RESPONSE TO REVIEWERS

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: This Review discusses an interesting medical topic. However, there are the following main problems: 1. The author cited too few relevant references, exaggerating the the role of Kynurenine pathway of tryptophan metabolism in pathophysiology and therapy of major depressive disorder. 2. The metabolic pattern diagram is too simple. It is suggested to display it visually for the readers to understand. 3. In the absence of research data support, some personal hypotheses were conducted.

Response: We thank the Reviewer for their constructive comments.

(1) The reason for the fewer references cited is that the paper was prepared as a Commentary Review, rather than a full review. In line with the invitation from the Editors-in-Chief, I believe I opted for a Minireview, mainly to avoid any likely duplication were we to submit a full review. We are however very happy to expand the text in the revised version. We believe that we are not exaggerating the role of the kynurenine pathway (KP), but are simply bringing into focus recent developments in depression research that strongly suggest an important role of the pathway in both the serotonin deficiency and the glutamatergic activation that underpins cognitive and other neurological dysfunctions. We hope that our text will stimulate further research in this important area of mental health in the light of recent developments.

(2) Thank you. Figure 1 has now been upgraded with chemical formulae.

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: With more and more advanced research in the field of treatment resistant depression, the focus of treatment strategies is shifting from the monoamine system to other biological mechanisms. One of such critical systems is the glutamatergic system. The kynurenine pathway plays a critical role in generating cellular energy in the form of nicotinamide adenine dinucleotide. In this pathway, tryptophan is converted into several bioactive molecules including serotonin while majority of it is converted into kynurenine and its breakdown products. Th authors have done justice in describing the tryptophan metabolizing enzymes and kynurenine pathway. Through a series of steps kynurenine is converted into quinolinic acid, which has NMDA receptor agonist properties and kynurenic acid, which is an NMDA receptor antagonist. A hypothesis suggests that the competing actions of quinolinic acid and kynurenic acid at the NMDA receptor may play role in inflammation and glutamate models of depression. Ref:Savitz J. The kynurenine pathway: a finger in every pie. Mol Psychiatry. 2020. The authors have discussed the kyeurenine pathway underlying MDD pathophysiology and being a target of antidepressant therapy briefly in the last section of the review. May be more focus & elaboration on that instead of the very brief section on role of anti-inflammatory medications such as celecoxib in MDD therapy would improve the quality of this review article and provide higher clinical utility. The tables and figures are helpful.

Response: We thank the Reviewer for their kind comments.