Review of: "The role of pH in cancer biology and its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapeutics"

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Potential competing interests: No potential competing interests to declare.

The manuscript, entitled "*The role of pH in cancer biology and its impact on cellular repair, tumor markers, tumor stages, isoenzymes, and therapeutics*", reviews the progression of studies about the effects of pH on several biological phenomena on a cellular scale. The manuscript is basically written well, and the manuscript may be suitable for publishing. However, I recommend publishing this manuscript after addressing the following points.

1. The authors should show the quantitativity of pH for all the contents of the manuscript. For instance, what is the range of possible pH variation of some events in organisms, typical examples of optimum pH of isoenzymes, and what is the correlation between these? The discussion is lack of quantitativity.
2. Please add references for the sentence "Tumor development stages exhibit distinct pH dynamics, with acidic extracellular destruction and alkaline intracellular replication." in the introduction part.
3. "Exploiting the pH gradient holds promise for inhibiting cancer growth." The context of this sentence is unclear. What is the evidence to claim this?
4. In section 2, can you explain how to measure or detect pH variations (or H^+ concentration) in both inflammatory and cancer environments? It would help that this manuscript will be one of the frontiers among recent reviews around this topic.
5. There is no reference in the sentence starting from "The impact of pH regulators on immune cell~", which may be unacceptable even though some impacts are introduced, and Figure 1 is made based on these. Scientific evidence and reliability are lacking.
6. In section 3, the authors mention the correlation between cell repair and cancer development. However, the only example about tumor makers is shown to claim it. It should not be enough, and I recommend discussing it from more diversified evidence or perspectives.
7. Please check the quality of Figure 3. Some texts have an unexpected gray background.
8. In section 4, it would be better to show some typical examples of isoenzymes and the difference in optimum pH. Then, it should be correlated to the pH variation range that can be seen in biological systems.
9. Also, for the successive sentences "Enzymes can originate from one or multiple gene loci, ~", it would be better to show typical examples and discuss based on molecular levels, namely, how pH alters such processes biochemically.
10. In section 5, I think the part below, "Regarding the understanding of hydrogen ion strategies and cancer development,

there is a new theory for treating cancerous tumors through metabolic activity," should be highlighted more in this manuscript and made into an independent paragraph. Accompanied by this, please summarize previous studies into a new figure, which relates to the mentioned new theory.