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# Protective role of *Nigella sativa* in chemotherapy-induced alopecia

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## Abstract

Chemotherapy-induced alopecia affects the pathological as well as the psychological aspects of the cancer patient. In the present study, the protective role of *Nigella sativa* was evaluated in both adult and newborn albino rats. The anagen phase was first induced. *N. sativa* oil, *N. sativa* decoction (5%, 10% and 15%) and minoxidil lotion (standard) were applied daily to the rats two days after the depilation. During the anagen VI phase of the hair follicles, alopecia was induced by giving cyclophosphamide 125 mg/kg, ip to the adult rat and 50 mg/kg to the newborn rats. Cyclophosphamide-induced the alopecia to the whole depilated area of skin in adult rat while alopecia totalis was observed in the newborn rat disease control group. *N. sativa* oil, *N. sativa* decoction (5%) showed a significant protective effect against cyclophosphamide-induced alopecia. In conclusion, it is evident that *N. sativa* provides significant protection against chemotherapy-induced alopecia.

## Introduction

Various anti-cancer agents like cyclophosphamide, doxorubicin, etoposide, and daunorubicin are preferred for the treatment of cancer. However, chemotherapy-induced alopecia is the serious adverse effect of these medicines.

Normally, human hair contains anagen, catagen and telogen hair follicles. Anagen hair follicle actively accumulates cytochrome and produces the hair shaft rapidly. Telogen hair follicle is not able to produce neonatal hair shafts until the hair follicle mature into the anagen hair follicle (Chen et al., 2016).

During chemotherapy, the hair follicle is promoted to telogen phase rapidly as a result of anticancer agent-induced apoptosis. Thus, cancer chemotherapy causes disruption of the follicular structure resulting in the inhibition of hair follicle proliferation (Lindner et al., 2012). Sixty-five percent of the patients on chemotherapy experience this problem and 8% patients are reluctant to take chemotherapy because of this adverse effect (McGarvey et al., 2001; Trüeb, 2009).

Currently, there are only two drugs approved by FDA to prevent the hair loss including minoxidil and finasteride (Varothai and Bergfeld, 2014). These agents partially retard the hair loss but do not efficiently stop it. Topical application of minoxidil causes the itching, irritation, and redness of the skin. While, finasteride is licensed to treat the alopecia in men only (British National Formulary, 2012).

A number of searches has been conducted on the scalp cooling technique. The scalp cooling promotes the local vasoconstriction which reduces the blood flow ultimately decrease the uptake of chemotherapeutic agents by the hair follicle. The effectiveness of this scalp cooling technique has been reported from 52-83% after intake of the single chemotherapeutic agent. The effectiveness is greatly reduced after the administration of multiple chemotherapeutic agents. The scalp cooling does not provide protection against certain chemotherapeutic classes like taxanes (Christodoulou et al., 2002; Van den Hurk et al., 2013). The common adverse effects associa-

ted with the cooling cap system include headaches (induced by cold), shoulder and neck discomfort, and pain because of wearing the cooling cap for a longer time period (Breed et al., 2011). These adverse effects mainly affect the patient compliance.

*Nigella sativa* oil has been used traditionally for the prevention of hair loss for thousands of years. Keeping in view this folklore use of *N. sativa* oil, the current study was planned to evaluate the preventive role of *N. sativa* oil in chemotherapy-induced alopecia.

## Materials and Methods

### *Collection of plant material*

*N. sativa* seeds were obtained from an herbalist in Faisalabad, Pakistan and authenticated by an experienced botanist (Assistant Professor, Department of Botany, and Government College University Faisalabad). Seeds were washed and dried under shade. Finally, seeds were powdered with an electric microniser.

### *Preparation of decoction*

*N. sativa* decoction (5, 10, 15% w/v) were prepared by adding 5, 10 and 15 g of powdered seeds in 100 mL distilled water and boiled it for 10 min with the closed lid. Then filter this decoction with a muslin cloth. This decoction was freshly prepared every day. *N. sativa* oil was purchased from an herbalist prepared by cold press method.

### *Chemicals*

The cyclophosphamide injection (Pharmedic Laboratories), ether and formalin (Merck Pharmaceuticals) were purchased from the local market.

### *Acute dermal irritation/corrosion test*

Before applying the prepared decoction and oil to animals, acute dermal irritation/corrosion test was performed according to OECD guideline 404. Depilation was done on 6 $cm^2$ area of the dorsal surface of rat and 0.5 mL of *N. sativa* oil and *N. sativa* decoction were applied to the depilated area on separate animals for 4 hours (The Organization for Economic Co-operation and development, 2015). Within the first 4 hours, decoction and oil produced no visible corrosion (irreversible skin damage) and irritation (reversible skin damage). So, the decoction and oil were considered safe for the rats and applied freely on the rat skin.

### *Induction of anagen phase*

The animal hair should be in the anagen phase (active growing phase of hair cycle) to evaluate the protective effect of a drug because the skin in telogen phase (resting phase) contains the hair growth inhibitors (Paus et al., 1990). Rats were anesthetized by giving the 4% chloral hydrate (ip). The telogen phase hair from the dorsal surface of rat was removed from an area of 6 $inch^2$ (3 inches long and 2 inches wide). There was no need of depilation in case of newborn rat because, on the $8^{th}$ day, their hair starts growing and already present in the anagen phase.

### *Experimental design for adult rat study*

Thirty-five healthy female rats were used and kept in the animal house at least seven days prior to the start of the study in order to acclimatize them. They were provided chow in diet and had access to water *ad libitum*. The animals were kept in individual cages in a well-ventilated room, at a temperature of 25 ± $1^oC$ and humidity at 65-70% with 12 hours light-dark cycle.

The animals were divided into seven groups (n=5). Group A: normal control; Group B: disease control received cyclophosphamide (125 mg/kg, ip); Group C: standard group given cyclophosphamide (125 mg/kg, ip) plus minoxidil lotion (2%) topically; Group D-G: treatment groups which were administered *N. sativa* decoction 5, 10 or 15% and *N. sativa* oil topically respectively. All the treatment groups were first treated with the cyclophosphamide (125 mg/kg, i.p.) and then *N. sativa* decoction or oil.

Both decoction (5, 10 or 15%) and oil were applied topically to treated groups daily from the second day of depilation until the animals were sacrificed. A single injection of cyclophosphamide (125 mg/kg, ip) was administered to all the rats with the exception of normal control on the $9^{th}$ day after depilation. The normal control received an equal volume of saline solution. The animals were sacrificed under an ether atmosphere after 35 days treatment and the skin was removed for histological analysis of hair growth.

### *Experimental design for newborn rat study*

Eight days old rats were used. The animals were divided into four groups (n=5). Group A: normal control; Group B: disease control received cyclophosphamide (50 mg/kg, i.p); Group C: treated with *N. sativa* decoction (5 %, i.p); Group D: treated with *N. sativa* oil (2 mL/kg, i.p). After 30 min of treatment; Group C and D were injected cyclophosphamide (50 mg/kg, i.p). The cyclophosphamide was injected only once on day 1. But *N. sativa* oil and decoction (5%) were administered to newborn rat for five consecutive days. The animals were sacrificed under an ether atmosphere and the skin was removed for histological analysis of hair growth.

### *Alopecia scoring*

After injecting the cyclophosphamide, the dorsal skin surface was examined daily to visualize the alopecia symptoms. Hair loss was quantified visually by taking photographs daily. Hair loss was scored as follows:

Grade 0: no detectable alopecia; Grade I: mild alopecia (<50% hair loss); Grade II: moderately severe alopecia (50% hair loss); Grade III: total alopecia (>90% hair loss)

### *Histological analysis of hair follicles*

Skin samples from the sacrificed rats were preserved in formalin solution (10%). After preparation of slides, longitudinal sections of skin samples were observed and photographed under digital photomicrograph to evaluate the follicle morphology and percentage hair follicles in the anagen and catagen phase.

### *Statistical analysis*

Results were expressed as mean ± SEM. Both one way and two-way ANOVA was applied by using graph pad prism $p \leq 0.05$ was considered as statistically significant.

## Results

### *Prevention of alopecia in adult rat*

On the day 9 of depilation, there was almost equal hair growth on each group. After the chemotherapy, there was normal hair growth up to 5 days but alopecia started appearing on the 6th day of chemotherapy. Prominent macroscopic changes appeared on the 10th day of treatment. Alopecia grading was done on the 10th day of chemotherapy (Table I). Alopecia totalis was observed in disease control. Grade 2 alopecia was observed in most of the animals of the standard. By contrast, there was diffused alopecia observed in *N. sativa* decoction and oil. 5% decoction showed significant preventive effects as compared to 10% and 15% decoction. However, the results of the oil were comparable with 5% decoction (Figure 1).

### *Effect on hair length in adult rat*

The hair length was determined on day 9, 20 and 35. The hair was simply plucked from depilated area. The length of ten hair was measured of each rat from each group and mean ± SEM was calculated. The hair length on day 9 was not significantly high in any treated groups in comparison with disease control. On day 20, there was a significant change because disease control developed alopecia totalis. There was few tiny hair on the scalp of disease control. Mean hair length of the treated groups on day 35 was slightly lower than normal control. These results showed that *N. sativa* offered significant protection against chemotherapy-induced alopecia but have no effect on the hair length. There was no significant hair growth on day 9 in

**Table I**

**Alopecia grading on 10th day of chemotherapy**

| Treatment | No. of rats | Alopecia grades | | | |
|---|---|---|---|---|---|
| | | 0 | I | II | III |
| Normal control | 5 | 5 | 0 | 0 | 0 |
| Cyclophosphamide | 5 | 0 | 0 | 2 | 3 |
| Cyclophosphamide plus minoxidil | 5 | 1 | 1 | 3 | 0 |
| Cyclophosphamide plus 5% *N. sativa* decoction | 5 | 3 | 2 | 0 | 0 |
| Cyclophosphamide plus 10% *N. sativa* decoction | 5 | 2 | 3 | 0 | 0 |
| Cyclophosphamide plus 15% *N. sativa* decoction | 5 | 2 | 2 | 1 | 0 |
| Cyclophosphamide plus *N. sativa* oil | 5 | 3 | 2 | 0 | 0 |

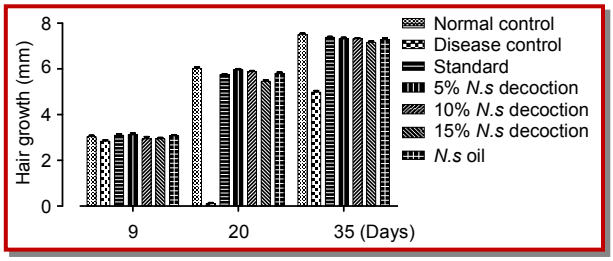


Figure 2: Hair growth (mm) in different groups on day 9, 20 and 35

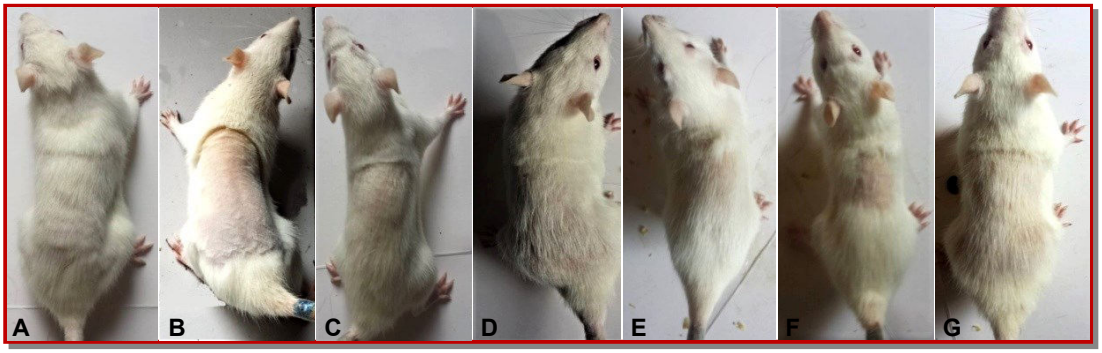


Figure 1: Macroscopic changes in different groups on 10th day on chemotherapy; A: normal control, B: disease control, C: standard, D: 5% *N. sativa* decoction, E: 10% *N. sativa* decoction, F: 15% *N. sativa* decoction, G: *N. sativa* oil

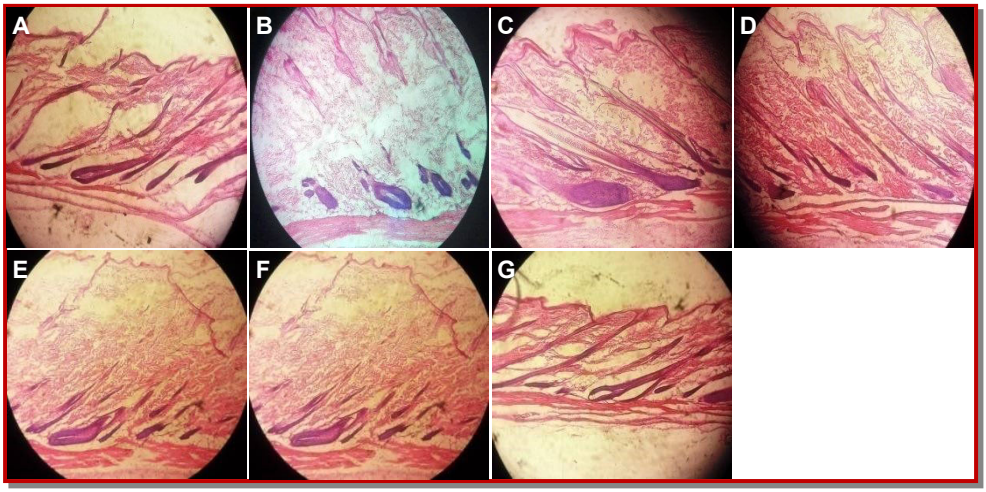


Figure 3: Photomicrograph retrieved on day 20 of experiment; A: normal control, B: disease control, C: standard, D: 5% *N. sativa* decoction, E: 10% *N. sativa* decoction, F: 15% *N. sativa* decoction, G: *N. sativa* oil

treated groups when compared with the disease control. But there was statistically significant difference of p<0.001 on day 20 and 35 of standard and treated groups as compared to the disease control (Figure 2).

### *Effect on the hair follicle damage in adult rat*

Dystrophic hair follicle was observed in the longitudinal section of the disease control and standard skin patches. The hair follicle was severely damaged in the disease control which indicated that anagen phase had been terminated and catagen phase had been induced. There were an irregular shaft and distorted the hair bulb. *N. sativa*-treated groups showed less dystrophy and relatively healthier hair follicle (Figure 3).

### *Anagen telogen ratio (A/T ratio) in adult rat*

Morphometry studies showed a significance decrease in the anagen hair follicle due to injected cyclophosphamide in the disease control. On the other hand, 5% decoction and oil preserved the anagen hair follicle and percentage of anagen hair follicle was 81.0 and 81.8 respectively (Figure 4). There was a statistically significant difference of p<0.001 in the treated groups with reference to the disease control.

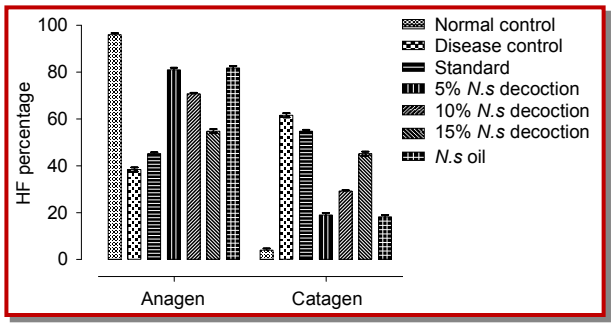


Figure 4: Percentage of hair follicles in either anagen or catagen phase

### *Stimulation of hair regrowth in adult rat*

Chemotherapy-induced alopecia was reversible after a certain period of time. It took 15 days to reproduce hair shaft. The hair regrowth was significantly close to the normal control in treated rats. However, there was a partial regrowth seen in disease control (Figure 5).

### *Prevention of alopecia in newborn rat*

Alopecia grading was done on day 7 of the experiment, two days after the termination of chemotherapy. The oil

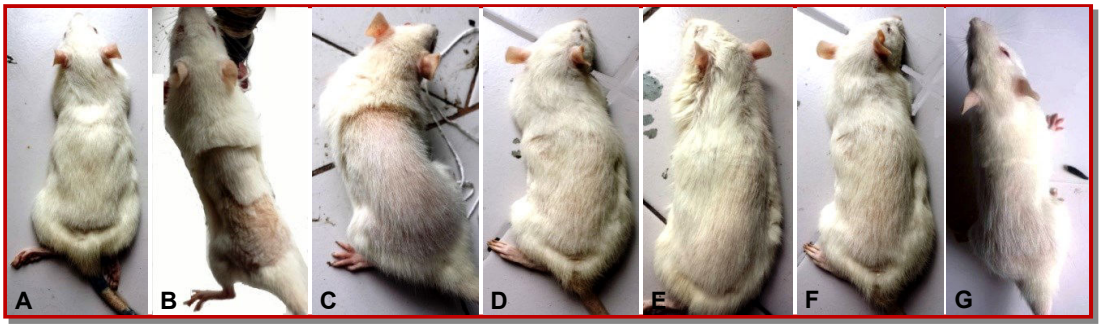


Figure 5: Macroscopic changes in different groups on day 35 of experiment; A: normal control, B: disease control, C: standard, D: 5% *N. sativa* decoction, E: 10% *N. sativa* decoction, F: 15% *N. sativa* decoction, G: *N. sativa* oil

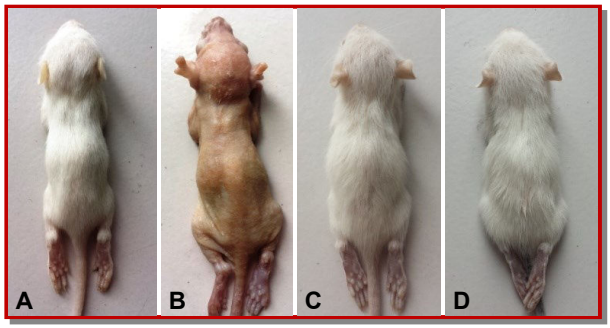


Figure 6: Macroscopic changes in different groups on day 7 of experiment; A: normal control, B: disease control, C: 5% *N. sativa* decoction, D: *N. sativa* oil

**Table II**

**Alopecia grading on day 7 of experiment**

| Treatment | No of rats | Alopecia grades | | | |
|---|---|---|---|---|---|
| | | 0 | 1 | 2 | 3 |
| Normal control | 5 | 5 | 0 | 0 | 0 |
| Cyclophosphamide | 5 | 0 | 0 | 2 | 3 |
| Cyclophosphamide + 5% *N. sativa* decoction | 5 | 4 | 1 | 0 | 0 |
| Cyclophosphamide + 5% *N. sativa* oil | 5 | 3 | 2 | 0 | 0 |

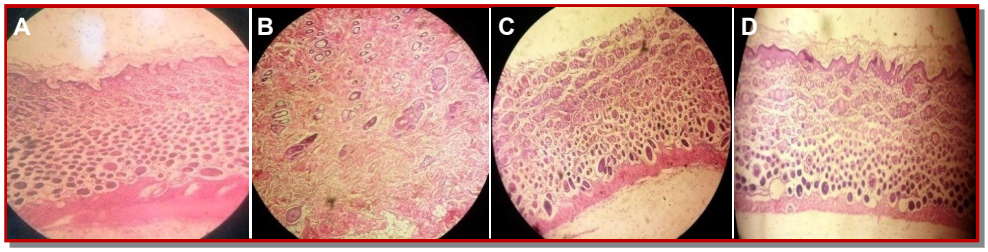


Figure 7: Photomicrograph retrieved on day 7 of experiment; A: normal control, B: disease control, C: 5% *N. sativa* decoction, D: *N. sativa* oil

and 5% decoction showed significant prevention from the alopecia and animals had prominent hair growth (Figure 6). However, no hair growth was seen in the disease control and cyclophosphamide produced Grade 3 alopecia in the treated rats (Table II).

***Effect on the hair follicle in newborn rat***

Dystrophic hair follicle was observed in the skin histology section of the disease control and standard. Hair follicle was severely damaged in the disease control which indicated that the anagen phase had been terminated and the catagen phase has been induced. There were distorted hair shaft and bulb. *N. sativa*-treated groups showed less dystrophy and relatively healthier hair follicle (Figure 7).

## Discussion

In the present study, clipper was used for the depilation purpose. It does not harm delicate skin of rat-like little creature. There are multiple methods for depilation including shaving, clipping, waxing, plucking, and use of depilated creams. Among all these methods, clipping is the most reliable method for anagen synchronization. It does not cause gross skin trauma. Moreover, studies show that it does not alter normal hair follicle physiology (Villasante et al., 2015).

There are two documented animal models for chemotherapy induced alopecia. One is an adult rat or mice model and other is newborn rat model. In the present study, both models were used in order to evaluate the prophylactic effect of *N. sativa* on chemotherapy induced alopecia. Both the models have some advantages and disadvantages. However on the major advantage to using adult model is that hair follicle is fully grown in contrast to newborn model (Wang et al., 2006).

Before performing the present study, a skin test was performed in order to evaluate any type of allergy caused by *N. sativa* decoction and oil. *N. sativa* is one of the safest drugs. It causes no allergy. However, topical application of FDA approved drugs for alopecia (minoxidil) causes the itching, irritation, and redness of skin (British National Formulary, 2012).

*N. sativa* oil and 5% decoction offered same results for prevention of chemotherapy induced alopecia. On the other hand, 10% and 15% decoction showed less protection against chemotherapy induced alopecia. Minoxidil lotion showed partial protection from chemotherapy induced alopecia while in the case of *N. sativa* oil and decoction, there was diffused alopecia. There was reduced hair density (no of hair per square inch) but no visible bald patches were made. Anagen to telogen ratio was highest in the case of *N. sativa* oil but cyclophosphamide rapidly promoted the hair to telogen phase in disease control group. Previous data showed that chemotherapy induces the reversible alopecia that is subset after termination of chemotherapy. In our study, there was maximum hair regrowth on the day 35 of the experiment.

There is an increased hair follicle damage during chemotherapy induced alopecia (D'Agostini et al.,

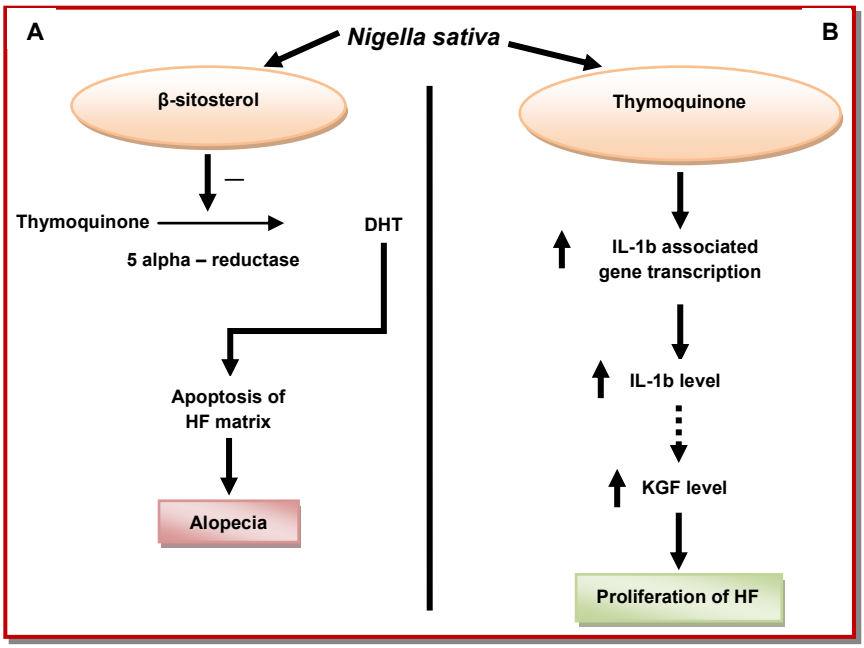


Figure 8: (A) β sitosterol inhibits 5 alpha-reductase. Hence, there is decreased production of DHT resulting in prevention from apoptosis. (B) Thymoquinone increases the level of IL-1 which enhances proliferation of HF by increasing secretion of KGF

DHT: dihydrotestosterone, HF: hair follicles, IL-1: interleukin-1, KGF: keratinocyte growth factor

2007). Cyclophosphamide treatment induces matrix deterioration. As a result, there is premature catagen formation and rate of telogen shedding is increased (Paus et al., 2013). *N. sativa* oil and decoction encouraged hair growth by inducing hair follicle in the anagen phase. In the present study, the histological analysis revealed almost normal hair follicle with regular hair shafts and hair bulb. These results suggested that hair follicle could be protected by *N. sativa* from cyclophosphamide-induced damage.

Antioxidants play a crucial role in hair growth and *N. sativa* seeds are rich in anti-oxidant. Finasteride (FDA approved drug for baldness) is a 5 alpha-reductase inhibitor. It reduces the production of dihydrotestosterone from testosterone. Dihydrotestosterone is involved in apoptosis and hence causes chemotherapy induced alopecia (Dallob et al., 1994). *N. sativa* is rich with β-sitosterol and it is a very potent natural dihydrotestosterone blocker (inhibits 5 alpha–reductase) (Figure 8) and luckily it has no other side effects on the reproductive system as other FDA approved drugs have (Cabeza et al., 2003).

Studies have revealed that thymoquinone cause to increase the level of a pro-inflammatory cytokine called IL-1β (Haq et al., 1995; Randhawa and Al-Ghamdi, 2002). This cytokine is responsible for activation of a gene related to the expression of keratinocyte growth factor (KGF). This KGF stimulates the hair follicle for proliferation and differentiation (Chedid et al., 1994).

Thymoquinone (a major constituent i.e 30–48%), has anti-inflammatory effects because it suppresses pro-inflammatory cytokines like IL-3, IL-4, IL-5, TNF-a. It inhibits expression of COX-2 and PGD2. It reduces the activation NF-kB. All these characters contribute to the hair cycle regulation (Gali-Muhtasib et al., 2006). So, *N. sativa* plays a positive role in the treatment for androgenetic alopecia. In a clinical study, 2 mL of a topical formulation including *N. sativa* essential oil (0.5%), glycerin (3%), lavender essential oil (0.4%) and alcohol (60%) to make 100 mL was applied daily on patients affected with telogen effluvium for 3 months. Studies showed promising results for the treatment of telogen effluvium. Moreover, it also improves the hair density and thickness within 3 months treatment (Rossi et al., 2016; Rossi et al., 2013).

Iron deficiency also contributes to the development of hair loss because iron is a known cofactor for ribonucleotide reductase that is a rate-limiting enzyme for DNA synthesis (Trost et al., 2006). Hair follicle matrix cells are one of the rapidly dividing cells present in the body. So they are more sensitive even to a slight decrease in iron load. As a result, there is diminished hair growth due to iron deficiency (Fiedler and Gray, 2003; Kantor et al., 2003). There are some studies which suggest that iron deficiency contributes to the development of alopecia areata, telogen effluvium, androgenetic alopecia, and diffuse hair loss (Trost et al., 2006). *N. sativa* is a good source of iron (Al-Jassir, 1992). So in the light of above studies, use of *N. sativa* is one of rational therapies for the treatment of alopecia induced by iron deficiency. Moreover, *N. sativa* also contains

zinc and magnesium which promote the hair growth efficiently.

It is evident from the previous multiple studies that *N. sativa* showed cytotoxic effects in different types of cancer including lung cancer, breast cancer, cervical cancer, ovarian cancer and colorectal cancer (Majdalawieh and Fayyad, 2016). *N. sativa* showed cytotoxic, anti-proliferative, pro-apoptotic, anti-oxidant, anti-metastatic, and NK-dependent cytotoxic effects due to its main constituent thymoquinone (Majdalawieh et al., 2017). As *N. sativa* have promising results for the treatment of cancer. There is a great need to give attention on this spice for the treatment of cancer so patients can easily get rid of side effects associated with chemotherapy including chemotherapy-induced alopecia.

Eight-day-old rats were used in present study. Hair starts to grow in this age, so there is no need to induce the anagen phase. As, hair is already in the anagen phase in newborn so single cyclophosphamide injection produced alopecia totalis in disease control group on day 7 of the experiment. These findings are comparable to a number of studies on newborn rat model in which single intraperitoneal injection produce the alopecia totalis (Hussein and Ardalan, 1993). Hair loss was started from the head and then extended to the whole body of the animal within two days.

There is one major advantage to using newborn rat model is that it is easy to assess hair loss as compared to the adult model. However, hair growth factors and cytokines level are different in both newborn and adult rat which may contribute to the different results of same phytochemicals in different models. That's why both models were used to evaluate the protective effect in alopecia.

In the present study, preventive role of *N. sativa* was evaluated first by using adult albino rat model. In this study, *N. sativa* oil and 5% decoction showed promising results. That's why only *N. sativa* oil and 5% decoction was used in a newborn rat model. Similar to adult rat model, *N. sativa* oil and decoction also preserved the hair. There was a complete coat of hair on treated group.

In the light of the discussion of above studies, it is clear that *N. sativa* oil and 5% *N. sativa* decoction effectively prevent the cyclophosphamide-induced alopecia. However, diffused alopecia was observed in the treated group which reduces the hair density. *N. sativa* showed promising results in the treatment of chemotherapy induced alopecia due to its two active components i.e. thymoquinone and β sitosterol.

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