APPENDIX

I PUBLICATIONS


II PRESENTATIONS

International

Appendix

Mutagens & Genetic Diversity for Health & Agriculture, Panjab University, Chandigarh, 12 to 14 March, 2010.


Appendix


National


Tamoxifen-loaded liposomal topical formulation arrests hair growth in mice

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Summary

Background For several decades, androgens have dominated endocrine research in the domain of hair growth control. However, it has long been known that oestrogens also tend to alter hair follicle (HF) growth and cycling significantly by binding to locally expressed high-affinity oestrogen receptors (ORs). Tamoxifen (TAM) is a selective OR modulator.

Objectives The current work aims to investigate the effect of topically applied TAM on the hair growth of mice.

Methods Test formulations were applied once daily on the shaved back area of the mice for a period of 5 weeks. The effect of these formulations was studied by visual and histological examinations.

Results Animals treated with saline and placebo gel formulation showed significant hair growth on the 20th day. The number and length of follicles were also found to be normal. In contrast, no hair growth was observed in the animals treated with TAM gel, even after the termination of treatment. The HFs were found to be arrested in telogen phase with clear signs of follicle dystrophy.

Conclusions The hair growth-retarding effect of TAM observed in the current study clearly demonstrates its OR agonistic effect on hair growth. This work also provides a distinct lead towards the possible potential of TAM liposomal gel in the treatment of hirsutism.
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A very effective means of delivery, especially for topical administration. The current studies have been undertaken to develop a topical liposomal formulation of TAM, and to investigate its efficacy in retarding hair growth on shaved mouse skin.

Materials and methods

TAM citrate and saturated phospholipid (soy phosphatidylcholine 98H) were generous gifts from Biochem Pharmaceutical Industries (Mumbai, India) and Lipoid GmbH (Ludwigshafen, Germany), respectively. Triethanolamine (TEA) and sorbitan monooleate were procured from Sigma Chemicals Co. (St Louis, MO, U.S.A.). Carbopol® 980 was obtained ex-gratis from Lubrizol Co. (Wickliffe, OH, U.S.A.). All other chemicals used in the study were of analytical grade.

Preparation of lipid vesicular systems

Drug-loaded liposomes for topical application were prepared by the thin-film hydration technique, as described previously. Briefly, a dry film of lipid (phospholipid/sorbitan monooleate 4:1 w/w) and drug were hydrated in water to obtain the liposome suspension. Separately, Carbopol® gel was prepared by dispersing it in warm demineralized water and stirring at 800 r.p.m. (Remi Mechanical Stirrer, Mumbai, India) for 30 min. This Carbopol® dispersion was neutralized by the addition of TEA at 1:15 w/w Carbopol®/TEA. Mixing was continued until a clear transparent gel was formed. Finally, the liposomal suspension was added to the clear gel to obtain a vesicular gel formulation for topical application. Analogously, the placebo vesicular gel formulation was prepared employing the identical composition and method of preparation, but without addition of the drug.

Animals

Adult female laca mice, aged 4–5 weeks, with mean weight of approximately 25 g, were obtained from Central Animal House, Panjab University (Chandigarh, India). They were housed in polypropylene animal cages and acclimatized for a week with a 12-h day and night cycle prior to the treatments at a temperature of 25–27 °C and a relative humidity of 50–55%. The mice were provided with a standard rodent diet.

Fig 1. Effect of various topical formulations on hair growth of laca mice after 5 weeks of treatment. (a) Photographic images of dorsal side of mice exhibiting the effect of different treatments (group I–group III) on hair growth. (b) Photomicrographs showing hair follicles (HFs) mainly in the reconstructed anagen stage VI (marked by white arrows) with normal appearance and no sign of dystrophy in group I and group II mice. However, in group III mice, most HFs are seen in the telogen phase (marked by white arrows). Micrographs also portray abnormally dilated hair canals in group III without the hair shaft (marked by yellow arrows), confirming the signs of dystrophy (original magnification × 100).

(c) Skin sections shown here (original magnification × 400) are the magnified images of the corresponding images in (b).

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Drinking water was provided ad libitum. Taking cognizance that the research work adheres to the guidelines for the care and use of laboratory animals, all the animal investigations were performed as per the protocol approved by the Panjab University Animal Ethics Committee, duly approved for the purpose of control and supervision of experiments on animals by the Government of India.

TAM was topically applied once daily for a period of 5 weeks in the following manner: the shaved back area of the mice was divided into three experimental groups, each composed of eight animals, as follows: animals treated with normal saline solution (group I, control); animals treated with placebo gel (group II, blank); animals treated with active gel, equivalent to 0.1% w/w of TAM (group III, active). The formulations were applied once daily on the shaved back area of the mice for a period of 5 weeks.

Laboratory analysis

Twenty-four hours after the last application of the formulations, treated skin areas were photographed employing a digital camera (Model 90i; Nikon, Tokyo, Japan), the mice were decapitated by spinal dislocation, and their carcasses incinerated. Pieces of skin were punched out at the centre of the back of each mouse using a biopsy punch (Stiefel, 6 mm diameter), and were fixed with formalin. The fixed skin sections were appropriately processed and stained with haematoxylin and eosin. The processed skin sections were examined microscopically using a high-resolution microscope attached to judge follicular behaviour in response to the administered treatments.

Results

As depicted in Figure 1 (a), the animal groups treated with saline and placebo gel (I and II) started to exhibit hair growth on the 15th day. The animals showed significant hair growth on the 20th day onwards. In contrast, no hair growth was observed in animal group III treated with TAM gel, even after the termination of treatment. In this case, the arrowed HF s were found to be in telogen phase.

As illustrated in Figure 1 (b, c), animal groups I and II showed normal skin structures and HFs (i.e. anagen VI). The number and length of follicles were also found to be normal. However, animal group III exhibited no such normal growth patterns, with the HFs found to be arrested in telogen phase with signs of follicular dystrophy.

Discussion

These results are in close agreement with those of earlier studies showing that the naturally occurring 17β-estradiol arrests HFs in telogen phase, and produces profound and prolonged inhibition of hair growth, whereas treatment with the biologically inactive stereoisomer 17α-estradiol did not alter hair growth. Thus, the hair growth-retarding effect of TAM observed in the current studies clearly demonstrates its OR agonistic effect on hair growth. The present study also reveals appreciable pharmacodynamic activity of topically applied TAM, justifying the development of its topical gel formulation. The work provides a distinct lead towards the possible potential of TAM liposomal gel in the treatment of hirsutism.

What's already known about this topic?

- Hirsutism, a condition of excessive growth of body hair in females, particularly on visible areas such as the face and chest, often causes great psychological distress.
- The existing treatments for excessive facial hair can lead to adverse reactions such as ingrown hair and infections.
- A convenient topical formulation that reduces production of facial hair would be of significant benefit to women with this condition.

What does this study add?

- This work provides a distinct lead towards the possible potential of tamoxifen liposomal gel in the treatment of hirsutism.

Acknowledgments

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References

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Tamoxifen-encapsulated vesicular systems: cytotoxicity evaluation in human epidermal keratinocyte cell line

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Abstract

Aim: Tamoxifen is a nonsteroidal estrogen receptor modulator indicated in the treatment of breast cancer. Apoptosis has been reported to be a major mechanism for its antitumor effect. Tamoxifen has also shown significant potential in treating various dermatological disorders including psoriasis, characterized by hyperproliferation of epidermal keratinocytes. An endeavor was made in the current studies to investigate the potency of vesicle-encapsulated tamoxifen on human epidermal keratinocyte cell lines.

Methods: Drug was encapsulated in the phospholipid-based vesicular systems, namely, conventional liposomes and flexible-membrane liposomes. In vitro cytotoxicity evaluation of the formulations was carried out employing MTT cell proliferation assay. Results: A composition-dependent strong inhibition in the viability of epidermal keratinocyte cells was observed. Conclusion: The encouraging findings of this work construe immense potential of the tamoxifen-encapsulated vesicular systems in the management of psoriasis.

Key words: HEK001; liposome; MTT assay; phospholipid; skin; topical

Introduction

Tamoxifen (TAM) is a nonsteroidal selective estrogen receptor modulator widely employed in the chemotherapy of breast cancer. It provides effective treatment for the patients with metastatic breast cancer and reduces the risk of recurrence and death from breast cancer when administered as an adjuvant therapy. Use of TAM is specifically indicated in postmenopausal women suffering with breast cancer. A case study reports the treatment of a breast cancer patient with TAM who was also suffering with chronic plaque psoriasis. Serendipitously, it was found during the study that her psoriasis responded quite favorably to TAM administration. There are a few more such reports in support of TAM in the management of psoriasis.

TAM is currently available only as the oral dosage forms. Systemic absorption of TAM can result in the increased risk of endometrial cancer, deep vein thrombosis and pulmonary embolism, alteration in liver enzyme levels, ocular disturbances, etc., accountable to its wide distribution in the body. Accordingly to surmount these problems, our research group developed liposomal systems of TAM for direct topical application to the target skin sites (i.e., breast and psoriatic lesions), which could serve the desired objectives more efficiently without affecting other naive body organs. Development and characterization of the test formulations has already been reported by us earlier. In this study, we aim to explore the in vitro cytotoxicity of these developed lipid vesicular systems employing human epidermal keratinocyte (HEK001) cell line.
Materials and methods

Materials

TAM citrate and saturated phospholipid (soya phosphatidylcholine; 90H) were the generous gift samples from M/A. Biochem Pharmaceutical Industries (Mumbai, India) and Phospholipid GmbH (Nattermannallee, Germany), respectively. Dimethyl sulfoxide, 3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyltetrazolium bromide (MTT), fetal bovine serum, ethylenediamine tetraacetic acid, trypsin, cholesterol, and sorbitan monoooleate were procured from M/A. Sigma Chemicals Co. (St. Louis, MO, USA). The HEK001 (ATCC-CRL-2404®) cell line and keratinocyte serum-free (KSF) medium were obtained from American Type Culture Collection (Manassas, VA, USA). All other chemicals used in the study were of analytical grade.

Methods

Cell culture and growth conditions

Epidermal keratinocyte cells were grown in the KSF medium containing 5 ng/mL of human recombinant epidermal growth factor and 2 mM l-glutamine (without bovine pituitary extract and without serum). The cells were grown in a CO₂ incubator (Thermo Electron Corporation, Milford, MA, USA) at a temperature of 37°C with 98% humidity and 5% CO₂ gas environment. The HEK cells were grown in a T-75 cell-culture flask. When the cells were growing in the logarithmic phase (i.e., about 80% confluent), the culture media was removed and cells were rinsed with the Ca²⁺/Mg²⁺-free phosphate buffer saline of pH 7.4. To this, 2.0 mL of 0.53 mM ethylenediamine tetraacetic acid solution containing 0.05% (w/v) of trypsin was added to detach the cell layers. Detached cells were dispersed gently by pipetting into the fresh KSF medium containing 10% fetal bovine serum. Thereafter, the cell suspension was transferred into the centrifuge tubes and spun for 5 minutes at 125 x g at 4°C temperature. The supernatant was discarded, and the sedimented cells were resuspended in the fresh KSF medium. The required cell suspension (1 x 10⁴/100 µL) was distributed into a 96-well plate and incubated in the CO₂ incubator.

Preparation of lipid vesicular systems

Drug-loaded liposomes (TAM-Lipo) for topical application were prepared by thin-film hydration technique, as described previously. Briefly, a dry film of lipid (phospholipid and cholesterol; 2:1 weight ratio) was hydrated in water. The flexible-membrane liposomes (TAM-FMLipo), on the other hand, were composed of phospholipid and sorbitan monoooleate in a weight ratio of 4:1. Analogously, the placebo formulations were prepared employing the identical composition and methods of preparation, but without the addition of drug.

Cytotoxicity test

Cell proliferation was studied using modified MTT assay. The HEK cells (1 x 10⁴ cells) were grown in a 96-well tissue culture plate in 100 µL of complete KSF medium. The cells were treated with pure drug and vesicular suspensions (incorporated in 100 µL of KSF medium) at different drug concentrations, whereas the control cells received the placebo formulations only. The cells were incubated in a CO₂ incubator at 37°C for 48 hours. Cells were then washed twice with phosphate buffer saline. Thereafter, an aliquot of 20 µL of sterile MTT solution (2.5 mg/mL in phosphate buffer saline) was added to each well. Culture plates were gently stirred on plate-shaker (TiterTek™; Flow Laboratories, Meckenheim, Germany) and incubated in CO₂ incubator at 37°C for 2 hours. The plates were centrifuged at 1200 x g for 15 minutes. The supernatant was discarded, whereas MTT-formazon crystals were dissolved in 100 µL of dimethyl sulfoxide. The plates were further stirred for 20 minutes and the optical density (OD) was measured at 570 nm taking 620 nm as the reference wavelength using an ELISA plate reader (Thermo Electron Corporation). The tetracizolium compound (i.e., MTT) was bioreduced by cells into colored formazan product that absorbs light at 570 nm. The viability of cells was computed from the OD of the MTT-formazon violet color crystal, as the OD is known to be directly proportional to the number of viable cells present. The IC₅₀ values of the different tested formulations were calculated by plotting the graphs of cell viability at different graded concentrations of drug in the formulations.

The photomicrographs of the treated cells were taken with the help of DP-12 digital camera coupled to a IX-70 microscope (Olympus, Tokyo, Japan).

Statistical analysis

Two-way analysis of variance was performed, employing SigmaStat software version 2.0 (Jandel Scientific, San Rafael, CA, USA), on the raw data of cell viability obtained with three tested formulations at different dose levels.

Results and discussion

Microphotographs of the HEK001 cell samples following various treatments are depicted in Figure 1. The photomicrographs vividly indicate significant reduction in the cell viability with all the three treatments investigated, namely TAM, TAM-Lipo, and TAM-FMLipo. Close supervision of the microphotographs reveal the unambiguous superiority of vesicularly entrapped drug (i.e.,...
TAM-FMLipo and TAM-Lipo formulations) in reducing the cell growth vis-a-vis the free drug. Two-way analysis of variance on the cell viability data indicates statistically significant high values of Fisher’s criterion \[ F(2,12) = 358.42, P < 0.001 \] for different formulation treatments as well as for their different dose levels \[ F(6,12) = 3881.35, P < 0.001 \], vouching considerable influence of both studied treatments and drug dose levels.

Figure 2 portrays quantitative measure of cell viability of the aforesaid three treatments at various drug concentrations. As indicated in the figure, all the tested formulations were found to induce cytotoxicity in human epidermal keratinocyte cells following 48 hours of incubation. Significantly higher efficacy (=twice) was observed in the case of vesicularly entrapped drug vis-a-vis free drug. The inset of the Figure 2 vouches for the same. This enhanced efficacy may be ascribed to the lipo-solublized state of the drug, owing to its entrapment within multiple lipoidal domains of vesicles. Furthermore, the phospholipid lamella in the periphery of the vesicles may integrate with cell membrane facilitating internalization of the vesicular contents. Several studies\(^{19-23}\) reported in the literature vouch for such internalization of vesicular content in cell. Lower cellular uptake may be attributable to the absence of such facilitated transport in case of free drug.

**Conclusion**

The encouraging results of this study indicate tremendous promise of vesicular systems in ameliorating the efficacy of TAM through topical route of administration for the management of psoriasis. Accordingly, it can be
concluded that the phospholipid-based vesicular systems help in generating and retaining the most favorable physicochemical state of the drug to improve its cellular interactions.

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Declaration of interest
The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References
Studies on tamoxifen encapsulated in lipid vesicles: Effect on the growth of human breast cancer MCF-7 cells

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Abstract
Tamoxifen is a nonsteroidal estrogen-receptor modulator widely used in the treatment of breast cancer. Apoptosis has been reported to be a major mechanism for its antitumor effect. In the current studies, an endeavor was made to investigate the efficacy of vesically encapsulated tamoxifen on human breast cancer MCF-7 cells. Phospholipid-based vesicular systems viz. conventional liposomes and elastic-membrane liposomes were employed to encapsulate the drug. The MTT colorimetric assay was used to determine the efficacy of the tested formulations. The results demonstrated composition-dependent strong inhibition in the viability of MCF-7 cells with encapsulated tamoxifen vis-a-vis free drug. The encouraging findings from the current work construe immense potential of the lipid-based vesicular systems in the treatment of breast cancer.

Keywords: Apoptosis; cytotoxic; MTT assay; breast cancer; topical liposome; phospholipids

Introduction
Tamoxifen (TAM) is a non-steroidal selective estrogen-receptor modulator that is widely employed in the chemotherapy of breast cancer (Barnadas et al., 2008; Barker, 2006) and provides effective treatment for patients with metastatic breast cancer, as well as reducing the risk of recurrence and death from breast cancer when administered as an adjuvant therapy. Use of TAM is specifically indicated in postmenopausal women suffering with breast cancer (estrogen receptor positive) (Neven and Van Den Broecke, 2007; Lin and Winer, 2008). TAM is also being evaluated for its possible use as a chemopreventive agent in women with high risk of developing breast cancer (Jordan and Brodie, 2007; Geller and Vogel, 2006).

TAM is currently available only in oral dosage form. Systemic absorption of TAM can result in the increased risk of endometrial cancer, deep vein thrombosis and pulmonary embolism, alteration in liver enzyme levels, ocular disturbances, etc., which is ascribable to its wide distribution in the body. This propensity of adverse effects invariably leads to a high degree of patient noncompliance and avoidance toward TAM therapy (Bernstein and DellaCroce, 2007; Lavie et al., 2008; Machado et al., 2005). To surmount these problems, accordingly, our research group developed liposomal systems of TAM for direct topical application to the breast without affecting other naive body organs (Katare et al., 2006). The characterization of the developed topical formulations has already been reported by us earlier (Bhatia et al., 2004). The current study aimed to explore the in vitro cytotoxicity of these developed lipid-vesicular systems employing the human breast cancer MCF-7 cell line.
Materials and methods

Materials

TAM citrate and saturated phospholipid (soya phosphatidylcholine) were the generous gift samples from Biochem Pharmaceutical Industries (Mumbai, India) and Phospholipid GmbH (Nattermannallee, Germany), respectively. Dulbecco’s modified Eagle’s medium (DMEM), 3-(4, 5-dimethylthiazole-2-yl)-2, 5-diphenyloxazolium bromide (MTT), fetal calf serum (FCS), 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES), penicillin, streptomycin, trypsin, sodium pyruvate, dimethyl sulfoxide (DMSO), ethylenediaminetetraacetic acid (EDTA), cholesterol, and sorbitan mono-oleate were procured from Sigma Chemical Co. (St. Louis, Missouri, USA). Human estrogen positive breast cancer cell lines MCF-7 were obtained from the National Cancer Institute (Frederick, Maryland, USA). All other chemicals used in the study were of analytical grade.

Cell culture, growth conditions, and treatment

Breast cancer cells were grown in DMEM containing 10% FCS, 10 mM HEPES, 1.0 mM sodium pyruvate, 25 mM sodium bicarbonate, 100 units/mL of penicillin, and 100 μg per mL of streptomycin. The cells were grown in a CO2 incubator (Thermo Electron Corporation, Milford, Massachusetts, USA) at 37°C with 98% humidity and 5% CO2 gas environment. Cells grown in the monolayer cultures were detached with trypsin (0.1% w/v)/EDTA (1 mM) solution. Soon after the cells were ready to detach, the trypsin-EDTA solution was removed. Cells were dispersed gently by pipetting in complete growth medium, centrifuged at 200 x g for 5 minutes. The required cell suspension (1 x 10⁴/100 μL) was distributed into a 96-well plate and incubated in the CO2 incubator. The cells were refreshed after 16 hours by adding fresh complete DMEM medium. These refreshed cells were subsequently treated with the test formulations.

Preparation of lipid-vesicular systems

Drug-loaded liposomes (TAM-Lipo) for topical application were prepared by the thin-film hydration technique, as described previously (Bhatia et al., 2004). Briefly, a dry film of lipid (phospholipid and cholesterol; 2:1 ratio) was hydrated in saline water. The elastic-membrane liposomes (TAM-EMLipo), on the other hand, were composed of phospholipid and sorbitan mono-oleate (5:1 ratio).

Cytotoxicity test

Cell proliferation was studied by using a modified MTT assay (van de Loosdrecht et al., 1994; Bhushan et al., 2007). Human (1 x 10⁴ cells) breast cancer MCF-7 cells were grown in a 96-well tissue-culture plate in 100 μL of complete medium. The cells were exposed at different concentrations of tested formulations containing 100 μL of final medium, whereas the control cells received only the placebo (vehicle) formulations. The cells were incubated in the CO2 incubator at 37°C for 48 hours. Thereafter, an aliquot of 20 μL of sterile MTT solution (2.5 mg/mL in phosphate-buffered saline; PBS) was added to each well. The culture plates were gently stirred on a plate shaker (Titertek; Flow Laboratories, Meckenheim, Germany) and incubated in the CO2 incubator at 37°C for 2 hours. The plates were centrifuged at 1200 x g for 15 minutes. The supernatant was discarded, and MTT-formazon crystals were dissolved in 100 μL of DMSO. The plates were further stirred for 20 minutes, and the optical density (OD) was measured at 570 nm, taking 620 nm as the reference wavelength, using a microplate reader (Thermo Electron Corporation). The tetrazolium compound (i.e., MTT) is bioreduced by cells into colored formazan product that absorbs light at 570 nm. The viability of cells was computed from the OD of the MTT-formazon violet-colored crystal, as the OD is directly proportional to the number of viable cells present (van de Loosdrecht et al., 1994). The IC50 values of the different tested formulations were calculated by plotting the graphs of cell viability at various graded drug concentrations in the formulations (Bhushan et al., 2007).

Statistical analysis

A two-way analysis of variance (ANOVA) was performed, employing SPSS software (version 10.0.1; SPSS Inc., Chicago, Illinois, USA), on the raw data of cell viability obtained with three tested formulations at different dose levels.

Results and discussion

Microphotographs of the MCF-7 cells samples following various treatments are depicted in Figure 1. The photographs obtained with all the three treatments investigated viz. TAM, TAM-Lipo, and TAM-EMLipo, vividly indicate a significant reduction in cell viability in a dose-related manner. Close supervision of the microphotographs reveal the unambiguous superiority of TAM-EMLipo formulations (Figure 1A) over TAM-Lipo formulation (Figure 1B) in reducing the cell growth vis-à-vis the free drug (Figure 1C). A two-way ANOVA on the cell viability data indicates statistically significant high values of Fisher’s criterion [F(2,12) = 15.58, P < 0.001] for different formulation treatments, as well as for their different dose levels [F(6,12) = 535.01; P < 0.001], vouching...
Cytotoxicity of tamoxifen lipid vesicles

Figure 1. Effect of various treatments of TAM formulations (free and encapsulated) on the survival of MCF-7 cells. Maximum reduction in the viability of cells is clearly visible with the treatment of TAM-EMLipo formulation.

Figure 2. Cytotoxicity of TAM and its liposomal formulations in human breast cancer cell line. Each data point represents the Mean ± SD of 8 wells, carried out in triplicate under analogous conditions. The inset figure depicts the bar diagram of the IC50 values of the different investigated TAM formulations.

for a significant influence of studied treatments as well as drug-dose levels.

Figure 2 portrays a quantitative measure of cell viability of the aforementioned three treatments at various drug concentrations. As indicated in Figure 2, all the tested formulations were found to induce cytotoxicity in human breast cancer MCF-7 cells following 48 hours of incubation. Higher efficacy was observed in the case of drug encapsulated within lipid vesicles vis-à-vis free drug (IC50: 8.5 μM). The inset of the figure also ratifies lower IC50 values of the vesiculated TAM vis-à-vis free drug. This enhanced efficacy may be ascribed to the phospholipid-based vesicular systems hold appreciable potential in ameliorating efficacy and safety of TAM when using the topical route of administration.

Conclusion

Accordingly, it can be concluded that the phospholipid-based vesicular systems hold appreciable potential in ameliorating efficacy and safety of TAM when using the topical route of administration.

Acknowledgments

Declaration of interest: The authors report no conflicts of interest.

References


