One of the beneficial effects of plant adaptogen extracts is their anti-stress effect. From this point of view evening primrose oil (EPO) may be classified as an adaptogen because some authors reported its beneficial effect in avoiding stress-induced gastro-intestinal ulcer formation [1-4]. In one of this study [3] the rats were fed EPO – enriched diet 14 days before the experiment. In the experiment, animals were subjected to the 7-hours long water-restraint stress. Diet with addition of 5% EPO decreased the creation of gastric ulcers by 50%.

Evening primrose oil is extracted from the seeds of various Oenothera species [5]. It is a source of Ω a-6 essential fatty acids, among them, linoleic acid (LA) (59-76%) and γ-linolenic acid (GLA) (8-10%). The first step of linoleic acid metabolism is δ-6-desaturation to GLA. The γ-linolenic acid forms di-homo-γ-linolenic acid (DGLA) further converted to prostaglandin E_1 (PGE_1) or to arachidonic acid metabolites (PGE_2, leukotrienes, thromboxane).

Atopic eczema and diabetes represent examples of inadequate δ-6-desaturation.These diseases are characterized by impaired forming of active products from linoleic acid. The γ-linolenic acid and its metabolites are important for normal function of nerves. Disorders of nerve function occur in more than 90% of diabetics. Linoleic acid concentrations are normal or above normal in diabetic patients. However, the concentrations of its active metabolites are consistently below normal [6]. The evening primrose oil is botanical product non-affecting glucose level, that is believed to improve symptoms of neuropathy [7]. As it was experimentally demonstrated in rats, neuroactivity of EPO is mediated by cyclooxygenase and its substrates [8].

The evening primrose oil was also described as effective in atopic dermatitis and mastalgia, but optimal dosing standards and treatment regimens need clarification in adequate clinical trials [9-13].

Anti-tumor activity of evening primrose oil

Ramesh *et al*. [14] reported tumoricidal action of EPO, both *in vitro* and *in vivo*. This killing effect was correlated to an threefold increase in generation of free radicals in the tumor cells. The *in vitro* effect of n-6 fatty acids on normal and v-Ki ras transformed NIH-3T3 cells and other tumor cell lines was also described [15, 16].

It was reported, that *in vivo* EPO can influence carcinogen-induced papilloma formation in mice [17] and the progression of transplantable murine mammary gland adenocarcinoma [18]. Evening primrose extract induced caspase-independent apoptosis in Ehrlich ascites tumor cells, without similar effect on viability of mouse embryo fibroblast cells [19].

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Up to date, no convincing evidence of EPO beneficial effects in cancer patients was presented [20, 21].

Immunotropic activity of evening primrose oil

Evening primrose oil contains aromatic compounds with radical scavenging and cyclooxygenase and neutrophil elastase inhibitory activities (3-O-trans-caffeoyl derivatives of betulinic, morolic and oleanolic acid) [22]. Antioxidant properties of evening primrose seed extracts was concentration-dependent [23].

In the *in vivo* study on immunomodulatory effect of dietary lipids in rats, EPO decreased the adhesion of their lymphocytes to macrophage monolayers [24]. Other authors reported that primrose oil in *in vivo* experiments in mice, alone or in combination with fish oil, influenced macrophage/smooth muscle cell interaction what may be beneficial for avoiding atherogenic process [25].

Peritoneal macrophages of mice fed diet containing EPO presented enhanced PGE_1 synthesis [26]. Peritoneal granulocytes of rats fed for 8 weeks diet containing 15% EPO produced decreased amounts of PGE_2 [27].

Diet supplemented with 20% EPO suppressed natural killer (NK) cell activity of spleen lymphocytes collected from rats [28]. Evening primrose oil-enriched diet of rats influenced their serum-cytokine levels: interferon γ (IFN-γ) and MCP-1 levels were significantly decreased, the level of tumour necrosis factor α (TNF-α) was stimulated [29]. In atopic dermatitis patients , however, presenting low IFN-γ level, EPO significantly increased the level of this cytokine [10].

Feeding weanling rats diets containing EPO (but also fish and olive oil) resulted in suppression of lymphocyte proliferation [30]. GLA and arachidonic acid (AA), and some AA metabolites induce T-regulatory cell activity and reduce pro-inflammatory cytokines production. In experimentally induced T-cell mediated autoimmune disease GLA prevent or reduce the severity [31]. However, diets with high supply of GLA precursor, linoleic acid (LA) increased significantly the production of pro-inflammatory cytokines [32].

In Sommer *et al*. study [33] of the effect of EPO on the *in vivo* angiogenic activity of blood mononuclear leukocytes (cutaneous test in mice) highly statistically significant decrease of this activity was observed when cells were collected from rheumatoid arthritis (RA) patients. No effect was seen when cells were collected from the blood of healthy donors.

Filewska *et al*. [34] studied the effect of EPO (OEPAROL) feeding mice and rabbits for four weeks on the number and metabolic activity (chemiluminescence test – CL) of blood granulocytes. In animals receiving higher doses of EPO (125 or 250 mg/kg in mice, 50 mg/kg in rabbits) significant lowering of granulocytes number was observed. In the same time, CL activity of these cells increased significantly. These doses corresponded (applying a coefficient of 7 for adjustment of differences between mouse and human in relation the surface to body mass) to the doses recommended by EPO producers for humans. Number and activity of granulocytes return to the pre-feeding levels 5 weeks after feeding termination.

In the view of these results, it might be necessary to verify EPO doses recommended for human.

Contrary to the effects obtained in immunological angiogenesis, where topical application of EPO diminished skin neovascular reaction to the factors released by RA patients lymphocytes, EPO increased angiogenesis induced in mice skin after grafting of human lung cancer cells [35]. It was confirmed in further experiments where feeding mice linoleic acid (LA) significantly enhanced L1 Sarcoma tumor growth, vascularity and angiogenic activity [36]. In conclusion: experimental data suggest that EPO and pure linoleic acid may be harmful for cancer patients.

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