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Response to Reviewer's comments on the MS 19987

Reviewer 1 #

The authors sought to identify the correlation between the global warming and the longevity of animals by providing the evidences of the influences of altered temperature on animal's active oxygen species metabolism. This is an interesting review that presents a good overview of aspects of reactive oxygen species which are important in determination of animal's longevity. In addition, this review is well written, although there are several small errors in English usage. Overall, this manuscript can be considered for publication if further improvements are made.

Reply: We are grateful to the reviewer for the appreciation and recommendation of this article for publication. We have corrected the manuscript by a native English speaker to fix the language issues.

Minor concerns: 1. The authors should pay more attention to the English writing and are suggested to proof the manuscript carefully. Page 2 line 9: "example" to "examples", page 3 line 25: delete "although", page 8 line 3: delete "about", page 9 line 18: "much" to "many", page 10 line 9: delete "on", page 11 line 16: please reorganize the sentence "and any changes with these components", page 18 line 9: "is" to "are", page 24 line 3: insert "are" before expected.

Reply: All the indicated lines are corrected as per the suggestions.

2. The readers may be confused about the subtitles including "Mitochondria and the active oxygen species metabolism" on page 6, "Effects of global warming on human body" on page 12, and "Temperature, protein misfolding, diseases and longevity" on page 15, because they are the only sub-sections under each major sections. Please divide each major section into more sub-sections. 3. For the whole structure of the review, please consider changing the orders of some sections. For examples, "ACTIVE OXYGEN SPECIES METABOLISM" on page 4 could be combined with "ACTIVE OXYGEN SPECIES METABOLISM, TEMPERATURE AND AGING" on page 7,

"MITOCHONDRIAL DIASTIBUTION OF ANIMALS IN POLAR AND EQUITORIAL LINES" on page 17 could be combined with "Mitochondria and the active oxygen species metabolism" on page 6.

Reply: We reshuffled the sections of the manuscript as per the suggestions to make the manuscript more clear.

4. In Fig.2, the annotations of x/y-coordinate are not clear.

Reply: The annotations in x/y coordinate are changed to make it unambiguous.

Reviewer 2

In the paper "Longevity of animal's by ROS and disease susceptibility under high temperature" by Paital et. al. submitted for publication in WJBC authors intended to show that rise in atmospheric CO₂ and global temperature would inflict oxidative stress in human and animals. The very idea to connect the two subjects is worthwhile.

Nevertheless, the part in the paper on ROS reveals that the authors have rather poor grip on the subject. Examples: On p6. ROS "are highly reactive in nature and can oxidize lipids to lipid peroxide, proteins to protein carbonyls and nucleic acids to their respective adducts". First of all, ROS vary in reactivity as well as in mechanisms and consequences of their action on cells. Second, not clear why among numerous products of protein oxidation by ROS only protein carbonyls were mentioned. Also superoxide radical in reaction with biomolecules acts mostly as reductant rather than oxidant. Antioxidant enzymatic system was described in a way that was accepted let say 10 years ago. Extremely important peroxiredoxins, glutaredoxins, thioredoxins were not mentioned.

Reply: The line ROS "are highly reactive in nature and can oxidize lipids to lipid peroxide, proteins to protein carbonyls and nucleic acids to their respective adducts" does not solely indicate that ROS are very specifically reacts with lipids, proteins and nucleic acids. Also the line exclusively does not indicate that "ROS don't vary in reactivity as well as in mechanisms and consequences of their action on cells ". Since, these are three major macromolecules, explanation about them only was mentioned. Since protein carbonyls are the major oxidation products of proteins by ROS, we mentioned only about them. We did not want to have only descriptive elaboration about ROS and antioxidants in the MS which could alone take >50% space in the MS. However, we edited the sentence to make it clearer. The roles of different ROS other than oxidants were mentioned in the text. The accepted enzymatic and non-enzymatic antioxidant systems were explained in the MS. We feel very sorry if the reviewer felt that we have poor grip on the above subject as because we have not mentioned about peroxiredoxins, glutaredoxins, thioredoxins systems and there were minor errors in

explaining the terminologies in ROS metabolism. To fix this issue, we emphatically added about peroxiredoxins, glutaredoxins, thioredoxins systems in the MS at the appropriate section and corrected the commented lines to remove the errors.

In Fig.1 low molecular compounds, namely ascorbic acid and others were presented as “Direct neutralization of ROS”. Modern science says that antioxidant action of those molecules occurs not via direct scavenging.

Reply: We removed the word “direct” from the figure.

There is disagreement between the title and the subject of the paper. In title was mentioned high temperature while the Abstract and paper devoted to effect of global warming.

Reply: We changed the title of the paper as “Longevity of animals under ROS stress and disease susceptibility due to global warming” to resolve the issue.

Authors did not elaborate on how a few degrees raise in the mean global temperature could result in ROS production in human. In the chapter on the effect of global warming on human body and health other topics were discussed.

Reply: There are also possibilities/instances of rise in mean temperature of $\sim 6^{\circ}\text{C}$ in several places of world. And rise in $\sim 6^{\circ}\text{C}$ temperature can not be considered as “few degree”. However, the above point is discussed as a whole by considering human being as one of the homeotherms in sections “ADAPTATION OF ANIMALS AND OS UNDER HIGH HABITAT TEMPERATURE” and “GLOBAL WORMING, HUMAN HEALTH AND AGING”. For example: Although few degree rise in temperature is unable to affect human physiology directly, it can aggravate temperature dependant diseases such as insect vector born diseases and that indirectly can affect human live and longevity. As much works have not been done on ROS production in humans as a function of temperature, the section “effects of global warming on human body “ under the major heading “GLOBAL WORMING, HUMAN HEALTH AND AGING” was limited to issues related to possible causes that may shorten human longevity based on the available literature.

Many important claims in the paper were supported by references of low credibility. For example, on p20 “The skin of people in hot climates certainly seems to age faster than that of people who live in colder climates [96]. “ Too many references to internet sites rather than scientific journals. Some statements in the paper like on p.19 “For example, the northern people live longer and people exposed to hunger and hot climates during generations live shorter lives.” were not substantiated.

Reply: The references which were collected from the authentic websites were only cited in the MS. We disagree that there were too many web references cited because only 10 web references were there out of total 163 references. Many of the 10 web references were from highly reputed world class organizations such as The Columbia Electronic Encyclopedia (<http://www.infoplease.com/encyclopedia/science/body-temperature-warm-blooded-animals-homeotherms.html>), World health organization

(<http://who.int/uv/health/en>), and University of Minnesota (<http://enhs.umn.edu/current/5103/uv/harmful.html>).

Reviewer 3

This manuscript describes hyperthermia and longevity in ROS condition. This is a good review to conceive concept on high temperature and ROS. ROS which is generated during metabolism, could affect high molecular weight molecules and subsequently, animal life time. Once ROS is produced, it is subject to neutralization mediated by various enzymes. However, at high temperature, homeostasis control would be collapsed and thus ROS would not be removed efficiently and followed by aging. ROS is generated by mitochondria and it may function as a toxic substance. Due to the global warming, many terrestrial, marine lives are affected. Thus it is highly likely that high temperature would cause disruption of homeostasis. Therefore, to avoid heat stress, hibernation and aestivation were employed in some animals. In contrast, homeotherms adapt to these temperature changes by adjusting body temperature to meet the needs. Although it is worth for publication, there are several parts which need further revision.

Reply: We are thankful to the reviewer for the appreciation and recommendation of this article for publication. We have revised the manuscript as per the suggestions to meet the comments of the reviewer.

Comments on this manuscript are; This manuscript depicts too broad ranges of longevity and diseases with some overlapping parts. One way to avoid this would be adding new figures or Tables.

Reply: We added one more figure (Fig. 2) and we reshuffled (as asked by one of the reviewers) and edited the text to avoid over lapping parts.

1. More explanation on Fig 1 and Fig. 4 would be helpful to understand these figures.

Reply: Fig. 1 and 4 are explained further in text and respective legends to fix the issue asked by the reviewer.

Please add additional description in the figure legends. 2.

Reply: Additional descriptions are provided in legends of the figure 2.

Active oxygen species metabolism and active oxygen species metabolism, temperature and aging: Some overlapping terms should be avoided for clear understanding. Please rewrite it clearly. Also add a diagram how ROS is generated in mitochondria. **Reply:** We highly appreciate the reviewer for this comment and modified the headings/subheadings accordingly, for example, "active oxygen species metabolism, temperature and aging" to "Oxidative stress, temperature and aging" and so on. A figure is added showing how mitochondria is responsible to generate ROS.

3. P11: Pathogens transmission according to temperature change? In these days, it would be more possible to transmit pathogens by high speed vehicles such as transmission of pathogens via airplane travel. Please add these facts also.

Reply: We do completely agree with the reviewers that the risk of mode of transmission of pathogens via air passages, more exactly via airplanes is high. For example, the instances of H1N1 and Ebola viruses. However, we wrote the article on the basis of rise in temperature/global warming and its effects via ROS and disease susceptibility on longevity of animals. So, transmission of pathogens via air passages does not fit exactly into the above concept. Therefore, we did not include the suggested topic in the MS. Hope the reviewer will understand the issue.

4. p12: UV irradiation may contribute to carcinogenesis and increase cancer incidence. However, UV is generally known to cause DNA damage and generates abnormal nucleotide adducts thus leading to mutation rather than ROS. Thus it would not contribute for decrease of life time, and would not be related to the title of this manuscript "Longevity of animal's by ROS and disease susceptibility under high temperature".

Reply: We completely agree with the reviewer's comments. Although, we have not correlated exposure of UV radiation with that of ROS generation in humans, we correlated it with longevity in humans via immuno suppression. Global warming is related to ozone layer depletion, UV radiation penetration and exposure by humans to it, DNA mutation, skin cancer and immuno suppression which may affect longevity in humans. Therefore, we presented the sub-topic as such.

5. P17 "MITOCHONDRIAL DIASTIBUTION OF ANIMALS IN POLAR AND EQUATORIAL LINES": There is a spell error.

Reply: The word "DIASTIBUTION" is corrected to "distribution".

6. Table 1. Please explain what is "GSSG".

Reply: GSSG is explained as "oxidised glutathione".

7. P23. Fig.3: Wrong symbol is used.

Reply: We did not find any wrong symbol. So, we beg apology that we have made no change in response to this commit.