Review paper

Use of diet supplements, synthetic drugs and herbal remedies with immunotropic activity during pregnancy. II. *Zingiber officinale* Roscoe (Ginger)

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Abstract

This mini-review summarizes some experimental and clinical data about safety of ginger (Zingiber officinale Roscoe) treatment during pregnancy. Ginger is used in many cultures in the management of nausea and vomiting in pregnancy. There is some evidence from animal and human studies that Ginger is not teratogenic. However, the mutagenicity of ginger extracts is a controversial subject, because they contain mutagenic and anti-mutagenic compounds. Experimental studies in mice and fish revealed immunostimulatory and anti-inflammatory properties of ginger.

Key words: *Zingiber officinale, ginger, pregnancy, mouse, fish, human, antiemetic, immunotropic, anti-inflammatory, antioxidant.*

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Rhizoma zingiberis is the dried rhizome of *Zingiber officinale* Roscoe (African ginger), (*Zingiberaceae*). The plant is cultivated in the tropical regions of the world and is used in many cultures in the management of nausea and vomiting in pregnancy. There is also some experimental evidence from animal studies performed in dogs and pigeons that ginger's antiemetic activity is peripheral and does not involve the central nervous system [1].

Many women use herbal remedies during pregnancy, but the data regarding safety of this kind of treatment are limited [2-5]. Studies evaluating the safety and effectiveness of ginger use in pregnant women for management of nausea and vomiting revealed, that in low doses ginger may be beneficial for patients not responding to traditional therapies. However, most of meta-analyses could not demonstrate the postoperative antiemetic effectiveness in nausea and vomiting, as well as in the cases of nausea and vomiting of other etiology. The observational study showed the absence of significant side effects on pregnancy outcomes. The use of ginger in early pregnancy reduce nausea and vomiting similarly to, or better than vitamin B6. It was also presented that ginger is as effective as dimenhydrinate in the treatment of nausea and vomiting during pregnancy and has fewer side effects [6-13].

There is some evidence from human and animal studies that Ginger is not teratogenic. Zingiber officinale extract examined in rats caused neither maternal nor developmental toxicity at daily doses of up to 1000 mg/kg body weight. Evaluation of developmental toxicity of an herbal supplement containing ginger in rats gave no evidence of reproductive toxicity at 430 mg/kg per day or below. In the study of Wilkinson, performed in rats, the effect of ginger tea supplied in drinking water was evaluated. No maternal toxicity was observed, however embryonic loss in the treatment groups was double that of the controls. Fetuses exposed to ginger tea were heavier than controls and had more advanced skeletal development. Whether it might be connected with osteolysis – decreasing effect of zerumbone

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(sesquiterpene derived from ginger) remains the matter of speculation. Mutagenicity of ginger extracts is a controversial subject, because they contain mutagenic (6-gingerol and shogaols) and anti-mutagenic (zingerone) compounds [1, 14-19].

Plant-based immune stimulation provides an alternative to conventional therapy of infections. Experimental studies in fish and mice revealed, that rhizome of *Zingiber officinale* Roscoe (ginger) possess anti-inflammatory and immunomodulatory properties. Ginger fed for 14 days to rainbow trout led to control of experimental infection with *Aeromonas hydrophila*. At 0.5 g ginger per 100 g of feed, mortality was 0, comparing to 64% in the controls. In ginger fed fish, increased number and enhanced activity of macrophages, neutrophils an lymphocytes were observed [20]. Rainbow trout fed diet containing 1 % of lyophilized aqueous extract of ginger exhibited significant enhancement of nonspecific immune response and increase of total protein in plasma [21]. Acetone extract of ginger improved growth, immune activity and survival of tilapia (*Oreochromis mossambicus*) [22].

Chinese authors observed the effect of gingerol on endotoxemia mouse model induced by heatstroke. The energy metabolic level of celiomacrophage, its phagocytic ability, activity of superoxide dismutase, were increased, and the level of malondialdehyde in plasma was decreased in gingerol-treated animals [23]. It was reported by Carrasco *et al.* that ginger essential oil recovered the the humoral immune response in immunosuppressed mice [24]. However, in *in vitro* proliferation assays, ginger effects were immunosuppressive [25]. Anti-inflammatory effects of ginger and its compound 6-gingerol are partly connected with its inhibitory effect on LPS-induced macrophage activation and function, and proinflammatory cytokines production [26, 27]. Zhou *et al.* investigated the immunomodulatory effects of the essential oil of ginger both *in vitro* and *in vivo* in mice [28]. They report that *in vitro* ginger oil significantly inhibited T lymphocyte proliferation, decreased the number of T helper cells, increased the percentage of T suppressor cells and inhibited interleukin 1α (IL-1α) secretion by peritoneal macrophages. *In vivo*, administration of ginger oil weakened delayed-type hypersensitivity reactions. Authors concluded that ginger may exert beneficial effects in a number of clinical conditions, such as chronic inflammation and autoimmune diseases.

In modulation of macrophage function, 14 compounds isolated from ginger were active. They mostly inhibited LPS-induced nitric oxide production, some of them significantly reduced inducible nitric oxide synthase expression. One of them (compound 8) significantly stimulated phagocytosis [29]. Ginger exerted indirect inhibitory effect on the growth of influenza virus via macrophage activation leading to production of tumor necrosis factor α (TNF-α) [30]. Aqueous extract of ginger, enriched of gingerols, injected i.p. before airway challenge of ovalbumin – sensitized mice resulted in suppressing Th2-mediated immune responses and might thus provide a possible therapeutic application in allergic asthma [31].

Ginger is a strong anti-oxidant substance and may mitigate or prevent generation of free radicals [32]. The most potent anti-oxidant and anti-inflammatory properties exhibited 6-shogaol and 10-gingerol [33]. 6-shogaol inhibits production of TNF-α, IL-1β, and nitric oxide from LPS-stimulated macrophages [34]. 6-shogaol inhibits monosodium urate crystal induced inflammation in mice, an experimental model for gouty arthritis [35]. Ginger is also potent inhibitor of cyclooxygenase and thromboxane synthase [1].Compounds found in ginger are capable of inhibiting PGE2 production [36]. Amelioration of collagen-induced arthritis [37] and modulating effect on ulcerative colitis [38] in rats resulted from anti-oxidant and anti-inflammatory properties of ginger extracts. Compounds of ginger water extract protect skin against UVB irradiation damage [39]. 6-shogaol and 6-gingerol inhibit TNF-α mediated down-regulation of adiponectin expression in adipocytes [40]. The water extracts of ginger has detoxifying and anti-oxidant effects and are recommended to use them to avoid alcohol toxicity [41]. Ginger-derived phenolic compounds possess anticarcinogenic and antiangiogenic properties [42-47]. 6-gingerol inhibited both vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF) – induced proliferation of endothelial cells and new vessels formation. It may be useful in the treatment of tumors, but may be very dangerous for embryogenesis. Unfortunately, no information is available concerning the effect of ginger compounds on embryonic angiogenesis. However, a lot of phenolic compounds behave as angiogenesis inhibitors. We previously reported that chocolate feeding of pregnant mice resulted in epigallocatechin-related embryonic angiogenesis suppression and bone mineralization disorder [48].

In the available literature we have not found papers about immunotropic effects of ginger in pregnant animals and their progeny. Previously, we reported various abnormalities in immune system of progeny of mice fed various other plant-derived substances during pregnancy and lactation period [49].

Ginger is on the US.Food and Drug Administration's GRAS (Generally Recognized As Safe) list. Recommended dosage of ginger root for pregnancy nausea and vomiting is 250 mg one to four times daily. The British Herbal Compendium documents no adverse effects of ginger. However, the German Commission E Monographs do not recommend ginger root for nausea and vomiting of pregnancy [50, 51].

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