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RESEARCH ARTICLE



The efficacy of HDDPiW-jSB solution on docetaxel-induced alopecia of rats

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ABSTRACT

Objective: Chemotherapy induced alopecia (CIA) is one of the most common side effects in cancer patients, however; it doesn't have an effective pharmacological treatment yet. In this study we aimed to research the protective effect of newly developed HDDPiW-jSB solution on docetaxel (DTX)-induced rat alopecia model.

Material and Methods: Docetaxel (10 mg/kg/week) was administered to the 6–8 months old rats for three weeks. HDDPiW-jSB solution was applied once or twice a week for 4 weeks beginning prior to one week before DTX. Rat hair follicles were evaluated with hematoxylin-eosin and immune-histochemical staining.

Results: In the first stage of this study, alopecia was successfully developed by DTX (10 mg/kg/three times) application. In the second stage of the study, application of HDDPiW-jSB solution, did not change the study parameters significantly on control group. The solution improved the anagen hair follicle count and Bcl-2 levels in the skin samples of DTX-induced alopecic rat groups, especially when applied twice weekly. Additionally, level of Caspase 3 was decreased. HDDPiW-jSB solution was safe when applied on the skin.

Conclusion: Topical HDDPiW-jSB solution could be effective and safe for the protection of DTX-induced alopecia in rat models.

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KEYWORDS

Chemotherapy induced alopecia; docetaxel; hair loss; oncology; animal research

Introduction

Alopecia is the partial or total loss of scalp hair that can be seen due to genetic factors as well as in many clinical conditions such as, endocrinologic, immunologic-rheumatologic and oncologic diseases and drug treatments [1,2]. Alopecia is also one of the most common side effects of cancer treatments. Chemotherapy induced alopecia (CIA) can be seen in approximately 65% of the patients and it affects all body hair such as the eyelashes and eyebrows besides the scalp. It has been frequently reported after the use of common chemotherapy (CT) agents (busulfan, cyclophosphamide, thiotepa, melphalan, etoposide, carboplatin, docetaxel, and paclitaxel) as well as other cancer treatment modalities [2,3]. Alopecia has a negative impact on physical appearance, body perception and self-esteem though it is usually reversible. Sometimes alopecia is described as the most traumatising and painful experience, especially by women with cancer [4,5].

Docetaxel (DTX) is a member of taxane family, microtubule antagonist CT agents widely used in oncology practice [6]. It has been reported that patients who had received taxane-based treatment regimens had more likely experienced CIA [3].

HDDPiW-jSB is a vitamin-based product, developed to protect the patient from CIA. It was experienced clinically by the

two authors of this study on themselves before. One author used the solution while under DTX and cabazitaxel-induced alopecia for prostate cancer with complete success and the other under the treatment of combination CT regimen of doxorubicin plus cyclophosphamide followed by trastuzumab plus weekly paclitaxel for breast cancer with partial success on scalp, with complete protection of eyebrows and eyelashes. This encouraged the authors for the presented study.

Up to now, the best and only FDA accepted treatment is scalp hypothermia to reduce and/or prevent CIA, unfortunately, there is no effective pharmacological treatment option [3,7]. Therefore, we aimed to study the efficacy of HDDPiW-jSB solution on DTX-induced rat alopecia model.

Material and methods

Animals and experimental design

Wistar rats, 6–8 months old albino male, between July 2022 to February 2023, were obtained from Animal Care and Research Unit of University of Aydın Adnan Menderes, and all experiments were performed according to the principles and guidelines of Animal Ethical Committee's approval (HADYEK 64583101/2020/075). A total number of 44 male rats were used

in this study. To avoid the confounding effect of oestrogen and hormonal cycle variations, male animals were preferred.

The study was conducted in two stages. In the first stage, the application dose of DTX, which was chosen in accordance with the purpose of the study, to cause hair follicle loss without causing lethal toxicity was determined. While establishing the experimental model, we aimed to mimic the clinical condition of DTX (Doxitax[®] sol, Kocak Farma, Istanbul, Turkey) treatment, well known for the side effect on hair growth. Dykes et al. stated that maximum tolerable dosage of DTX was 33 mg/kg and lethal dosage was 50 mg/kg on mice [8]. These investigators administered DTX once weekly to the rats for three times. Another research that was performed by Bissery et al. showed that non-lethal maximum dose of DTX was 32.2 mg/kg [9]. In another study, DTX produced oxidative stress at 10 mg/kg dosages [10]. Based on these previous studies, we have planned the first stage of experimental study groups as 10 mg/kg (low dose) and 30 mg/kg (high dose) weekly DTX, for three weeks, to assess the hair tissue response.

Taking this data as the basis, three groups were created for the first stage.

- Control Group (n=6): Serum physiologic (%0.9) was administered intra-peritoneal (IP) to the rats in this group once a week for three weeks, it was planned to sacrifice the animals at the 22nd day.
- DTX10 Group (n=8): DTX 10 mg/kg was administered IP to the rats in this group once a week (days 0, 8 and 15) of the study; it was planned to sacrifice the animals at the 22nd day.
- DTX30 Group (n=8): DTX 30 mg/kg was administered IP to the rats in this group once a week (days 0, 8 and 15) of the study; it was planned to sacrifice the animals at the 22nd day.

Considering the microscopic findings obtained in the first stage of the study, the second stage was subsequently started using the siblings of the same set of rats. At this stage, three groups were formed with the aim of determining the effectiveness and safety of the solution to be applied experimentally. Considering the results obtained in the first stage, the application dose for DTX was decided as 10 mg/kg/weekly for three weeks. On the second stage, HDDPiW-jSB solution were applied 1 ml on the one cm² interscapular region of the hairy area, making it completely wet and air-blotted for 2–3 min. This was done starting one week before the administration of DTX in all groups. The rats were caged separately to avoid licking or plucking to each other. HDDPiW-jSB is a vitamin-based product (mainly a mixture of multi-vitamin in specifically adjusted concentrations, developed by the authors S. & D. Barutca, depending on their clinical and patient experiences), developed to protect the patient from CIA. The solution especially contains a unique concentration of dexpanthenol.

The second stage of experimental groups was as follows:

- HDDPiW-jSB Group (n=8): The solution was applied to the previously described dorsal area of the rats (no-DTX administration), twice a week (on Mondays and Thursdays),

for four weeks, to watch the safety of the solution. It was planned to sacrifice the animals at the 28th day.

- DTX10 + HDDPiW-jSB I Group (n=7): The solution was applied once a week (on Mondays), for four weeks (days 0, 8, 15 and 21); meanwhile IP DTX 10 mg/kg was administered on days 8, 15, 21 of the study; it was planned to sacrifice the animals at the 28th day.
- DTX10 + HDDPiW-jSB II Group (n=7): The solution was applied twice a week (on Mondays and Thursdays), for four weeks; meanwhile IP DTX 10 mg/kg was administered on days 8, 15, 21 of the study; it was planned to sacrifice the animals at the 28th day.

Anaesthesia of Ketamine and Xylazine (50 mg/kg and 5 mg/kg, respectively) were used for the sacrifice process.

Immuno-Histopathological staining

The hair skin samples were fixed in 10% neutral-buffered formalin solution (Chempur, Poland), treated with graded alcohol, xylol series, and blocked-in paraffin (Histowax, Histo-Lab. Ltd, Goteborg, Sweden). Obtained 4 μm sections of skin from paraffin blocks were stained according to the hematoxylin-eosin (H&E) method. The sections were taken both vertical and transversal (horizontal). The transverse sections were cut 1 mm below the epidermis and the number of follicles was counted (Figure 1). The vertical sections were used for immunohistochemical staining and the phases of the hair follicles, based on the report of Müller-Rover et al [11]. These sections were evaluated under the microscope and images were obtained (Olympus Stream Start BX 51, Olympus SP 350 digital camera, Japan).

On the first stage of study, the dose response of 10 mg/kg and 30 mg/kg DTX on hair follicles were evaluated. Then, the study was continued with 10 mg/kg DTX in order to reveal and interpret the possible protective effects of HDDPiW-jSB solution. Tissues were stained with H&E and follicles counted as anagen, catagen, telogen and terminal hair follicles in five areas (x40=1 cm²) of each sample. Next, immuno-histopathological staining of CD34 (Clone QBEnd10, Dako, Denmark), Bcl-2 oncoprotein (b cell leukaemia protein-2) (Clone 124, Dako, Denmark), apoptosis-related cysteine protease (caspase 3) (mouse monoclonal antibody, Vision Biosystems Novocastra, Newcastle, United Kingdom) were performed in three areas of each sample (x400). Olympus Stream Start BX51 microscope and Image J software were used for the analyses.

Statistical analyses

Statistical analyses were performed using the NCCS 2007 program (Number Cruncher Statistical System, Kaysville, Utah, USA). Data are expressed with the descriptive statistics (mean, standard deviation, minimum value, maximum value, median, quartiles, frequency, percent). Shapiro-Wilk test and graphical evaluation were performed to assess the normality of quantitative data. If the variances were heterogeneous, between the groups Mann-Whitney U test; amongst the group Kruskal-Wallis test and Dunn-Bonferroni test were used to evaluate for significance. Fisher-Freeman-Halton exact test was used for qualitative data. In all cases, $p < 0.05$ was considered as significant.

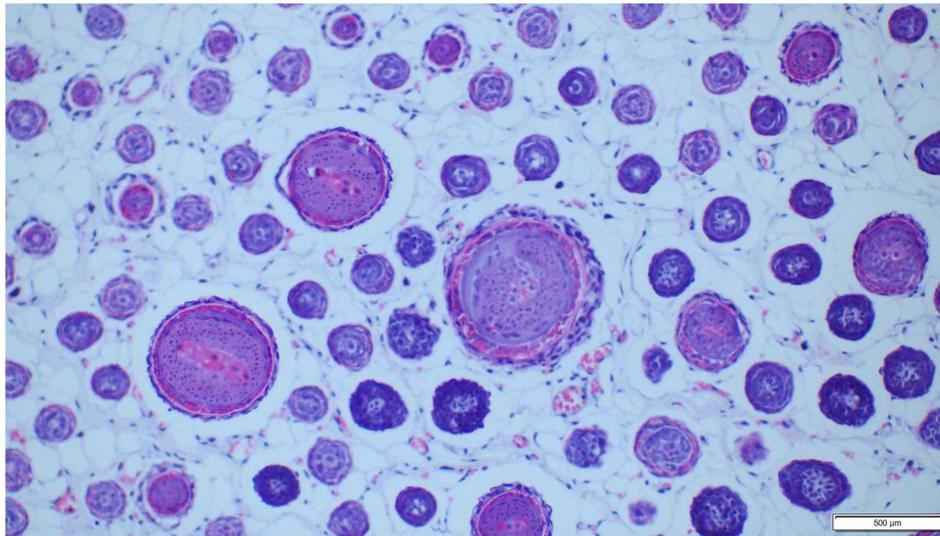


Figure 1. Hematoxylin-eosin staining of control group hair follicles (X200), transverse section.

Table 1. Hair follicle counts and immuno-histochemical findings of all study groups (X40 magnification).

	Control group (n=6)	DTX10 group (n=8)	HDDPiW-jSB Group (n=8)	DTX10+HDDPiW-jSB I Group (n=7)	DTX10+HDDPiW-jSB II Group (n=7)
Anagen hair follicle number	127.50 (83–150)	0 (0–0)	17.00 (0–70)	4.00 (0–55)	3.00 (0–15)
Catagen hair follicle number	6.00 (1–11)	34.50 (30–50)	1.50 (1–12)	12.00 (7–20)	8.00 (5–12)
Telogen hair follicle number	8.50 (7–10)	1.00 (1–3)	7.50 (4–11)	0 (0–1)	0 (0–1)
Terminal hair follicle number	139.50 (90–157)	0 (0–1)	70.00 (37–131)	0 (0–1)	0 (0–1)
CD34 (%)	30 (0–75)	1.5 (0–25)	35 (0–75)	2 (0–25)	25 (0–75)
Bcl-2 (%)	1 (0–1)	0 (0–0)	1 (1–2)	0 (0–0)	1 (1–2)
Caspase 3 (%)	0 (0–1)	2,5 (1–5)	0 (0–1)	1 (0–1)	0 (0–1)

All results were shown as median (minimum-maximum). DTX: Docetaxel.

Results

We started with two different dosages of DTX at the first stage of this study. In the DTX30 group, 3 out of 8 rats had died at the end of the second week due to toxicity. In the DTX10 group we could successfully produced alopecia and none of the rats had died. So, the DTX30 group was excluded from the study and 10mg/kg of DTX was selected for the second stage.

Hair follicle counts and immuno-histochemical findings of the study groups are summarised in Table 1. Anagen hair follicle counts of DTX10 group was dramatically dropped to zero while catagen hair follicles were increased; increment of caspase 3 and decrement of Bcl-2 were significant as compared to the control group (Table 2, Figures 2 and 3). The difference of CD34 values were not significant in-between the study groups.

Application of HDDPiW-jSB solutions along with DTX10, significantly ameliorated the anagen hair follicle counts (Table 3). In the DTX10+HDDPiW-jSB II group, Bcl-2 values as an anti-apoptotic marker in skin samples were significantly higher as compared to both HDDPiW-jSB and DTX10+HDDPiW-jSB I groups (Table 3). Additionally, Bcl-2 staining of the follicular epithelium was higher in the DTX10+HDDPiW-jSB II group (Figure 4). Also, the caspase 3 values as an apoptotic enzyme activity marker were lower in all solution groups as compared to the DTX10 group (Table 3).

Table 2. Statistical comparison of hair follicle phases and immuno-histochemical findings of the groups in the first stage of the study.

	Control group (n=6)	DTX10 group (n=8)	p Value
Anagen hair Follicles	113.33±50.25 127.50 (83–150)	0±0 0 (0–0)	0.001
Catagen hair Follicles	6.67±6.09 6.00 (1–11)	41.75±18.80 34.50 (30–50)	0.002
Telogen hair Follicles	8.83±3.66 8.50 (7–10)	1.38±0.74 1.00 (1–3)	0.001
Terminal hair Follicles	121.00±52.28 139.50 (90–157)	0.25±0.46 0 (0–1)	0.001
Bcl-2value (%)	0.83±0.75 1.00 (0–1)	0±0 0 (0–0)	0.009
Caspase 3 value (%)	0.33±0.52 0 (0–1)	2.75±1.75 2.5(1–5)	0.005

Results were shown as both mean±standart derivation and median (minimum-maximum). DTX: Docetaxel.

When all groups are considered, we determined that catagen hair follicle numbers were the highest in DTX10 group (Figure 3). In contrary, in the HDDPiW-jSB solution groups catagen hair follicle numbers were decreased.

Interestingly, aforementioned values (hair follicle counts and Bcl-2, caspase 3, and CD34 values) of the HDDPiW-jSB Group (without DTX) were not statistically different from the Control Group ($p \geq 0,05$). Also, no skin toxicity was observed secondary to HDDPiW-jSB solution in our study.

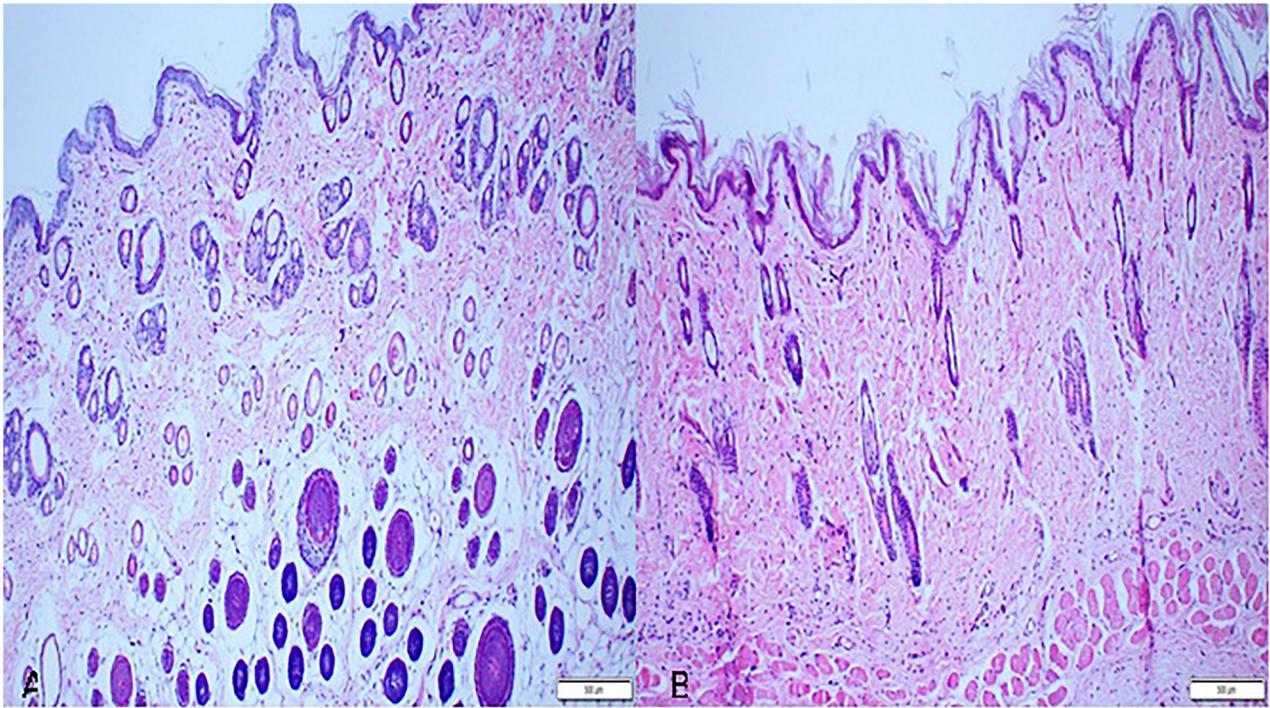


Figure 2. Hematoxylin-eosin staining of hair follicles. (A) Control group (X100), (B) DTX 10 group (X100).

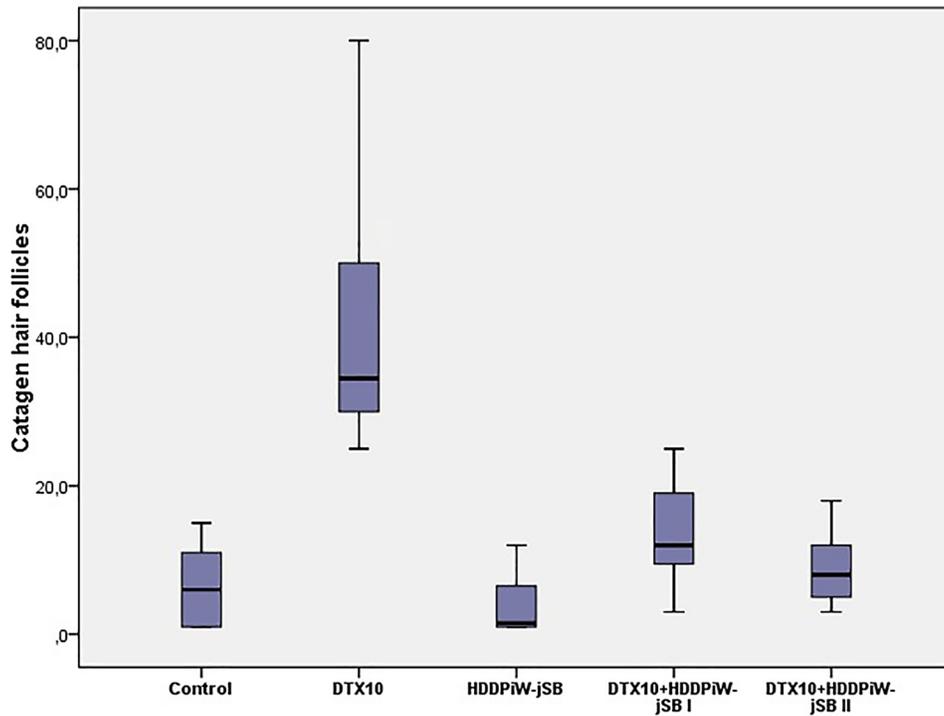


Figure 3. Box-plot graphics of catagen hair follicle numbers in the study groups.

Discussion

It was stated that rat hair follicles could be a suitable model for human hair tissue studies [11,12]. In our study, we would like to mimic the real clinical patient scenario, without traumatising the hair follicles by plucking; we only induced the rat experimental alopecia model with DTX. Weekly 10mg/kg for three weeks of DTX was successfully achieved alopecia.

Hair follicles are composed of epithelial and mesenchymal tissues, which evolve from the stem cells. The key stages of hair follicles are anagen, catagen, telogen and, exogen phases. Normally, the majority (90%) of the hair follicles are in anagen phase (growth), 1–2% in catagen phase (regression), and 8–9% are in telogen phase (resting, no mitotic activity, quiescence) [1].

Under the influence of CT agents, massive apoptosis occurs in the proximal bulb and the percentage of hair follicles in the anagen phase decrease [3]. These hair follicles transform to dystrophic catagen phase instantly, hence; CIA known as anagen effluvium [13].

The acute toxicity of DTX to skin and skin annexes have been described in previous clinical trials [14]. Alopecia was reported in 74.2% of 965 breast cancer (BC) patients treated with DTX [15]. In a previous study on BC patients ($n=744$) under TAC CT regimen (DTX plus doxorubicin and cyclophosphamide), alopecia incidence (all grades) was 97.8%. Nabholz et al. described, for the first time, four patients with persistent alopecia (>2years) following TAC regimen for metastatic BC [16]. Similar to previous papers, DTX administration decreased the numbers of anagen hair follicles and increased the catagen follicles in the first stage of our study.

The role of nutrition and diet in the treatment of alopecia represents a dynamic and growing field of research. In many studies, vitamins and minerals such as vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, iron, selenium and zinc have been investigated for the treatment of alopecia [17]. Studies with topical calcitriol have produced conflicting data on the prevention of alopecia. Although no benefit was shown in a Phase I study involving 12 patients who were treated with anthracycline and cyclophosphamide CT regimen for BC, it

was found to be reliable in another phase 1 study [18]. In another animal experiment, it was shown that α -lipoic acid applied in addition to cooling treatment improved CIA in a cyclophosphamide-induced alopecia model [19]. In conclusion, vitamin based treatments have not been fully effective in the protection of CIA in previous studies. However; in the second stage of this study, topical application of vitamin-based HDDPiW-jSB solution decreased the transformation of hair follicles into the catagen phase.

Dexpanthenol, the alcohol form of pantothenic acid (Vitamin B5), is a pharmaceutical ingredient used for its local anti-inflammatory, moisturising and regenerative effects [20]. In addition, dexpanthenol has been used in hair and scalp care products, especially for the prevention of hair loss in various forms and concentrations. In clinical studies, it was reported to improve androgenic alopecia as well as female pattern hair loss [21].

It has been reported that morphogenesis and cycle of hair follicles are strictly controlled and characterised by proliferation, differentiation and apoptosis. Bcl-2, a well-known inhibitor of apoptosis, is expressed in hair follicles and facilitates their growth. Decreased Bcl-2 levels were reported to result with selective loss of stem cells and disruption of hair follicle regeneration [22]. In our study HDDPiW-jSB solution was able to increase the Bcl-2 levels significantly, especially when it was applied twice a week along with DTX.

At the start of each new hair cycle, a cluster of stem cells at the base of the bulge become activated to proliferate [23]. The presence of perifollicular stem cells was evaluated by CD34 staining and there was no significant difference in-between our study groups. Hence the increment of Bcl-2 was not enough to trigger stem cells and this result suggested that the HDDPiW-jSB solution was only protective.

Caspase 3 is a highly expressed apoptosis mediator both in human and rat hair follicles and it was suggested that apoptosis inhibitors could be used for the treatment of CIA [24,25]. Caspase 3 leads to cell apoptosis and, is also considered a termination marker for the anagen phase [26]. In our study, DTX has significantly increased Caspase 3 levels while HDDPiW-jSB solution was able to decrease the Caspase 3 levels significantly, along with DTX.

Table 3. Statistical comparison of hair follicle phases and immuno-histochemical findings of DTX10 group of the first stage with the solution groups of the second stage of the study.

	DTX 10 Group ($n=8$)	DTX10+HDDPiW-jSB I Group ($n=7$)	DTX10+HDDPiW-jSB II Group ($n=7$)	<i>p</i> Value
Anagen hair Follicles	0 \pm 0 0 (0–0)	22.29 \pm 29.42 4.00 (0–55)	7.00 \pm 9.45 3.00 (0–15)	0.022
Catagen hair Follicles	41.75 \pm 18.80 34.50(30–50)	13.86 \pm 7.65 12.00 (7–20)	9.00 \pm 5.29 8.00 (5–12)	0.001
Telogen hair Follicles	1.38 \pm 0.74 1.00 (1–3)	0.57 \pm 0.79 0 (0–1)	0.29 \pm 0.49 0 (0–1)	0.016
Terminal hair Follicles	0.25 \pm 0.46 0 (0–1)	0.29 \pm 0.49 0 (0–1)	0.29 \pm 0.49 0 (0–1)	0.984
Bcl-2 value (%)	0 \pm 0 0 (0–0)	0 \pm 0 0 (0–0)	1.43 \pm 0.53 1.00 (1–2)	0.001
Caspase 3 value (%)	2.75 \pm 1.75 2.50(1–5)	0.71 \pm 0.49 1.00 (0–1)	0.57 \pm 0.79 0 (0–1)	0.009

Results were shown as both mean \pm standart derivation and median (minimum-maximum). DTX: Docetaxel.

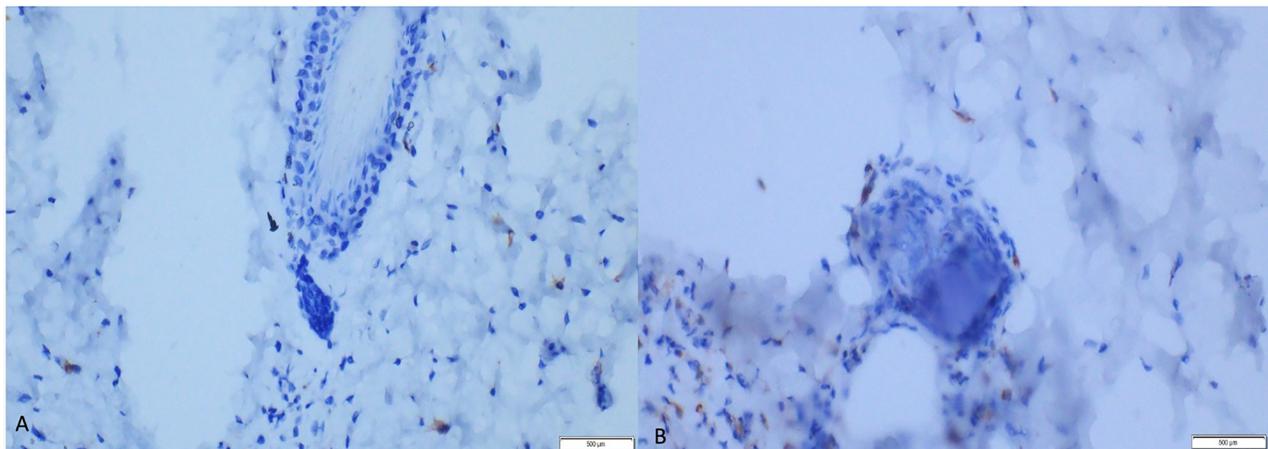


Figure 4. Bcl-2 staining of follicular epithelium. (A) DTX 10 group (X400), (B) DTX10+HDDPiW-jSB II group (X400).

In a cell culture study, dexpanthenol prevented apoptosis by decreasing caspase 3 and increasing bcl2 levels, thus; prolonged the anagen phase of hair follicles similar to our findings [27]. These data suggest that the effect of HDDPiW-jSB solution might be at least partially explained by the prevention of hair loss.

The limitation of this study is we could not establish a scalp hypothermia group to compare the treatment efficacy of HDDPiW-jSB solution due to technical difficulties such as the need to anaesthetise the rats for a certain period of time to keep them still. Future studies should also be conducted on different hair loss models, such as plucking and/or with different chemotherapy-induced hair loss.

Conclusion

Chemotherapy induced alopecia is one of the most common side effects in cancer patients, however; it does not have an effective pharmacological treatment yet. The results of our study suggested that HDDPiW-jSB solution was safe in rats and protected the hair follicles by inhibiting apoptosis under DTX treatment. It could prevent DTX induced transition of the hair follicles from anagen to catagen phase. The solution showed no significant effect without CT, so it was only protective. HDDPiW-jSB may be useful for the prevention CIA secondary to other CT agents with easy-to-use formulation than scalp cooling which is the only FDA approved treatment.

Author contributions

All authors have made substantial contributions to conception, design, acquisition of data; or analysis and interpretation of data; or have been involved in drafting the manuscript or revising it critically for important intellectual content.

Ethical approval

Aydin Adnan Menderes University for Animal Experiments (HADYEK 64583101/2020/075).

Disclosure statement

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Data availability statement

The data sets and data analysed in the study are available from the corresponding author on reasonable request.

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