Reviewer #:

The manuscript “Increasing the Efficiency of Accumulation of Recombinant Proteins in Plant Cells: The Role of Transport Signal Peptides” is based on an extensive literature review citing more than 200 studies conducted within this research field. This review highlights the role of transport signal peptides in plant science research, and gives insights the knowledge, applications, advantages and limitations of using such peptides to increase the accumulation of recombinant proteins in plant systems. The manuscript is well structured and illustrated with informative figures. I believe this manuscript is a timely review on this important technology and will therefore be of interest for a wide audience.

However, specific comments are listed below:

Major comments:

1. In the “Abstract” section, the authors use the term «**translocation»** (see - The problem of an increase the yield of recombinant proteins is resolvable using different approaches, including the translocation of a target protein to the cell compartments with a low protease activity), it should be noted that, as a rule, this term is used to refer to a type of chromosomal mutation in which a portion of a chromosome is transferred to a non-homologous chromosome. A different term should be chosen.
2. “Introduction” section. When the authors point out that “In the cytosol, proteins can undergo undesirable modifications altering their folding [13]; however, all improperly folded proteins are degraded according to ubiquitin proteasome proteolytic pathway [14]” Readers might take it this way: if degradation occurs only through misfolding, then it is not transport that is important, but ensuring the correct folding of the recombinant protein. An explanation is required of the role of recombinant protein transport in preventing its proteolytic degradation.
3. “Introduction” section. The authors indicate “These peptide signal sequences can be successfully used to target the recombinant proteins synthesized in plant cells to the compartments with a low protease activity”, and the question arises - is it known which compartments have low proteolytic activity or is this a further direction of research? Possibly a modern review - Philippe V Jutras, Isobel Dodds and Renier AL van der Hoorn. Proteases of Nicotiana benthamiana: an emerging battle for molecular farming. Current Opinion in Biotechnology 2020, 61:60–65. https://doi.org/10.1016/j.copbio.2019.10.006 - might be helpful to clarify this kind of issue.
4. “Intracellular Transport of Proteins to the ER and Its Derivatives” section. When the authors describe two types of protein transport (“Commonly, two types of protein transport to all eukaryotic cell compartments are distinguished, namely, cotranslational and posttranslational”), readers may find it interesting whether it is possible to predict which way the protein transport will go - co-translational or post-translational? It would be helpful to mention this in a clearer way.
5. Section - Using Signal Peptides Targeting to the ER and Its Derivatives to Increase the Accumulation Efficiency of Recombinant Proteins - it would be appropriate to give examples of signal peptides for protein transport in the ER, as is done for other plant cell compartments.
6. In my opinion, a table that presents examples of signal transport peptides that ensure the transport of recombinant proteins into different compartments of plant cells would be extremely useful for summarizing the material and for readers.

Minor comments:

1. It is more professional to use the term “N-terminus” instead of “N-end”, as well as the term “C-terminus” instead of “C-end”.