An oral botanical extract reduces fatigue in a radiation-induced fatigue mouse model

Michael Renner, BS¹; JiaWei Liu, PhD²; Leorey Saligan, PhD, RN, CRNP, FAAN¹

¹National Institute of Nursing Research, National Institutes of Health

²Legacy Healthcare

Background

- Fatigue is a common and highly distressing symptom following cancer treatments including radiation therapy. It is frequently undertreated in clinical practice [1].
- The etiology of cancer-related fatigue is poorly understood, but inflammation and mitochondrial dysfunction have been proposed [2].
- Currently, there is no US FDA-approved treatment for cancer-related fatigue.
- We previously observed significant correlations between changes in the expressions of eight mitochondria-related genes (e.g., BCL2) with worsening of radiation therapy-related fatigue [3].
- We also observed that Cellium, a safe botanical extract, inhibited inflammation and normalized BCL2 levels in human alopecia models.
- The goal of this study is to investigate the anti-fatigue effects of an oral botanical extract on a previously developed peripherally irradiated mouse model [4].

Experimental Procedures

- Irradiation:** Mice were irradiated after 2 – 3 weeks of acclimation. Prior to irradiation, mice were anesthetized with ketamine/xylazine given intraperitoneally. Mice were irradiated in a GammaCell 40 Irradiator (Best Theratronics) with custom-made lead shielding targeting the irradiation to the lower abdomen and upper thighs. The irradiation dose was 8 Gy per day for three consecutive days. Immediately following irradiation, mice were placed above heating pads until they recovered from the anesthesia.
- Voluntary Wheel Running Activity:** Mice were housed with a running wheel (Lafayette Neuroscience) that tracked wheel rotation in one-minute intervals for one week before and for two weeks after irradiation. Any minute during which the wheel turned was counted as one minute of activity.
- Two successive placebo-controlled experiments (N=40, n=20 Cellium, n=20 placebo) were conducted.
- Oral pharm grade Cellium (0.9 mg) mixed with pharm grade 1% saccharine or just plain 1% saccharine (placebo) were provided using sipper tubes as dietary supplement to mice before, during and following irradiation. All mice were given ad lib access to water and NIH-31 formula diet.

Results

Voluntary Wheel Running

Experiment 1: The average post-irradiation cumulative running distance of the Cellium-group was 47% greater than placebo-group. Cellium-group returned to initial running distance 8 days earlier than Placebo-group (no group-difference in bodyweight).

Experiment 2: The average post-irradiation cumulative running distance of the Cellium-group was 17% greater than placebo-group. Cellium-group returned to initial running distance 5 days earlier than Placebo-group (no group-difference in bodyweight).

Experiment 1: One week after irradiation, the average post-irradiation running speed of the Cellium-group was systematically improved in the active phase versus placebo-group. Note that a decrease in voluntary wheel running speed was most pronounced during the late hours of the active phase (i.e. dark cycle).

Experiment 2: One week after irradiation, the average post-irradiation running speed of the Cellium-group was systematically improved in the active phase versus placebo-group. Note that a decrease in voluntary wheel running speed was most pronounced during the late hours of the active phase (i.e. dark cycle).

Conclusions

- Irradiation had a large effect on running wheel activity, particularly during the later hours of the awake period.
- Dietary supplementation with Cellium showed faster recovery of physical function following irradiation compared to placebo.
- In addition, the wheel running speed of mice receiving dietary supplementation with Cellium significantly improved compared to mice in the placebo-group, specifically during the late hours of the active phase which is clinically relevant considering that fatigue has been reported to be worst in the evening in patients receiving radiation for cancer [5,6].
- There were no difference in body weight over time in the Cellium and placebo groups.
- Clinical application of using oral Cellium supplementation is warranted.

Animal Care

- This is an ACUC-approved study (H-0288). All aspects of animal testing, housing, and environmental conditions used in this study were in compliance with The Guide for the Care and Use of Laboratory Animals [7].
- Male mice (>6 weeks old at the beginning of each study) were housed individually on a standard 12:12 h light-dark cycle.
- Twice-daily health checks were maintained throughout the study. There were no obvious signs of distress after irradiation, and mice that showed clear signs of illness or pain were excluded from the study.

References

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Contact Information

- Dr. Saligan : saliganl@mail.nih.gov
- Dr. Liu: j.liu@legacyhealthcare.ch