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Journal Name:	European Journal of Medicinal Plants
Manuscript Number:	**Ms_EJMP_23992**
Title of the Manuscript:	**The role of monocarboxylate transporters and their chaperone CD147 in lactate efflux inhibition and the anticancer effects of Terminalia chebula in neuroblastoma cell line N2-A**
Type of the Article	**Original Research Article**

General guideline for Peer Review process:

This journal's peer review policy states that **NO** manuscript should be rejected only on the basis of '**lack of Novelty'**, provided the manuscript is scientifically robust and technically sound.
To know the complete guideline for Peer Review process, reviewers are requested to visit this link:

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~~PART 1~~PART 1: Review Comments

	Reviewer's comment	**Author's comment** *(if agreed with reviewer, correct the manuscript and highlight that part in the manuscript. It is mandatory that authors should write his/her feedback here)*
Compulsory REVISION comments	**There are substantial editorial and grammatical errors throughout the manuscript. It is essential for the authors to seek proofreading assistance/ service to enhance the readability of the manuscript.**	
	Lines 27, 155 – 165, 284 – 291, 369 – 372 **Given the expression of IG50, it is more appropriate for the authors to describe the study as a cell growth study rather than a cell proliferation study. Please revise throughout the manuscript.**	**We revised and- changed ~~the cell~~named proliferation ~~study~~ to cell ~~was described as a~~ growth throughout the manuscript~~study~~.**

	Lines 32 – 34, 377 – 378 **The authors should provide the basis of postulating "novel compounds/ novel targets" in TCE.**	We revised ~~promising~~Promising compounds new targets
	Lines 43 – 46 **The importance of lactate efflux in the pathophysiology of cancer was poorly explained. Please revise.** **Also, it is unclear as to how on one hand intracellular acidosis could initiate early apoptosis, and on the other hand enhance cancer cell invasive etc. Please justify.**	The importance of lactate efflux in the pathophysiology of cancer: The[N1] acidic intracellular pH will eventually initiate apoptosis, [4, 5] through different mechanisms such as promoting the permeability of mitochondria membrane [6], activating endonucleases that cause DNA fragmentation [7], or activating caspase-3 protease, the key[N2] indicator of apoptosis that deactivates essential metabolic proteins [8]. We revised and clarified; On the other hand, extracellular acidosis will enhance cancer cell invasiveness…
	Lines 56 – 61 **There is a lack of coherence in this paragraph. This is predominantly due to poor elaboration on the correlation between the use of natural product in cancer treatment and MCT. Please revise.**	The paragraph was revised. *Moreover, flavonoids were found as MCTs inhibitors*
	Lines 81 – 88 Plant Extraction: **The authors should justify the basis of selecting ethanol as the main solvent for extraction.**	We revised and added the justification in Line 88 as follows: *The screened plants were extracted with ethanol, the most common organic solvent~~s~~ in pharmacological studies evaluating the activity of medicinal herbs [21].*
	Line 84 "The identified…" **There should be a linking phrase indicating that it is a subsequent experiment. Please revise.**	**We~~E~~ revised** Further, the identified plant extract for more investigation,
	Lines 89 – 95 Cell Culture **The authors should justify the basis of selecting N2-A and DI-TNC1 as the representative cell lines for cancer and normal cells, respectively.**	**Cell Culture** N2A is known for its high lactate production rate compared to other cell lines. It is considered an appropriate model to evaluate potential chemotherapy drugs for the treatment of cancer (Finklestein et al., 1975; Klebe and Ruddle, 1969; Mazzio et al., 2003) DI-TNC1are astrocyte ~~proliferative~~proliferative cell line with lower lactate efflux production compared to N2A cells. (an observation in our lab), ~~is very essential~~both cell lines used are constituents of the central nervous ~~system, and~~ ~~The~~system. The DI-TNC ~~it~~ is very ~~important in~~important in controlling brain energy metabolism (Magistretti and Pellerin,

		1999~~; ..~~ Pellerin et al., 1997)
	Line 99 **It is unclear as to why experimental media with reduced FBS was used. Please justify.**	**Experimental media** *~~High~~ A high level of FBS concentration was avoided as ~~interferes~~it interferes with the ~~l~~Lactate assay was observed. Because we do not want ~~to~~ eliminate ~~the~~ FBS since~~for~~ it is essential for cell growth. ~~Therefore,~~~~W~~weTherefore, we tried ~~a~~ different concentrations and we used media with 1% FBS as the most appropriate concentration to avoid interference and reaction with colorimetric lactate assay.*
	Line 100 **It is unclear as to why 4 h was selected as the exposure time. Please justify.**	**Exposure period** *We have done several preliminary experiments and we found that 4 hours of incubation is the optimum time. ~~Most importantly is because~~ TCE did not need a longer~~g~~ incubation period to have~~make its~~ toxic effect on the cancer cells. While microscopically monitoring cells with TCE, morphology, cell number~~..etc.~~ ~~etc.~~ changes were observed in this period of ~~short~~ time. Also, the exposure period was 4 h to make sure that the decrease of lactate production ~~attribute~~is attributed ~~s~~ to the effect of the plant extracts ~~and not because the~~ low concentration of FBS in the experimental media. ~~We did the experiments at different exposure periods and we found 4 hours is more convenient since~~*
	Line 132 **The description for MT3 is unclear. Please revise.**	**We revised and changed in the manuscript as follows:** *"MCT3 (2.5 µg/ml)"*
	Line 151 **The use of "previous study" in this context could be misleading to the reader. Please revise.**	**We revised changed as follows:** *"The applied conditions for the assay were similar to the caspase-3 apoptosis study"*
	Line 167 – 169, 230 – 231 **The expression of the number of independent studies and replicates was confusing. Please revise in accordance to the conventional way.**	**We revised and clarified ~~confusion~~ as follows:** *"All data points were obtained from the average of at least two independent ~~studies ....~~studies.* *Statistical analysis of all studies were presented as the mean ± SEM from the average of two independent experiments, n=4 each."*
	Line 182 and throughout manuscript. **Please correct "IC50 >500<1000 ug/ml"as "500<IC50<100 ug/ml". Please revise this throughout the manuscript and do likewise for all other related errors.**	**We revised and corrected in all manuscript.**
	Lines 201 – 203 "4 ethanol…" **Please revise the sentence in terms of the ranking of potency.**	**We revised** The other plant extracts were categorized according to their potency as following: 62 extracts (500 µg/ ml <

		IC50 < 1000 µg/ ml) and ranked as the ~~lease~~ least potent, 43 extracts (100 µg/ ml < IC50 < 500 µg/ ml), 6 extracts (50 µg/ ml < IC50 < 100 µg/ ml), and 4 ethanol plant extracts (IC50 < 50 µg/ml) and considered as the most potent.

	Lines 217 – 218 **It is unclear as to where the results of CHC were indicated within the manuscript.**	**We revised** The results were mentioned in text and not ~~presented~~ in a figure "~~(~~*Lactate efflux inhibition was less than 10% in N2-A cells treated with a-cyano-4-hydroxycinammic acid (CHC), at the highest tested concentration (250 µg/ml = 1.32 mM*"~~)~~.
	Figure 2: **It is known that Log 0 is ~~undefined~~undefined, as one can never get zero by raising anything to the power of anything else. The ~~authours~~authors need to ~~reexamine~~re-examine the dose response curve.**	**We revised** We changed the unit of the X axes to be expressed as antilog. That will reflect the actual concentrations of TCE used. Changing the units expression ~~does~~ did not affect the results.
	Figure 3 A, 5 and 6 B **The images were of poor quality. Please enhance the quality of the images.**	**~~WE~~ We revised and quality was ~~e~~enhanced as we possibly could** ~~We did~~
	Line 382 **It unclear as to purpose of "uncategorised references" in this manuscript. Please justify.**	**We revised ~~and corrected~~and corrected the ~~uncatagorized references~~uncategorized references.**
Minor REVISION comments	**Lines 21 – 22 "Among…."** **The statement appears to be a hanging sentence. Please revise.**	**We revised and corrected as follo~~wes~~:** *"Terminalia chebula plant extract was the most potent lactate efflux inhibitor in N2-A cells among the 900 tested ethanol plant extracts"*
	Lines 24 – 25 "The plant extract…" **The authors should include the IC50 of "the plant extract" for comparison with phloretin.**	**We revised and the following was added:** *"The plant extract was more potent (IC_{50} of 3.59 ± 0.26 µg/ml)"*
	Lines 40 – 41 "… the cancer cell of…" **"the cancer cell of" should be removed. Please revise.**	**We revised** Unlike normal cells, solid ~~tumor~~tumor relies
	Line 60 **Please correct "consequents" to "consequential".**	**We revised and corrected to** *"Furthermore, the consequential"*
	Line 67 **Please ~~add~~add, "were" after "L-lactate assay kit".**	**We revised** L-lactate assay kits were
	Lines 68 – 70 "Water-soluble…" **The statement appears to be a hanging sentence. Please revise.**	**We revised and corrected to** *"and water-soluble tetrazolium (WST) proliferation assay kits from G-Biosciences (St. Louis, MO, USA). EnzChek® Caspase-3 Assay were purchased from Life Technologies Inc., (Grand Island, NY, USA)."*
	Line 78 **The authors should use comas (,) instead of semi-colon (;).**	**We revised** transferring buffers, standard protein ladder,

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	Line 83 **Please ~~add~~add, "were" after "Plant-ethanol mixture".**	**We revised** The plant-ethanol mixtures were
	Line 87 **Please correct "e thanol" as "ethanol".**	
	Line 98 **Please correct "m" as "ml".**	**We revised** 50 - 1000 µg/ml
	Line 105 **Please correct "FCE" as "TCE".**	**We revised** TCE Studies
	Line 129 **Please correct "rocker" as "rocking".**	**We revised** ~~incubated~~Incubated on a rocking shaker
	Line 144 **Please correct "each of" as "of each".**	**We revised** Lastly, 50 µl of each samples
	Line 154 **Please state the manufacturing country.**	**We revised** phase - contrast inverted microscope Olympus 1 X 7I (Pittsburgh, USA) at 20X magnification.
	Lines 272 – 273 **Please correct the spacing errors.**	**We revised**
	Line 352 **Please correct "Sk-N-SH" as "SK-N-SH".**	**We revised** SK-N-SH
Optional/General comments		