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Genotoxicity of Gasterolan (An Herbal Product) on Chromosomes of Cultured Human Lymphocytes and Rat Bone Marrow

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Abstract: It is well known that many components of herbal products are mutagens. Because of increasing use of medical herbs, in the present study the genotoxicity of Gasterolan was investigated using cultured human lymphocytes and rat bone marrow. Gasterolan (Goldaru Company, Esfahan, Iran) is used as an antispasmodic, carminative and for spastic disorders of the gastrointestinal tract. The drug contains hydroalcoholic extracts of *Foeniculum vulgare* fruits, *Matricaria chamomilla* flowers and *Mentha piperita*. The cultured human lymphocytes were treated with 0.5 and 0.75% (v/v) of Gasterolan and 0.75% of ethanol for 14 h. Chromatid break was used as a marker for damage. Ethanol did not increase the frequency of chromatid break ($Z = 0.0068$, $p = 0.948$). The frequency of chromatid break is significantly increased in 0.5 ($Z = 2.75$, $p = 0.006$) and 0.75 ($Z = 7.47$, $p<0.001$) percent of Gasterolan. Considering that ethanol does not increase the frequency of chromatid break, the observed effect is probably due to some components present in the herbal product. Investigation of rat bone marrow metaphases show that chromatid breaks increased as a function of harvest time (from 2-8 days after beginning the treatment) ($r = 0.998$, $df = 2$, $p = 0.002$). More studies are necessary to find components that increased chromosomal aberrations.

Key words: Chromatid break, genotoxicity, gasterolan, herbal medicine, human chromosomes, rat bone marrow

INTRODUCTION

Several diverse lines of evidence indicate that medicinal plants represent the oldest and most widespread form of medication. Until the last century most medicines were derived directly from plant or animal sources (Halberstein, 2005). People use herbal products for healing themselves and their children. Most of them believe herbal products have no dangerous effects and are safe since they have natural source. But, are herbal products safe really.

An oral herbal drop, Gasterolan (Goldaru Company, Esfahan, Iran), exists in Iran's market. It is an antispasmodic, carminative drug and is used for treatment of spastic disorders of gastrointestinal tract. The drug contains hydroalcoholic extracts of *Foeniculum vulgare* fruits, *Matricaria chamomilla* flowers and *Mentha piperita*. It has been demonstrated that some herbal extracts have genotoxic effects on cultured human lymphocytes (Saadat, 2006; Wang *et al*., 1993; Gadano *et al*., 2002). It has been demonstrated that *M. chamomilla* extract causes cytogenetic abnormalities in cultured human lymphocytes (Saadat, 2006). Because of increasing use of medical herbs, in the present study the genotoxicity of Gastrolan was investigated, using *in vivo* and *in vitro* conditions.

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MATERIALS AND METHODS

Culture of Human Lymphocytes

Blood samples were obtained from healthy subjects and collected into heparinized tubes. None of the individuals had confounding factors (e.g., current illness, on chemotherapy, exposure to radiation and chemicals, cigarette smoking). Lymphocytes were cultured as described previously (Saadat, 2006). The cultured cells treated for 14 h with 0.5 and 0.75% (v/v) of the drug and 0.75% of ethanol.

Rat Bone Marrow Metaphases

The Wistar male rats were treated with drinking water contained 2% (v/v) of the drug. The rat bone marrow metaphases were acquired 2, 4, 6 and 8 over nights after beginning of the treatment. The bone marrow metaphases, with out any treatment, was used as control. Chromosomes were stained with Giemsa.

Statistical Analysis

The human and rat metaphases were analyzed for the chromatid breaks. Statistical significance was determined using the proportional Z-test. Also the Pearson's correlation analysis was done. A probability of $p<0.05$ considered statistically significant difference.

RESULTS AND DISCUSSION

The cultured human lymphocytes were treated with 0.5 and 0.75% (v/v) of Gasterolan and 0.75% of ethanol. The frequency of chromatid breaks in negative control (without Gasterolan or ethanol), ethanol, 0.5 and 0.75% of the drug were 1.4 (out of 202 metaphases), 1.4 (out of 201 metaphases), 5.4 (out of 202 metaphases) and 17.5 (out of 194 metaphases) percent, respectively. Ethanol did not increase the frequency of chromatid break ($Z = 0.0068$, $p = 0.948$). The frequency of chromatid break is significantly increased in 0.5 ($Z = 2.75$, $p = 0.006$) and 0.75 ($Z = 7.47$, $p<0.001$) percent of the drug. Considering that ethanol does not increase the frequency of chromatid break, the observed effect is probably due to some components present in the herbal product.

The frequency of chromatid breaks in control and treated rats after 2, 4, 6 and 8 days of the beginning of drug administration were 1.3 (out of 300 metaphases), 1.7 (out of 291 metaphases), 2.7 (out of 292 metaphases), 3.7 (out of 295 metaphases) and 5.0 (out of 299 metaphases), respectively. Pearson's correlation coefficient analysis showed that the frequency of chromatid breaks increased as a function of harvest time ($r = 0.998$, $df = 2$, $p = 0.002$).

M. chamomilla and *M. piperita* extracts have genotoxic effect on cultured human lymphocytes and *Drosophila melanogaster* Somatic Mutation and Recombination Test (SMART) *in vivo* (Lazutaka *et al*., 2001; Saadat, 2006) but there is no report about genotoxic activity of *F. vulgare*. On the other hand a clear desmutagenic effect of *M. piperita* and *M. chamomilla* against hydrogen peroxide was reported (Romer-Jimernez *et al*., 2005). Protective effects of *M. piperita* on benzo (a)pyrene-induced lung carcinogenicity and mutagenicity in Swiss albino mice was reported (Samarth *et al*., 2006a, b). Also *M. piperita* leaf extract provides protection against radiation induced chromosomal damage in bone marrow of Swiss albino mice (Samarth and Kumar, 2003).

It is reported that *F. vulgare* extract is an inhibitor of CYP3A4 that involved in detoxification of xenobiotics (Subehan *et al*., 2006). It is suggested that inhibition of drug-metabolizing enzyme may lead to increase plasma levels of drug administered concomitantly, to prolong the pharmacological effects and to increase incident of drug induced toxicity (Subehan *et al*., 2006). Taken together, inhibition of CYP3A4 by *F. vulgare* extract may be aids genotoxic activity of *M. chamomilla* and *M. piperita* extracts.

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