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Rosemary Leaf Offers Cellular Protection

Genomic Instability Decreases in HIV Patient by Complementary Therapy with *Rosmarinus officinalis* Extracts.

Lazalde-Ramos BP, Zamora-Perez AL, Ortega-Guerrero AI et al. *J Med Food* 2020; **23**(10): 1070-1076

Infection with human immunodeficiency virus (HIV) alone or when treated with antiretroviral drugs increases oxidative stress and may cause further tissue damage. A clinical study in Mexico investigated the use of rosemary leaf on genomic instability in HIV patients. The average age of the patients was 40.5 years, and the average duration of the disease was 7.08 years. Sixty-seven patients, all of whom continued their current antiretroviral drug treatment (ATRIPLA; consisting of efavirenz, emtricitabine and tenofovir disoproxil fumarate), were divided into three groups: drug-only and patients treated with rosemary tea or rosemary extract. The tea group were instructed to drink the preparation during the day instead of drinking water. Rosemary leaves (4 grams) were added to one liter of boiling water, allowed "to boil" for 3 minutes, and the solution was then filtered to remove the leaves.[1,2] A concentrated methanol extract was provided to the other herb group.[3] Genomic instability was evaluated using the buccal micronucleus cytome assay. This assay measures DNA damage and markers of cell death and cell proliferation. Samples of oral mucosa were taken at the beginning, and after one and 4 months. The cells were spread, fixed and stained on slides and the abnormalities were counted. The number of cells with nuclear abnormalities was determined among 2000 cells. For example, in healthy controls (n = 22) there were 0.56 cells with micronuclei per 2000 cells, compared with 0.81, 0.82 and 1.00 for the HIV patients in the drug-only, tea and extract groups respectively, at baseline. The increase or decrease in these cells, as a percentage, from baseline was calculated.

- The groups that received rosemary in addition to drug therapy showed a decrease in the number of cells with certain abnormalities from baseline compared with the group that only received drug therapy – *see Table 1 for the changes from baseline after 4 months of treatment*.
  - For example, in the drug-only group, binucleated cells increased from 16.72 per 2000 cells to 25.31 after 4 months, an increase of 51.4%. In the rosemary tea group, binucleated cells decreased from 11.68 cells to 5.18 cells (-55.6%), and for the group who consumed the rosemary methanol extract, binucleated cells decreased from 5.30 to 1.60 cells (-69.7%).
  - Note: As illustrated by these results for binucleated cells, the baseline level of cells with abnormalities was often higher in the drug-only group (in 5 of the 7 abnormalities). It is not known if this variation at baseline affects the significance of the results.
- Changes from baseline after 30 days were also significant for many cell abnormalities for the herb groups, particularly those treated with methanol extract.

	Drug Only	Rosemary Tea + Drug	Rosemary Methanol Extract + Drug
binucleated cells	51.4	-55.6 *	-69.7 *
cells with nuclear buds	0	-31.1	-43.3
condensed chromatin cells	-2.0	-51.7 *	-54.2 †
karyorrhectic cells	12.7	-46.1 *	-52.3 *
micronuclei	50.3	-36.4	-79.1 †
pyknotic cells	-16.3	-56.3	-24.3

Table 1. Changes (%) from baseline after 4 months in the frequency of cellular abnormalities.
§ **Notes:** Results that were statistically significant compared to baseline are shaded. There were no significant results for any group at 4 months for the frequency of karyolitic cells. All results rounded to one decimal point. * Significant compared to the drug-only group ($p < 0.01$). † Significant compared to the drug-only group ($p < 0.05$).

Reviewer's Notes:

1. It is not clear whether this was an infusion (leaves steeping in boiling water for 3 minutes) or a decoction (leaves continued to be boiled), probably the former as the preparation is referred to as an infusion and a tea.
2. Many of the same researchers conducted a study, also in Mexico, involving 16 individuals with type 2 diabetes. They consumed a similarly prepared infusion each day made from 5 grams of rosemary leaf, for a period of 30 days. From baseline, significant decreases in the number of cells with micronuclei and certain nuclear abnormalities (binucleated cells, cells with abnormally condensed chromatin or karyorrhexis) were found (*CIMEL* 2016; **21**(2): 10-13).
3. After maceration in methanol, chlorophyll was removed using activated carbon, and the remaining liquid extract was concentrated. The resulting dry extract was about 7:1 in strength, making the administered dose equivalent to about 2.9 g/day of dried leaf. However, the removal of chlorophyll means the dried herb equivalent dose is likely to be higher.

Key Finding

Substantial doses of rosemary leaf may decrease the genomic instability in HIV patients.

More & Nuanced Evidence for EPO in Mastalgia

Clinical Factors Affecting the Therapeutic Efficacy of Evening Primrose Oil on Mastalgia.

Balci FL, Uras C, Feldman S. *Ann Surg Oncol* 2020; **27**(12): 4844-4852

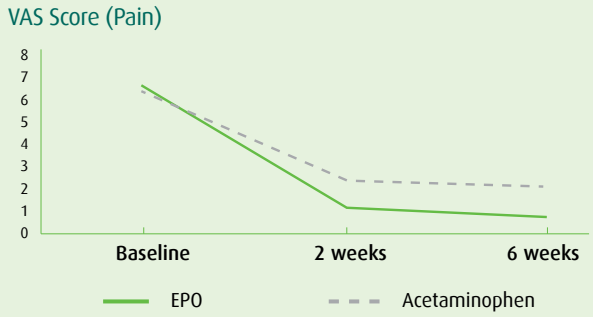
Evening primrose oil has been evaluated in clinical studies for the treatment of mastalgia, with conflicting results to date. A retrospective, case-controlled study in Turkey investigated the effectiveness of oral use of evening primrose oil (EPO) on the severity of cyclical or noncyclical mastalgia. Enrolled women with mastalgia (mean age 42.2 years) were treated with EPO (2.6 g/day for 6 weeks) or acetaminophen (1000 mg/day for 2 weeks).* The visual analog scale (VAS), used to assess pain, was measured at baseline, and after 2 weeks and 6 weeks of treatment. A VAS score less than 1 at week 6 was accepted as therapeutic success (i.e. reduction in the severity of mastalgia). Clinical factors affecting the efficacy of EPO were also analyzed, using univariate and multivariate binary logistic regression tests. There was a long list of exclusion criteria, and included, for example: mastitis, use of vitamin E (more than 200 IU/ day) or EPO taken in the previous 2 weeks, use of nonsteroidal anti-inflammatory drugs and those who used danazol, bromocriptine or tamoxifen in the previous 3 months. Clinical review was extended for 6 months after treatment to determine whether patients had chronic mastalgia. Of the 1126 eligible patients randomly assigned, 1015 completed the study (581 in the EPO group, 434 in the drug group).

- Pain, measured as VAS score, was significantly reduced at weeks 2 and 6 in both groups. The reduction in pain was significantly greater for those taking EPO than acetaminophen. *See graph on next page.*
  - Successful treatment (pain relief, as a VAS score less than 1) at week 6 occurred in 82.6% of those treated with EPO, and 51.2% of those treated with acetaminophen.
  - Patients receiving EPO were 4.5–5.3 times more likely to have therapeutic success than those who received acetaminophen ($p < 0.001$).
- Factors not significantly affecting the efficacy of EPO treatment were age, blood levels of TSH or prolactin, sleep disturbance and presence of IUD (intrauterine device) without hormone use.
- Factors significantly affecting the efficacy of EPO treatment were hormone replacement therapy, IUD with hormone (levonorgestrel) use, iron deficiency, overt hypothyroidism and Hashimoto thyroiditis. For example:
  - A one unit decrease below the normal range for hemoglobin, ferritin or free T4 (free thyroxine) was associated with a 33.4%, 1.2% and 4.5% decrease, respectively, in the efficacy of EPO treatment.
  - A one unit increase of anti-TPO (antithyroid peroxidase) was associated with a 0.7% decrease in the efficacy of EPO treatment.
- Side effects (allergy, anxiety, blurred vision, constipation and nausea) were rare: recorded in 10 of the EPO group and 8 of the drug group ($p = 0.88$).
- There were no recurrences of mastalgia in either group at the 6-month follow-up.
- Replacement of iron or thyroid hormone efficiently treated mastalgia in patients that did not respond to EPO treatment.
  - Among patients with iron deficiency and resistance to EPO treatment, 69% received pain relief from orally administered iron (Fe^{2+}, 100 mg).

- Mastalgia patients with hypothyroidism or Hashimoto thyroiditis who did not respond to EPO treatment experienced 70–75% alleviation of mastalgia symptoms when administered with 50–125 mg of thyroxine.

- Of the women with sleep disturbances (insomnia, excessive sleepiness, abnormal events occurring during sleep) at baseline, 74% of those treated with EPO reported that they no longer had these problems or experienced improvement at the 6-month follow-up.

- Patients who did not succeed using EPO or acetaminophen still had mastalgia at a rate of 9.6% and 25.3% at the 6-month follow-up, respectively.



* **Reviewer's Note:** One of the trial authors confirmed this: the duration of treatment with acetaminophen for any pain is restricted to a maximum of 2 weeks in Europe. Patients randomized to the drug group, regardless of whether experiencing cyclical or noncyclical mastalgia, were treated for 2 weeks.

Key Finding

Evening primrose oil was a beneficial and well-tolerated treatment for mastalgia, although some factors affect the efficacy.

Korean Ginseng: Support for Drug-treated Major Depression

Effectiveness and Tolerability of Korean Red Ginseng Augmentation in Major Depressive Disorder Patients with Difficult-to-treat in Routine Practice.

Lee KH, Bahk WM, Lee SJ et al. *Clin Psychopharmacol Neurosci* 2020; **18**(4): 621-626

Korean ginseng (*Panax ginseng*) was prescribed to Korean patients with difficult-to-treat major depressive disorder in an uncontrolled trial.*

Diagnosis was based on criteria from the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM-5). Participants with a CGI-I (Clinical Global Impression-Improvement) score of 3 or more despite taking antidepressants for at least 6 weeks, and at least one previous clinical failure with antidepressant medication were included. Patients remained on their single antidepressant treatment (paroxetine, venlafaxine, duloxetine, sertraline, fluoxetine, escitalopram or mirtazapine) and commenced ginseng for a period of 6 weeks. The concentrated extract provided 42 mg/day of the major ginsenosides (of which, ginsenosides Rb1, Rb2, Rc, Rd, Re and Rg1 made up 38 mg/day). Clinical outcomes were assessed at baseline, week 2 and week 6 and used the Montgomery-Åsberg Depression Rating Scale (MADRS), Patient Health Questionnaire-15 (PHQ-15), Patient Satisfaction Score (PSS) as well as CGI-I. The primary endpoint was the remission rate, defined as a MADRS score of 10 or less. Of the 36 enrolled patients (average age: 47.8 years), 28 returned for at least one follow-up visit and 26 patients completed the study. The following results are based on data from 28 patients.

- The remission rate by the end of the study, assessed by MADRS score was 39.3%.

- The remission rate, in which CGI-I scores decreased from 3 or more at baseline (average was 4.2) to scores of 1 or 2 at the end of the study, was 57.1%.

- The response rate, defined as a 50% or more reduction in the MADRS score, was 42.9%.

- The mean change of MADRS score from baseline was significantly decreased by 44.4% (from 21.6 to 12.0 at week 6; $p < 0.001$).

- Somatic symptoms (PHQ-15) also significantly improved and patient satisfaction with the treatment significantly increased.

- One patient withdrew due to adverse events. All adverse events were mild to moderate, the most frequent was headache (25.0%; 7/28).

* **Reviewer's Note:** Although Korean ginseng has not been evaluated in this specific condition before, it has relieved depression in those who were in remission from a major depressive episode but still experiencing residual symptoms (*Asia Pac Psychiatry* 2015; **7**(3): 330-336). The uncontrolled study, also conducted in Korea, administered Korean ginseng extract for 8 weeks to 35 patients who remained on their antidepressant medication. The dose of extract was titrated to the recommended level within 4 weeks, providing 58 mg/day of ginsenosides Rb1, Rb2, Rc, Rd, Re and Rg1 for the duration.

Key Finding

Preliminary results suggest standardized Korean ginseng extract may provide support for patients with difficult-to-treat depression already taking antidepressant drugs.

Ginkgo Protects Against Drug-induced Hearing Loss

The Effect of *Ginkgo biloba* Against Ototoxic Hearing Loss on Advanced Stage Undifferentiated Nasopharyngeal Carcinoma Receiving Cisplatin Chemotherapy.

Hendriyanto D, Setiamika M, Primadewi N. *IJNPC* 2020; **2**(2): 44-46

A double-blind, clinical study conducted in Indonesia aimed to evaluate the ability of Ginkgo to prevent or ameliorate hearing loss caused by cisplatin chemotherapy. This study follows earlier preliminary evidence of the herbal extract's beneficial effects in cancer patients receiving cisplatin.[1] Ototoxicity is damage to the ear caused by exposure to toxic substances and is one of the serious side effects of cisplatin. The hearing loss is progressively irreversible, starting from 6000-8000 Hz frequencies, continues to decline if the therapy is continued and is accompanied by tinnitus. Twenty-two patients with advanced stage, undifferentiated nasopharyngeal carcinoma who were receiving cisplatin, were randomly assigned into a control group (cisplatin-paclitaxel and placebo) or treatment group, the latter receiving cisplatin-paclitaxel and oral (undefined) *Ginkgo biloba*, 80 mg/day.[2] Placebo or Ginkgo was taken one day before chemotherapy, for 45 days. At baseline, 91% of patients received cisplatin at a dose of 80–120 mg, and in 9% the dose was greater than 120 mg. Hearing examination was carried out before and after the first, second and third cycles of chemotherapy. The outer hair cells of the cochlea are the primary site of the cisplatin ototoxicity. Distortion product otoacoustic emissions (DPOAEs) can provide information regarding the functional status of these cells. Not detecting a response indicates the functioning of the outer hair cells is damaged. Pure tone audiometry was also performed.

- There was a significant difference in the incidence of hearing loss between the groups after the second and the third cycle of chemotherapy, as assessed by DPOAE examination. *See results in table.*
- Pure tone audiometry examination, based on American Speech-Language Hearing Association criteria, demonstrated that the incidence of hearing loss was higher in control group than in treatment group. The results were similar to those of the DPOAE examination.
- It is proposed that Ginkgo protects against hearing loss by reducing damage to the outer hair cells of the cochlear.

Incidence of Hearing Loss (%) measured by DPOAE

	Ginkgo	Control
baseline	0	0
after 1st cycle	0	27.3
after 2nd cycle	9.1	63.4 *
after 3rd cycle	27.3	81.8 *

Note: * Significant difference between groups ($p < 0.05$).

Reviewer's Notes:

1. An Indonesian study involving 20 patients with various cancers, found the incidence of hearing loss after the first chemotherapy cycle was significantly lower for those who received Ginkgo (80 mg/day of specialized, standardized 50:1 extract i.e. corresponding to 4 g/day of dried leaf) for 30 days, compared to those receiving chemotherapy alone (*ORLI* 2014; **44**(2): 96-103). Subsequently, a pilot study conducted in Brazil observed a significant decrease in hearing threshold at the frequency of 8000 Hz in the placebo group treated at the maximum cumulative cisplatin dose, compared to similarly-treated patients who received Ginkgo (240 mg/day of specialized, standardized 50:1 extract i.e. corresponding to 12 g/day of dried leaf). Fifteen cancer patients took placebo or Ginkgo two hours before the first dose of cisplatin and continued to take the herb or placebo during the entire cisplatin treatment. They were monitored up to 90 days. The cumulative cisplatin dose i.e. over the whole treatment, was 300 mg/m^2. There was no significant difference for the other frequencies studied. Ginkgo was said not to interfere with the antitumor activity of cisplatin, according to patient medical records (*Int Tinnitus J* 2015; **19**(2): 12-19). Both studies used distortion product otoacoustic emissions (DPOAEs) to monitor cisplatin ototoxicity.
2. Further information provided by one of the trial authors indicates that specialized Ginkgo extract (50:1), was provided, so the dose corresponded to 4 g/day of dried leaf, and provided 19.2 mg/day of Ginkgo flavone glycosides and 4.8 mg/day of terpene lactones.

Key Finding

Further evidence is presented for the potential effect of standardized extract of Ginkgo to prevent hearing loss in cancer patients receiving cisplatin.

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