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Liposomal hemp extract for the management of cachexia

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ABSTRACT

Background: The onset of cachexia, a body-wasting condition, is an ominous sign— it occurs in up to 80% of patients with cancer and is the ultimate cause of death in up to 20% of these patients. Moreover, cachexia can make treatment for cancer more difficult and less effective. With no approved treatment for cachexia, some patients have experimented with cannabis to increase their appetite. Findings on the use of cannabis as a treatment for cachexia have shown some promise; however, well-designed clinical trials of cannabinoids are necessary to provide guidance to both physicians and patients regarding formulation and dose.

Objective: The aim of this study as to use a mouse model to examine the effects of a liposomal cannabinoid-containing hemp extract on cancer-related cachexia.

Method: Bagg Albino c mice were inoculated with colon 26 tumor cells and followed until they developed signs and symptoms of cachexia. Upon onset of cachexia, the mice received a single dose of either 0.2 mg or 1 mg of a delta-9-tetrahydrocannabinol-free (THC-free) liposomal hemp extract containing 20% cannabidiol (CBD) and other cannabinoids. A control group received no treatment. Another dose of 0.2 mg liposomal hemp extract was given after a few days to mice that failed to respond to treatment, or to mice that initially responded to treatment but began to lose weight again after stabilizing.

Results: Of the 7 mice who were given 1 mg liposomal hemp extract, 4 gained weight and survived. Of the 7 mice who were given 0.2 mg of liposomal hemp extract, 2 gained weight and survived. Only 1 of the 9 mice in the control group survived.

Conclusion: The findings suggest the beneficial effects of liposomal hemp extract in treating and, in some cases, reversing cachexia and improving survival in a mouse model. This study revealed promising results that should be replicated in human subjects to test if similar results are seen and to determine an optimal dose.

KEYWORD: Hemp, Cannabinoids, Liposomal, Cancer, Cachexia, Mouse

INTRODUCTION

Cachexia is a body-wasting syndrome that affects up to 80% of patients with advanced cancer and is the direct cause of death in at least 20% of these patients [1]. In many cases, cachexia hinders a patient's treatment response and dramatically affects their tolerability to treatment [2]. To our knowledge, few therapies have been developed or approved to mitigate or prevent cachexia cancer. Although selective androgen receptor modulators, branched-chain amino acids, and omega-3 fatty acids have shown promise, limitation remains. [3,4]. Research on cachexia has been greatly overlooked; as a result, treating and managing cachexia is now considered one of the most important unmet medical needs in oncology [1-2,5,6]

Cannabinoids derived from Cannabis, including tetrahydrocannabinol (THC) and cannabidiol (CBD), have been increasingly used in drugs, dietary supplements, and functional foods and have been shown to alleviate nausea, vomiting, and pain associated with various diseases, including HIV/AIDS, multiple sclerosis, and in cancer chemotherapy [7-10]. As such, the use of cannabinoids has been explored for the treatment of cachexia in patients with cancer and HIV [11-12]. To our knowledge, the present study is the first to report on the use of a liposomal hemp product in treating and reversing cachexia. Liposomal encapsulation of nutritional compounds, vitamins, botanicals, hemp oil cannabinoids (including cannabidiol [CBD]), and other pharmacotherapies has shown a significant increase in absorption and efficacy. Previous studies have demonstrated liposomal encapsulation as a proven delivery system for hemp cannabinoids in the mitigation of cytokine-induced inflammation in vitro, with better outcomes than non-liposomal CBD [13-14].

In a recent pharmacokinetic study, we compared the blood levels of CBD in participants who consumed equivalent concentrations of a liposomal CBD-containing

hemp extract vs a non-liposomal CBD product [13]. The CBD concentrations in the blood of participants who consumed the liposomal preparation were nearly 7 times higher than CBD concentrations in participants who consumed the non-liposomal product, further confirming the efficacy of a liposomal delivery system for increased absorption. After the exciting results of these recent studies [13-14], we decided to pursue liposomal hemp extract as a potential treatment for cachexia.

MATERIALS AND METHODS

In this study, we employed the most widely used colon 26 cachexia animal model [15]. Bagg Albino c (BALB/c) mice were injected with colon 26 tumor cells. To ensure efficacy and ease of translation to clinical trials, we adopted the same enrollment criteria and efficacy end points as those used in humans with cancer; this included only initiating treatment with liposomal hemp extract at the onset of cachexia (described as a 5% body mass drop). In the work presented here, treatment with liposomal hemp extract significantly increased the survival rate of mice with cachexia, showing impressive efficacy on this aggressive disease model in terms of survival and quality of life.

Murine colon 26 tumor cells have been used in clinical cancer research for more than three decades [15]. This cell line is highly metastatic, a reliable model of cancer cachexia, and is often utilized to study the effects of various therapeutics on cachexia [16]. In this study, colon 26 cells were cultured in an RPMI-1640 medium supplemented with 10% fetal bovine serum at 37°C in 5% carbon dioxide. Tumor cells with viability >90% were chosen for the study. One million tumor cells were re-suspended in 100 µL of phosphate-buffered saline for injection. In all experiments, seven to eight-week-old BALB/c mice were used. Tumor cells were inoculated subcutaneously in the left flank of each mouse. Following tumor inoculation, the mice were returned to cages. The body weight and health conditions of the mice were monitored daily, starting seven days after tumor inoculation. Since all mice do not develop cachexia at the same rate, each mouse was treated individually after its body weight met the criteria for cachexia (ie, 5% loss of body weight).

Mice were divided into three treatment groups: a high-dose group (1 mg Colorado-grown, liposomal hemp extract, containing 20% CBD), low-dose group (0.2 mg liposomal hemp extract containing 20% CBD), and a control group that received no treatment. Mice in the high-dose group were given 1 mg liposomal hemp extract by oral gavage; if signs or symptoms of cachexia reappeared, the mice were given 1 or 2 low doses of liposomal hemp extract (0.2 mg). Mice in the low-dose group were treated with 0.2 mg liposomal hemp extract; mice that failed to respond to the first dose were given 1 or 2 additional doses of 0.2 mg liposomal hemp extract. The timing of this added dose varied, depending on how long it took for the mice to display signs of not responding to treatment. The control group did not receive any treatment. Body weights were recorded daily starting 10 days after inoculation, then for 15 days after the onset of cachexia and initiation of dosing in the treatment groups. Figure 1 shows the progression of mouse body weight across the three study groups (low dose, high dose, and control).

The mice were treated in compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals.

RESULTS

Of the 7 mice treated with 1 mg of the natural cannabinoid-containing liposomal hemp extract, 4 exhibited, restored body weight, and significant health improvements, and a reversal of cachexia (Figure 1A) compared to mice in the control group.

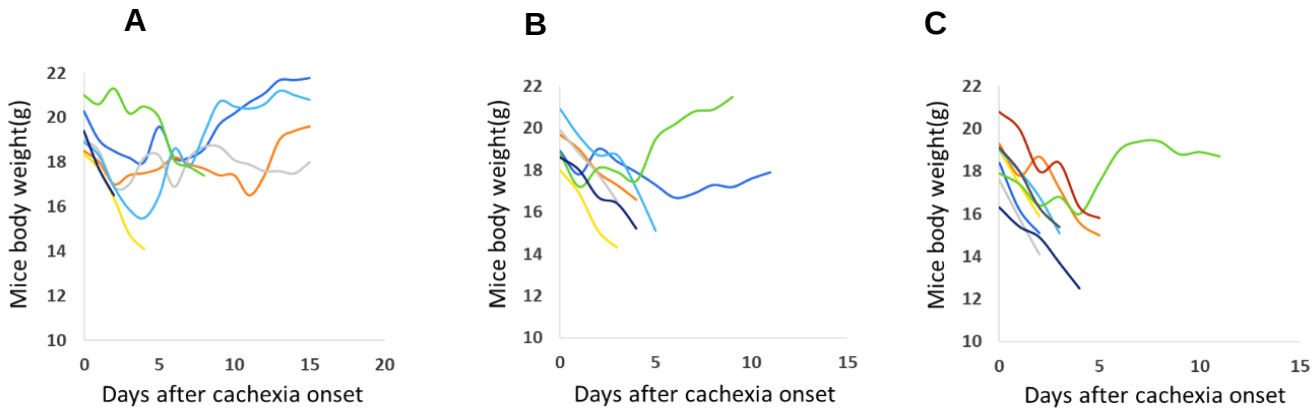

Figure 1. Liposomal hemp restored body weight and health of mice in both treatment groups. After cachexia onset, mice were enrolled into 1 of 3 groups: (**A**) Group 1 mice received 1 mg liposomal hemp by oral gavage (n=7). (**B**) Group 2 mice received 0.2 mg liposomal hemp by oral gavage (n=7). (**C**) Group 3 mice were enrolled as the control group and received no treatment (n=9). Body weight of the mice was measured daily during treatment; each colored curve represents the body weight of one mouse.

Of the 7 mice treated with the low-dose liposomal hemp extract, 2 showed significant improvements in body weight and overall health compared with the control group (Figure 1B). Only 1 mouse in the control group of 9 mice maintained its body weight and survived; the other 8 mice continued a weight loss trajectory that resulted in death (Figure 1C).

When plotted on a Kaplan–Meier survival curve [17] (Figure 2), liposomal hemp extract treatment demonstrated significantly improved survival, compared with control (p = 0.0345 for 1 mg compared to control). Overall, the Kaplan-Meier statistical analysis revealed significantly improved survival in the two groups that received the liposomal hemp extract, with the 1 mg group exhibiting the best survival.

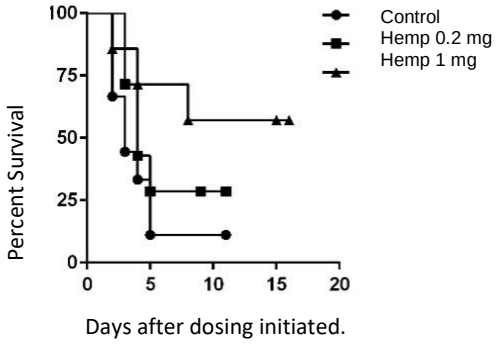

Figure 2. Liposomal hemp significantly increased the survival rates of mice in both treatment groups. After cachexia onset, mice were treated with 1 mg (n=7) or 0.2 mg (n=7) liposomal hemp by oral gavage. The mice in the control group received no treatment (n=9). Survival time of mice was recorded and plotted to fit the Kaplan–Meier survival curve (p = 0.0345, 1 mg vs control).

DISCUSSION

Cachexia is a serious condition that affects between 50-80% of cancer patients [18], as well as patients in advanced stages of diseases such as AIDS, Parkinson's disease, chronic obstructive pulmonary disease (COPD), chronic kidney disease, and multiple sclerosis [1,19]. Few approved pharmacological treatments for cachexia exist, including progesterone analogs and short-term steroids; however, these treatments, although they reduce the loss of fat, do not increase lean muscle mass [20]. Therefore, cachexia continues to be a complex challenge in oncology, as it not only interferes with cancer treatment progress [21] but also can ultimately lead to death in many patients.

Cachexia appears to be multifactorial, with elements of reduced appetite, inflammatory cytokine upregulation, mitochondrial dysfunction, increased protein degradation and decreased protein synthesis, and other metabolic and cell-signaling mechanisms. [18,22]

The use of cannabinoids, including THC and CBD, has been shown to address some of these metabolic perturbations and mechanisms, including appetite [23], cytokine dysregulation [24], and mitochondrial energy production [25]. Possible mechanisms for the anti-cachexia effect of this liposomal hemp extract may include cannabinoid-receptor-1 (CB_1)-induced increased appetite and lipogenesis, and inhibition of inflammatory mechanisms [25]. Reduced muscle wasting by upregulation of PPAR-γ [26] CBD has also demonstrated anti-metastatic activity, which appears to be related to upregulation of a tissue inhibitor of matrix metalloprotein-1 (TIMP-1) [27].

Based on the results of this study, liposomal hemp extract shows great promise in the treatment and reversal of cachexia in a mouse model. Cachectic mice inoculated with tumors had a significantly greater clinical response and survival when dosed with liposomal hemp oil.

CONCLUSIONS

Although results from our study examining liposomal hemp extract in the treatment and reversal of cachexia in a mouse model are very encouraging, more research is needed to discover whether this animal study will translate to humans. If shown effective, further studies are needed to determine the optimal therapeutic dose of liposomal hemp extract in humans.

Abbreviations: THC- tetrahydrocannabinol; CBD-cannabidiol

Authors Contribution: Emek Blair: Conceptualization, Methodology, Investigation, Resources, Data Curation, Formal Analysis. Alan Miller: Visualization, Writing-Original Draft, Writing- Review and Editing

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Ethics Statement: The mice used in this study were treated in compliance with the Public Health Service Policy on Humane Care and Use of Laboratory Animals.

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