
AN OBSERVATIONAL DESCRIPTIVE ANALYTICAL RESEARCH STUDY AND A SYSTEMATIC REVIEW ON THE CLINICAL PHARMACOTHERAPEUTICS OF ALVEOLAR ORGANOIDS

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ABSTRACT: *Stem cell-derived self-organizing three-dimensional organoids have emerged as a novel medical innovation to recapitulate respiratory diseases. This clinical research and systematic review was conducted for systematically reviewing the clinical pharmacotherapeutics of alveolar organoids, with thorough explanations and analyses of the medical study literature and evidence compiled from the different studies conducted, thus authenticating the multi-dimensional pharmacomolecular significance of alveolar organoids. The objective of this clinical research was an observational descriptive analytical research study and a systematic review on the clinical pharmacotherapeutics of alveolar organoids. The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration in June, 2016. At first, the steps of identification included the records which were identified through database searching and the additional records which were identified through other sources. This led to the steps of screening, which included the screened records, after the duplicates were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, in the eligibility step, the full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons. This led to the final inclusion step, where the studies were included in the qualitative synthesis of a systematic review, according to the inclusion criteria, and ultimately the studies were included in the quantitative synthesis. An observational descriptive analytical research study was also conducted on the clinical pharmacotherapeutics of alveolar organoids. This systematic review, performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, contributed 28 refined and relevant medical records, among total 37 records obtained from the study databases search. It also describes and thoroughly analyses the clinical pharmacotherapeutics of alveolar organoids which validates, clarifies, and elaborates this clinical research and systematic review. To conclude, this clinical research and systematic review provided the refined qualitatively synthesised medical records, study literature and databases on the clinical pharmacotherapeutics of alveolar organoids, with an explanatory observational descriptive analysis.*

KEYWORDS: observational descriptive analysis, systematic review, alveolar organoids, clinical pharmacotherapeutics, pharmacology, respiratory medicine, clinical research.

INTRODUCTION

Organoids are three-dimensional cell structures, grown in vitro from the stem cells. These stem cells are mainly isolated from the biopsies or from the pluripotent stem cells, that are extensively similar to the endogenous organs, in both their structural development and functional performance. The organoids are formed of cells which differentiate, undergo spatially restricted lineage commitment, and acquire the specific tissue patterning to develop into several endoderm, mesoderm, and ectoderm-derived tissues. Stem cell-derived self-organizing three-dimensional organoids have emerged as a novel medical innovation to recapitulate respiratory diseases.¹⁻⁶

This systematic review was conducted for systematically reviewing the clinical pharmacotherapeutics of alveolar organoids, with thorough explanations and analysis of the medical study literature and evidence compiled from the different studies conducted, thus authenticating the multi-dimensional pharmacomolecular significance of alveolar organoids.

Objective

The objective of this clinical research was an observational descriptive analytical research study and a systematic review on the clinical pharmacotherapeutics of alveolar organoids.

METHODS

The study was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration in June, 2016. At first, the steps of identification included the records which were identified through database searching and the additional records which were identified through other sources. This led to the steps of screening, which included the screened records after the duplicates were removed. From these screened records, few records were excluded, as per the exclusion criteria. Then, in the eligibility step, the full text articles were assessed for eligibility, from which few full text articles were excluded, according to the exclusion criteria, with adequate reasons. This led to the final inclusion step, where the studies were included in the qualitative synthesis of a systematic review, according to the inclusion criteria, and ultimately the studies were included in the quantitative synthesis.

The study selection criteria were the following:

- (a) The inclusion criteria were : The published articles on the clinical pharmacotherapeutics of alveolar organoids; the original research studies, systematic reviews, meta-analyses, case reports, case series, narrative reviews, study series, parallel studies and similar kind of studies or reviews, of any or all types, which were either qualitative, or quantitative, or both qualitative as well as quantitative; the publication time-frame within a span of the past 3 years; and any or all types of observational, descriptive and analytical research studies.
- (b) The exclusion criteria were : Irrelevant studies; and studies older than 3 years.

Each study was assessed for allocation concealment, blinding, reporting of losses to follow-up or missing outcome assessments, evidence of important baseline differences between the groups, analysis on an intention-to-treat basis and use of a sample size calculation. An observational descriptive analytical clinical research study was also conducted on the clinical pharmacotherapeutics of alveolar organoids.

RESULTS

The results of this Systematic Review

In accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, in identification stage, the study literature search on clinical pharmacotherapeutic applications of organoids, contributed 12 records in PubMed search, 7 records in EMBASE search, 9 records in Scopus search, and 9 records in additional databases search, identified through other sources. The records, after removing 4 duplicates, were 33. In the screening stage, the records screened were 33. From these records, 3 records were excluded, according to the exclusion criteria. In the eligibility stage, the full text articles assessed for eligibility were 30. From these records, 2 full text articles were excluded, according to the exclusion criteria. In the final inclusion stage, the records ultimately included in the qualitative synthesis, according to the inclusion criteria, was 28. These 28 records were the refined contributions of this systematic review. Thus, this systematic review contributed 28 refined and relevant medical records, among total 37 records obtained from the study databases search, as depicted in Figure 1.

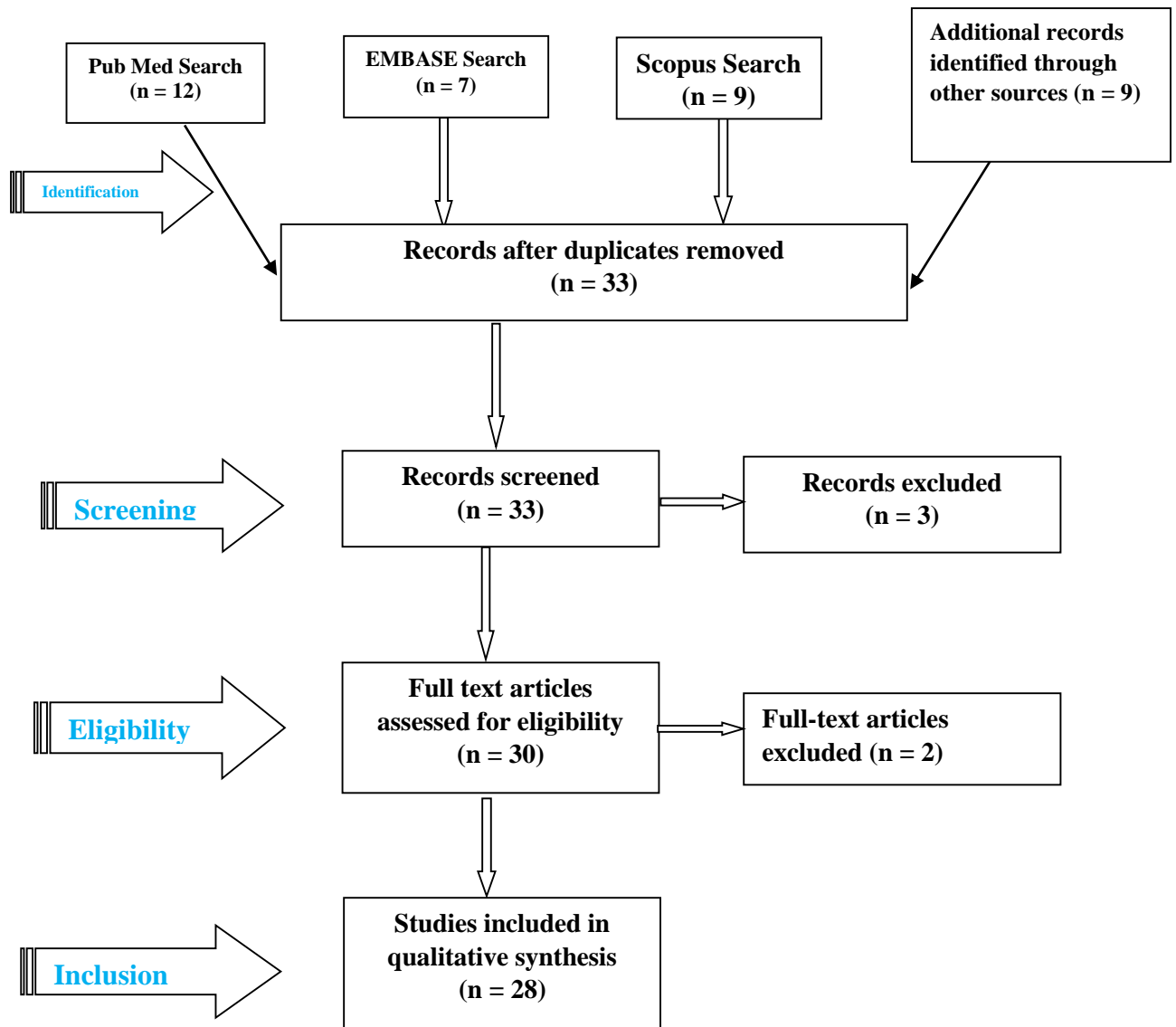


FIGURE 1: The Stages in PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009

The selective investigative and experimental elucidations on the clinical pharmacotherapeutics of alveolar organoids

From the analytical compilation of pharmacotherapeutic databases and evidences, the selective investigative and experimental elucidations on the clinical pharmacotherapeutics of alveolar organoids was also described, in complete details, to validate, elaborate and clarify the

quantitative and the qualitative details of this conducted observational descriptive analytical clinical research and systematic review.

DISCUSSION

In this study, in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, in identification stage, the study literature search on quinolones, and more specifically on the newer quinolones, contributed 12 records in PubMed search, 7 records in EMBASE search, 9 records in Scopus search, and 9 records in additional databases search, identified through other sources. The records, after removing 4 duplicates, were 33. In the screening stage, the records screened were 33. From these records, 3 records were excluded, according to the exclusion criteria. In the eligibility stage, the full text articles assessed for eligibility were 30. From these records, 2 full text articles were excluded, according to the exclusion criteria. In the final inclusion stage, the records ultimately included in the qualitative synthesis, according to the inclusion criteria, was 28. These 28 records were the refined contributions of this systematic review.

The following selected qualitative investigative and experimental elucidations on the clinical pharmacotherapeutics of alveolar organoids were described

Insults to the alveoli usually lead to inefficient gas exchange or even respiratory failure, which is difficult to model in animal studies. Stem cell-derived self-organizing three-dimensional organoids have emerged as a new avenue to recapitulate respiratory diseases. Alveolar organoids have improved the understanding of the mechanisms underlying tissue homeostasis and pathological alterations in alveoli. Region-specific stem/progenitors have been characterized for the maintenance of lung epithelia or to repair the lung epithelia after injury. These epithelial stem/progenitor cells can generate lung organoids that provide a powerful platform for the study of human lung development and respiratory diseases and have therefore attracted intense interest in medical research. Distal lung stem/progenitor cells generate organoids with low colony-forming ability when stromal cells are replaced by high concentrations of FGF10 and hepatocyte growth factor, which suggests that other growth factors are needed for alveolar organoid development. In contrast, isolated human distal lung epithelial cells, usually including basal cells, generate organoids in the absence of mesenchymal support. Organoid technology serves as a new pathological model to investigate cell-cell crosstalk and host-pathogen interactions and is a powerful platform for modeling human lung diseases and for drug screening and toxicity assays. This tool could replace some animal experiments, thereby minimizing animal use in respiratory research. A bank of human lung organoids could be established for cell or gene therapy. Generating personalized organoids would also open novel avenues for research into individual responses to therapies and thus also for the implementation of personalized medicine. Human PSC-derived AT2 cells form 3D alveolospheres without the need for feeder cells. These data suggest that autocrine growth factors play an essential role for such cells. Indeed, *in vitro* organoid cultures provide a useful platform to reveal the interactions between stem/progenitor cells and niche cells in the lung. It was found that lung endothelial cells also support BASC organoid cultures. Mouse AT2 cells can form organoids in the presence of CD45 and F4/80 and mouse macrophages. In an *in vitro*

organoid culture assay, the interactions between alveolar stem/progenitor cells and other structural and immune cells in the lung, were explored. Organoid culture of distal lung epithelial stem/progenitor cells can be performed *ex vivo*. Epithelial spheroid structures form when a mixture of distal lung progenitor cells and Matrigel is subcutaneously injected into the back of mice. When grafted under the renal capsule, adult $\alpha6\beta4$ and AT2 subset cells differentiate and regenerate epithelial structures within 1 week. Longer organoid culture of human PSC-derived lung epithelial progenitor cells under the renal capsule can even generate branching structures. An obvious benefit of *ex vivo* organoid culture is that a capillary network usually develops over the spheroid structures, which is not seen in *in vitro* assays. Human distal EpCAM type epithelial cells, including AT2 cells, can be isolated from peripheral lung tissue specimens by magnetic bead sorting (MACS). Co-culture of these EpCAM type cells with MRC5 human lung fibroblasts in Matrigel resulted in the formation of organoids that allows airway differentiation but not alveolar differentiation. Alveolar differentiation was promoted by inhibiting TGF- β receptor signaling in organoids derived from human distal airway $\Delta Np63$ and TTF-1 and stem cells. Human $\Delta Np63$ and TTF-1 and stem cells were also capable of differentiating into airway ciliated and Club cells in the presence of FGF10 and a γ -secretase inhibitor. The functional analysis of organoids usually includes several aspects. First, the colony-forming ability of distal lung stem/-progenitor cells is evaluated in *in vitro* organoid assays based on the percentage of the number of colonies to the number of plated stem/progenitor cells. The colony-forming efficiency (CFE) of mouse AT2 cells ranges from 0.5 to 2%, because of variations in culture conditions, whereas the CFE of distal airway stem/progenitor cells ranges from 0.5 to 4%. The CFE of human AT2 cells ranges from 2 to 8%. To investigate the self-renewal potential of stem cells, colonies are broken down into single cells followed by replating in Matrigel for organoid cultures. After 2-3 passages of the organoid cultures, the self-renewal capacity of stem/progenitor cells can be evaluated by comparing CFE among passages. Second, the average size of a colony, measured *via* the diameter or the surface area of individual colony, reflects the proliferation potential of the seeded stem/progenitor cells or swelling induced by water channels on the cell surface allowing the evaluation of the membrane permeability and secretion potential of the cells in the organoids. Culture medium can be supplemented with BrdU to allow for BrdU incorporation analysis in organoid end cultures. Alternatively, to further evaluate the proliferation of stem/progenitor cells, organoid cultures can be fixed, embedded, and sectioned for Ki67 immunostaining. Lastly, differences in the differentiation potential of stem/progenitor cells are evaluated by immunostaining sections for AT2 (pro-SPC) and AT1 (T1 α , aquaporin 5) cells. Organoid cultures can also be harvested to analyze these markers at the transcriptional level *via* quantitative polymerase chain reaction. Transcriptome analysis in bulk or at a single cell level can also be conducted for alveolar organoids. In addition, organoid cultures can be processed for electron microscopic analysis to visualize the general structures of the individual organoids established in *in vitro* or *ex vivo* assays. In the lung organoid system, discarded surgically removed human lungs, BALF samples, needle lung samples, dermal samples, are the tissue sources. The animal use is largely reduced. The genetic modulation is to be developed. There is cell-cell interaction. Usually a few cell types are involved. The research scale is translational type. The individual variations are personalised. The *in vivo* recapitulation is powerful in some aspects. Drug screening and tissue banking can be performed.¹⁻⁶

The therapeutic use of organoids would be an alternative to the challenging transplantation of organs with a short period of viability outside the body, such as the heart and lungs. Because of their characteristics, organoids have enormous potential for drug development and precision medicine, which aims to increase cost effectiveness and risk-benefit ratios of therapies by more precisely targeting therapies to individual patients.

This observational descriptive analytical clinical research and systematic review provided the refined qualitatively synthesised medical records, study literature and databases on clinical pharmacotherapeutics of alveolar organoids, with well-comprehensible elaborations.

CONCLUSION

Therefore, this clinical research and systematic review, performed in accordance with the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) Statement and Guidelines, 2009, described by the Cochrane Collaboration, June, 2016, contributed 28 refined and relevant medical records, among total 37 records obtained from the study databases search. It also describes the clinical pharmacotherapeutics of alveolar organoids, which validates, elaborates and clarifies this clinical research and systematic review.

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DECLARATIONS

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