Author’s response to reviews

Title: Absence of herb-drug interactions of Mistletoe with the Tamoxifen metabolite (E/Z)-Endoxifen and Cytochrome P450 3A4/5 and 2D6 in vitro

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Author’s response to reviews:

Dear Editors

We were pleased to have the opportunity to revise our paper, entitled “Absence of herb-drug interactions of mistletoe with the Tamoxifen metabolite (E/Z)-Endoxifen and Cytochrome P450 3A4/5 and 2D6 in vitro” (manuscript BCAM-D-18-00525R1).

(Former title “Interaction of standardized mistletoe (Viscum album) preparations with antitumor effects of the Tamoxifen metabolite (E/Z)-Endoxifen and with Cytochrome P450 isotypes CYP3A4/5 and CYP2D6 in vitro”).

We are pleased that the reviewers found the manuscript interesting and important in its field. The reviewer’s comments were helpful and we appreciated the constructive feedback on our original submission.

In revising the paper, we have carefully considered the comments and suggestions of Dr. Yogendra Nayak and Dr. Sajjad Ahmad and we addressed them point-by-point.
Thank you for the positive and helpful suggestions.

Sincerely,

Ulrike Weissenstein, PhD
(Corresponding author)

Point-by-point revision of Manuscript BCAM-D-18-00525R1
"Interaction of standardized mistletoe (Viscum album) preparations with antitumor effects of the Tamoxifen metabolite (E/Z)-Endoxifen and with Cytochrome P450 isotypes CYP3A4/5 and CYP2D6 in vitro"

Yogendra Nayak, PhD (Reviewer 4):

Dear Sir,

The manuscript entitled "Interaction of standardized mistletoe (Viscum album) preparations with antitumor effects of the Tamoxifen metabolite (E/Z)-Endoxifen and with Cytochrome P450 isotypes CYP3A4/5 and CYP2D6 in vitro" (manuscript number BCAM-D-18-00525R1) can be accepted for publication after major modifications. The work explains the importance of drug herb interaction due to enzyme induction in cancer therapy. Though, there are clinical studies which confidently says that there is no drug-herb interaction, the basic experimental support is given by this article. In the context of high use of alternative medicine along with modern medicine, this study plays important role. But, there are many lacuna to accept in current state of the article. Following clarifications/questions answer to be made before accepting this manuscript.

1. It is better if the conclusion of the study reflect in the title, such as 'absence of herb drug interaction'. This would catch many audience/readers. Usually people read titles at first then they read abstract.

The former title was replaced by:
Absence of herb-drug interactions of mistletoe with the Tamoxifen metabolite (E/Z)-Endoxifen and Cytochrome P450 3A4/5 and 2D6 in vitro
2. The manuscript has lot of grammatical errors especially punctuation. For example, the abstract results, the sentence 'All VAE preparations showed no statistically significant inhibition of CYP3A4/5 and CYP2D6 catalyzed tamoxifen metabolism' can be improved. It can be made short like 'VAE preparations did not show inhibition of CYP3A4/5 and CYP2D6 (p>0.001).

We amended the manuscript and used track changes to indicate our amendments.

The uniformity in the written article is important, especially when writing units 'ml' and 'mL'. All units in the manuscript are uniform now (µL, mL, L).

Sentences starting with numbers can be written in words to begin the paragraph/ sentence. (Page 10 line 222)

The sentence starts now as follows: “Three to five independent experiments…” (line 223)

3. References such as 6, 7, 25, 29, 32 etc required to be rewritten as per the author instructions.

The format of all references is now in accordance with the BMC CAM reference style.

4. Fig 1 and Fig 2, The authors should explain how they will get units more than 100% on Y-axis when % proliferation / inhibition is considered. Author need to explain the procedure or it has to be rechecked and explained how they have arrived at such values.

In the paragraph “Proliferation assay” (line 154-55) we wrote: “All values were expressed as percent inhibition of proliferation relative to cells cultured without estradiol (untreated control).” This is also valid for cells cultured in the presence of estrogen, where the proliferation is increased to about 190% when referred to untreated cells cultured without estrogen.

5. Number of figures/ photos can be reduced by clubbing some of them.

We newly combined Fig. 1 and Fig. 2 to Fig. 1 and Fig. 7 and Fig. 8 to Fig. 6.

Sajjad Ahmad, Ph.D (Reviewer 5):

1. In the given cytograms, the values in each quadrant should be rectified i.e., the number of all cells should be exactly 100% secondly the coma should be replace by dot. For example in the Q1 it should be 2.20 instead of 2,20.

We amended and replaced figure 3.

2. All the figures should be refined.

The original figure files we uploaded are of high quality.