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Original Research

Computational Drug Discovery in Patients with Endometriosis-Induced Infertility via Text Mining and Biomedical Databases

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Abstract

Background: Endometriosis (EMT) is the most common benign gynecological disease among women of reproductive age, causing infertility and seriously affects women's physical and mental health. However, the current treatment was not always effective. This study was designed to use publicly available data to identify drugs targeting the relevant gene with EMT-induced-infertility using computational tools. **Methods**: EMT and infertility genes were determined by text mining, and the GeneCodis program was used to analyzed gene ontology of the intersection of the two gene sets. A string database was used to analyze the protein-protein interaction network. The Drug-Gene Interaction database is queried for the rich gene set belonging to the identified pathways to find drug candidates that can be used in EMT-induced infertility. **Results**: Our analysis identified 550 genes common to both the EMT and infertility by text mining. Gene enrichment analysis and protein-protein interaction analysis found 39 genes potentially targetable by a total of 49 drugs that could be formulated for application, which have not been used in EMT-induced infertility. **Conclusions**: The findings from the present analysis can facilitate the Identification of existing drugs that have the potential of topical administration to improve EMT-induced infertility and present tremendous opportunities to study novel targets pharmacology using in silico text mining and pathway analysis tools. However, all the results were based on online bioinformatics databases, and as such require validation experiments. And some of the drugs highlighted as possibly relevant may be toxic and as such safely data is required before any experiments are undertaken in humans.

Keywords: differentially expressed genes; endometriosis; infertility; drugs; text mining

1. Introduction

Endometriosis (EMT) is the most common benign gynecological disease among women of reproductive age, with an estimated 10–15% [1]. It is a kind of chronic estrogen and progesterone-related inflammatory disease [2] characterized by dysmenorrhea, pain, and infertility [3]. It is reported that the infertility patients reduced by EMT are up to 25–50%, which seriously affects the quality of life of patients [4]. The American Society of Reproductive Medicine [5] proposes that EMT should be regarded as a chronic disease that requires lifelong treatment using medications with as few side effects as possible to avoid invasive procedures such as surgery.

Patients with EMT-induced infertility are widely concerned because of their low fertility [6]. Treatment methods for EMT include surgery and drugs to improve the patient's pregnancy rate and clinical treatment effect. The commonly used drugs include oral contraceptive (OC), progestin and gonadotropin-releasing hormone analogs (GnRH-a). A meta-analysis indicated that GnRH-a is more suitable as a non-surgical treatment for EMT than progestin and OC according to the comprehensive efficacy and side effects [7]. GnRH-a can effectively improve the condition of EMT; however, bone loss and low estrogen levels caused by long-term use can not be ignored [8,9]. The search for a drug with positive efficacy, good tolerance, and high-cost performance is the development direction of comprehensive and individualized EMT treatment. However, It is difficult to develop new drugs because of their complicated pathogenesis.

The traditional process of drug discovery and development is derived from physical experimentation and research of drug compounds, which requires much time, energy and financial resources. Fortunately, there has a prominent example of successful drug repurposing. It is reported that Sildenafil (Viagra), which was developed to treat angina, is effective in the treatment of erectile dysfunction [10]. Un-

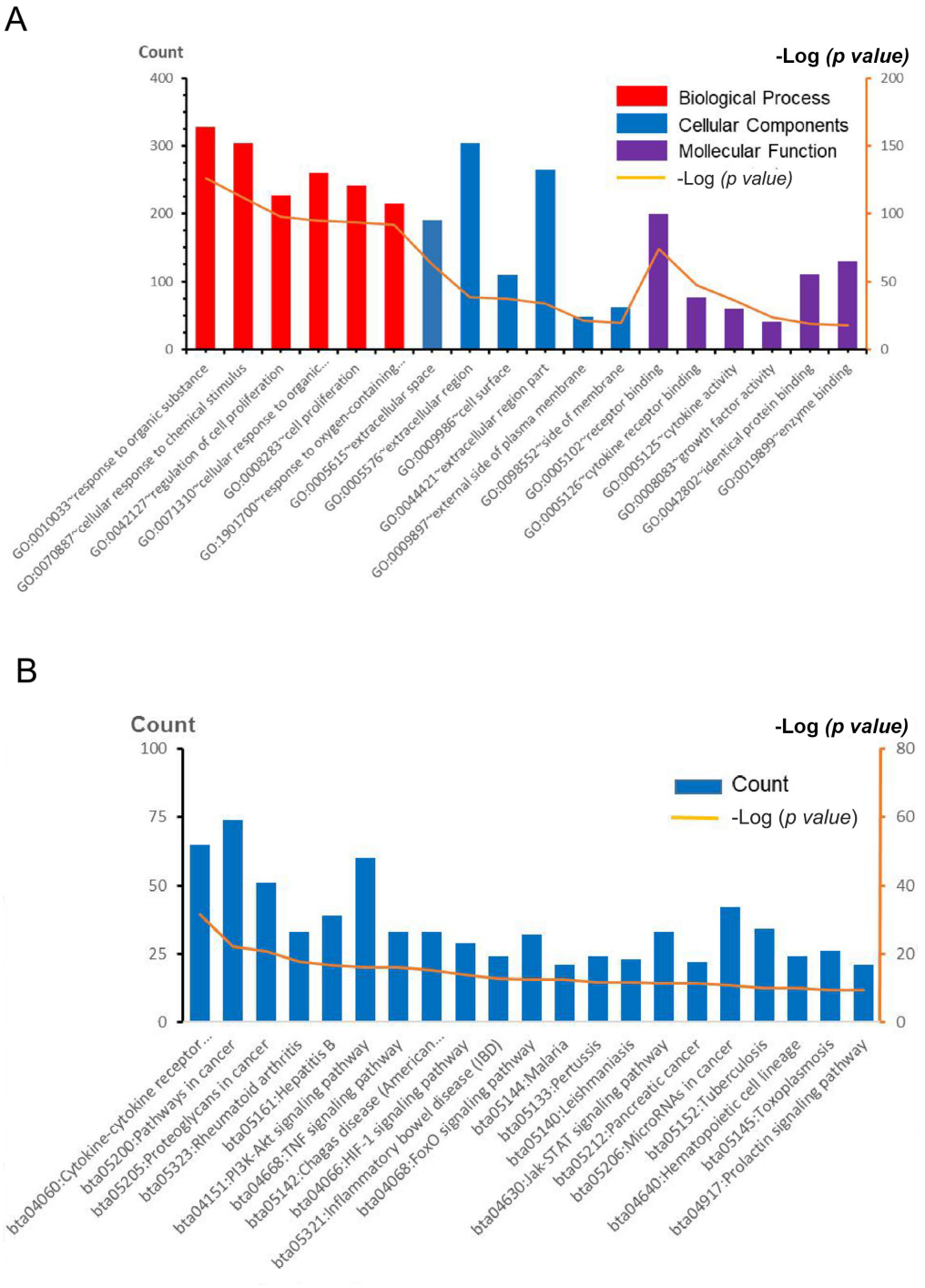

Fig. 1. Gene ontology analysis and significant enrichment of differentially expressed genes (DEGs) in EMT-induced-infertility. (A) Gene ontology (GO) analysis classified DEGs into BP, CC, and MF groups. (B) Significantly enriched signal pathway of differentially expressed genes (DEGs).

doubtedly, reusing existing drugs to treat other diseases can be a lower cost and possibly a faster alternative. Following the repurposing paradigm, this study aimed to explore new drug treatment options for EMT-induced infertility by mining the available published literature associated with biological databases and other analytical tools.

Text mining in the biomedical literature has been confirmed as an effective way to reveal the new relationship between genes and diseases [11,12]. When text mining is combined with biological knowledge and other analytical tools, new evidence on the potential to repurpose existing drugs can be obtained [13]. The computational prediction

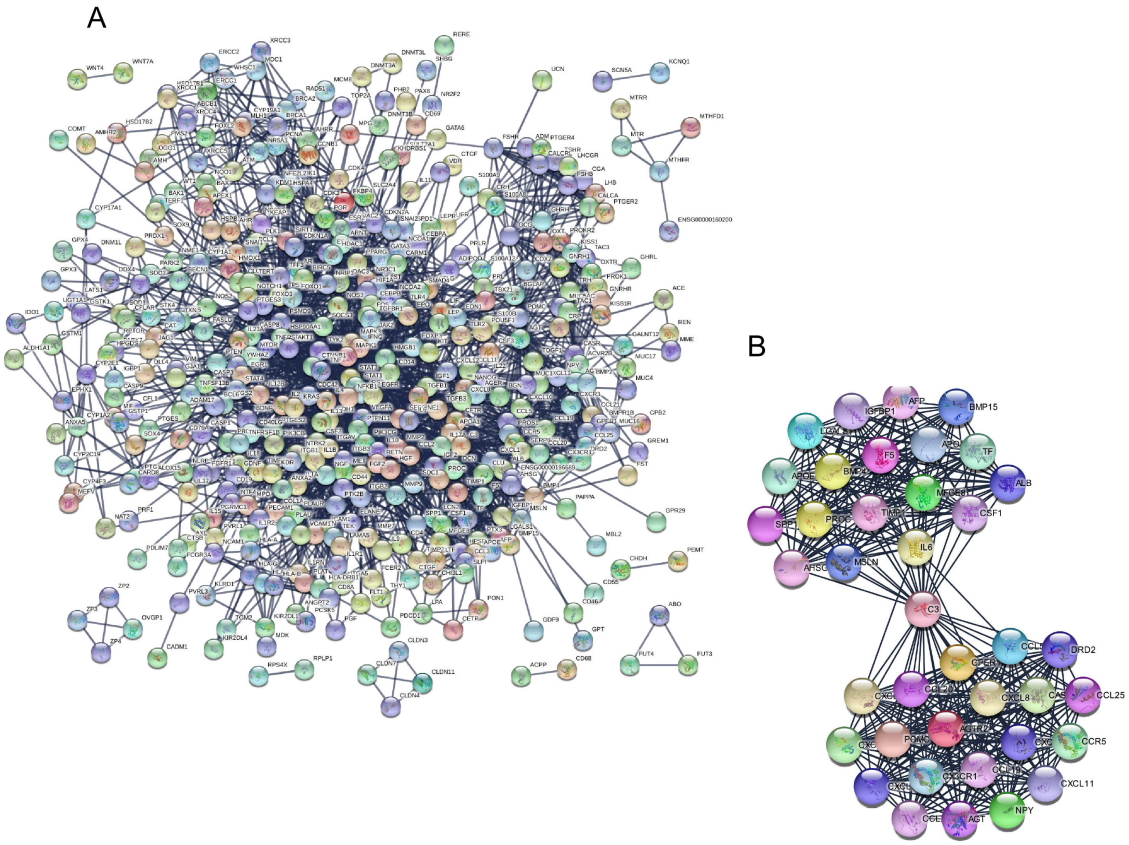

Fig. 2. Protein-protein interaction (PPI) network of differentially expressed genes. (A) Based on the STRING online database, 452 DEGs were filtered into the DEGs PPI network. (B) The most significant module from the PPI network.

of multi-target drugs has established multi-pharmacology as a promising alternative to solve some complex drug discovery through text mining [14]. Biological knowledge can be assorted and categorized with gene ontology (GO) hierarchical relationships [15]. The definition of GO biological processes can provide a framework for mapping relationships between biological entities and text mining concepts [15]. It is reported that the cellular signaling pathway maps combined with text mining can be used to expand the information of a specific signal transduction pathway and find a target gene or a targetable regulator of the target gene [16]. Several successful research outcomes studies have been reported, in which some are discovering new uses for existing drugs were found using GO and pathway analysis to link drugs with diseases [17,18]. The priority of a group of genes can be further determined by evaluating their influence on protein interaction networks. This technique is useful because it demonstrated some novel relationships by analyzing gene interactions that tend to accumulate in the network due to certain characteristics of the disease or pathological conditions [16].

In this study, we performed queries using the search terms endometriosis and infertility to produce a preliminary list of genes in exploring potential drugs for EMT-induced infertility. We then validated the relationship between the identified genes and generated a priority target set by analyzing the signal pathway. We created a list of high-priority target genes with an in-depth analysis of the genes' functional enrichments. Candidate drugs were then derived from a summary of the data on potential drug-gene interactions.

2. Materials and Methods

2.1 Gene Collection

The database genclip3 (http://ci.smu.edu.cn/genclip3/analysis.php) was used to perform text mining. We performed queries using the search terms endometriosis and infertility to produce a list of differentially expressed genes (DEGs). Then, we extracted all of the unique gene hits from each result. All of these genes were then used in the subsequent analyses.

2.2 Gene Ontology and Pathway Analysis

GeneCodis (http://genecodis.cnb.csic.es/), a web-based tool for integrating various sources of information with gene ontology and functional information [19]. It was used for the enrichment analysis of the genes corresponding to the EMT and infertility intersection. We used

Table 1. The Gene Ontology of the genes involved in EM-induced infertility.

Category	Term	Count	*p* value
GOTERM_BP_FAT	GO:0010033 response to organic substance	328	3.90E-127
GOTERM_BP_FAT	GO:0070887 cellular response to chemical stimulus	304	1.29E-112
GOTERM_BP_FAT	GO:0042127 regulation of cell proliferation	227	1.43E-98
GOTERM_BP_FAT	GO:0071310 cellular response to organic substance	261	1.01E-95
GOTERM_BP_FAT	GO:0008283 cell proliferation	241	3.58E-94
GOTERM_BP_FAT	GO:1901700 response to oxygen-containing compound	215	1.48E-92
GOTERM_CC_FAT	GO:0005615 extracellular space	190	1.87E-63
GOTERM_CC_FAT	GO:0005576 extracellular region	305	2.15E-39
GOTERM_CC_FAT	GO:0009986 cell surface	110	5.22E-38
GOTERM_CC_FAT	GO:0044421 extracellular region part	265	1.70E-34
GOTERM_CC_FAT	GO:0009897 external side of plasma membrane	48	6.97E-22
GOTERM_CC_FAT	GO:0098552 side of membrane	62	2.16E-20
GOTERM_MF_FAT	GO:0005102 receptor binding	200	8.64E-75
GOTERM_MF_FAT	GO:0005126 cytokine receptor binding	76	3.76E-48
GOTERM_MF_FAT	GO:0005125 cytokine activity	60	5.29E-37
GOTERM_MF_FAT	GO:0008083 growth factor activity	41	4.88E-24
GOTERM_MF_FAT	GO:0042802 identical protein binding	111	2.24E-19
GOTERM_MF_FAT	GO:0019899 enzyme binding	130	1.57E-18

Abbreviation: EM, endometriosis.

GeneCodis for enrichment analysis of the genes related to EMT-induced infertility. We put the genes obtained in the text mining step into the input set, and perform GO analysis on these. GO terms reflect genetic knowledge about the biological process (BP), cellular components (CC) and molecular function (MF) [20,21]. And then, this study selected the most significantly enriched biological processes. Genes with the selected annotations were performed for the next step and annotations of the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathways. Moreover, the Kyoto Encyclopedia of Genes and Genomes (KEGG) [22]. It provides data resources of known biological pathways to annotate a set of genes.

2.3 Protein Interaction Network

The STRING database (http://stringdb.org) integrates the protein-protein interactions of selected genes [23]. On the first page of the STRING database, we selected 'Multiple proteins' from the left menu bar, entered the genes chosen from the last step, and 'Homo sapiens' was selected as the organism. Regarding the confidence score, the stronger the evidence that two proteins interact with each other is, the higher the confidence scores observed. In this study, the confidence score is determined to medium (score 0.400). Although a lower confidence score may decrease the network's confidence, it may increase the inclusion criteria. Then, the protein-protein interaction network of the target gene is obtained. After that, PPI networks were built by using the Cytoscape software [24]. The plug-in Molecular Complex Detection (MCODE) built-in Cytoscape was used to select the significant gene modules of the PPI networks. The parameters were set as follows: MCODE scores >3 and the count of nodes >4. Finally, we selected one significant gene modules (including 40 genes) from the PPI networks for further validation analyses.

2.4 Drug-gene Interactions

We used DGIdb (http://www.dgidb.org), which aggregates drug-gene interaction data from 27 sources including DrugBank, PharmGKB, ChEMBL, NCBI Entrez, Ensembl, PubChem, various clinical trial databases, and literature available through NCBI PubMed to explore drug-gene interactions in the final list of genes, which were applied to find the potential targets in a search for ready-made drugs or small organic compounds [25].

3. Results

3.1 Results of Text Mining, Biological Process and Pathway Analysis

In exploring potential drugs for EMT-induced infertility, 550 genes were found to be related to EMT-induced infertility from the text mining searches.

We uploaded DEGs to the online website GeneCodis to identify GO Terms and KEGG pathways and classified them into three functional categories: biological process (BP), cellular component (CC), and molecular function (MF; Fig. 1). During this process, to ensure that only the most enriched annotations were chosen, a *p*-value cutoff (*p* = 1.00E-06) was set. As shown in Fig. 1A and Table 1, GO analysis showed that the DEGs were most significantly enriched in response to the organic substance. Moreover, the upregulated DEGs were significantly enriched in biological process, including muscle system process, muscle contraction, and regulation of muscle contraction (Fig. 1A and Ta-

Table 2. Signaling Pathway Enrichment Analysis of involved in EM-induced infertility.

Category	Term	Count	*p* value
KEGG_PATHWAY	bta04060:Cytokine-cytokine receptor interaction	65	2.41E-32
	bta05200:Pathways in cancer	74	6.92E-23
	bta05205:Proteoglycans in cancer	51	1.45E-21
	bta05323:Rheumatoid arthritis	33	1.60E-18
	bta05161:Hepatitis B	39	2.95E-17
	bta04151:PI3K-Akt signaling pathway	60	6.44E-17
	bta04668:TNF signaling pathway	33	1.14E-16
	bta05142:Chagas disease (American trypanosomiasis)	33	7.56E-16
	bta04066:HIF-1 signaling pathway	29	1.74E-14
	bta05321:Inflammatory bowel disease (IBD)	24	2.40E-13
	bta04068:FoxO signaling pathway	32	4.42E-13
	bta05144:Malaria	21	4.53E-13
	bta05133:Pertussis	24	2.34E-12
	bta05140:Leishmaniasis	23	3.11E-12
	bta04630:Jak-STAT signaling pathway	33	3.67E-12
	bta05212:Pancreatic cancer	22	3.94E-12
	bta05206:MicroRNAs in cancer	42	1.63E-11
	bta05152:Tuberculosis	34	1.23E-10

ble 2); Among the most significantly enriched GO Terms above the cutoff, those most relevant to EMT-induced infertility based on the available literature and research were selected. Therefore, the six most enriched biological process annotations were: (i) 'response to organic substance' (p = 3.90E-127); (ii) 'cellular response to chemical stimulus' (p = 1.29E-112); (iii) 'regulation of cell proliferation' (p = 1.43E-98); (iv) 'cellular response to organic substance' (p = 1.01E-95); (v) 'cell proliferation' (p = 3.58E-94); and (vi) 'response to oxygen-containing compound' (p = 1.48E-92), containing 328, 304, 227, 261, 241 and 215 genes from the query set, respectively. And the six most enriched cellular component annotations were: (i) 'extracellular space' (p = 1.87E-63); (ii) 'extracellular region' (p = 2.15E-39); (iii) 'cell surface' (p = 5.22E-38); (iv) 'extracellular region part' (p = 1.70E-34); (v) 'external side of plasma membrane' (p = 6.97E-22); and (vi) 'side of membrane' (p = 2.16E-20), containing190, 305, 110, 265, 48 and 62 genes from the query set, respectively. What is more, the six most enriched molecular function annotations were: (i) 'receptor binding' (p = 8.64E-75); (ii) 'cytokine receptor binding' (p = 3.76E-48); (iii) 'cytokine activity' (p = 5.29E-37); (iv) 'growth factor activity' (p = 4.88E-24); (v) 'identical protein binding' (p = 2.24E-19); and (vi) 'enzyme binding' (p = 1.57E-18), containing 200, 76, 60, 41, 111 and 130 genes from the query set, respectively.

In the process of KEGG pathway enrichment analysis, those most relevant to EMT-induced infertility based on the available literature and research were selected. The analysis of enriched pathway annotations resulted in 18 pathways containing a total of 74 unique genes (Table 2). The six most significantly enriched pathways were: (i) 'cytokine-cytokine receptor interaction' (p = 2.41E-32); (ii) 'pathways in cancer' (p = 6.92E-23); and (iii) 'proteoglycans in cancer' (p = 1.45E-21), (iv) 'rheumatoid arthritis' (p = 1.60E-18); (v) 'hepatitis B' (p = 2.95E-17); and (vi) 'PI3K-Akt signaling pathway' (p = 6.44E-17), containing 65, 74, 51, 33 ,39 and 60 genes from the query set, respectively.

3.2 Results of Protein-Protein Interaction

The protein-protein interaction network of the 452 target genes was illustrated based on the STRING online database (http://string-db.org) and Cytoscape software (Version 3.7.1) (Fig. 2). PPI network complexly contained 452 nodes and 2758 edges (Fig. 2A). Finally, 39 genes were selected to form a strong interaction network based on the MCODE. The significant module (39 nodes 384 edges, Fig. 2B) from the PPI network was selected, as determined by Cytoscape. The 39 genes included CXCR3, NPY, BMP4, IGFBP1, APOA1, IL6, PROC, APOE, POMC, TIMP1, AHSG, CXCL8, CX3CR1, TF, CXCL1, F5, DRD2, CCL5, GPER1, AFP, AGTR2, CXCL10, CXCL11, CXCL12, CCR5, CASR, SPP1, ALB, CCL19, CCL25, CCL21, C3, CCL20, AGT, LGALS1, MSLN, CSF1, BMP15 and MFGE8.

3.3 Results of Drug-Gene Interactions

They used the final list of 39 genes as the potential targets in the drug-gene interaction analysis, a list of 49 drugs meeting the standard requirements for drug treatments for EMT-induced infertility (Table 3). They included: Acepromazine, Acetophenazine, Alizapride, Amantadine hydrochloride, Amisulpride, Apomorphine, Aripiprazole, Bifeprunox, Brexpiprazole, Cabergoline, Cinacalcet, Clozapine, Haloperidol, Iloperidone, Levodopa, Levomepromazine, Lisuride, Loxapine, Mar-

Table 3. Candidate drugs targeting genes with EM-induced infertility.

Number	Drug	Gene	Drug-gene interaction	Score*	Approved?	Approved FDA	Reference (PubMed ID)
1	Acepromazine	DRD2	antagonist	7	Yes	Yes	15694263
2	Acetophenazine	DRD2	antagonist	9	Yes	Yes	6147851
3	Alizapride	DRD2	antagonist	5	Yes	No	7865862
4	Amantadine hydrochloride	DRD2	agonist	5	Yes	No	10443547
5	Amisulpride	DRD2	antagonist	8	Yes	No	12404702
6	Apomorphine	DRD2	agonist	12	Investigational	Yes	11343576
7	Aripiprazole	DRD2	antagonist	12	Yes	Yes	9083792
8	Bifeprunox	DRD2	agonist	6	Investigational	No	17393144
9	Brexpiprazole	DRD2	agonist	5	Yes	No	24947465
10	Cabergoline	DRD2	agonist	14	Yes	Yes	12721865
11	Cinacalcet	CASR	agonist	15	Yes	Yes	19261825
12	Clozapine	DRD2	antagonist	14	Yes	Yes	15781964
13	Dihydromorphine	POMC	agonist	3	Experimental	No	6292632
14	Domperidone	DRD2	antagonist	10	Investigational	No	15894081
15	Droperidol	DRD2	antagonist	8	Yes	Yes	2527092
16	Drotrecogin alfa	F5	inhibitor	13	Investigational	Yes	11893230
17	Fluspirilene	DRD2	antagonist	9	Yes	Yes	8935801
18	Ginseng	IL6	antagonist	3	Yes	/	17436372
19	Haloperidol	DRD2	antagonist	7	Yes	Yes	12887421
20	Iloperidone	DRD2	antagonist	7	Yes	Yes	12861482
21	Levodopa	DRD2	agonist	10	Yes	Yes	11978145
22	Levomepromazine	DRD2	antagonist	5	Yes	No	2870716
23	Lisuride	DRD2	agonist	6	Yes	No	18691132
24	Loxapine	DRD2	antagonist	13	Yes	Yes	9570468
25	Maraviroc	CCR5	antagonist	13	Yes	Yes	16298345
26	Menadione	PROC	activator	8	Yes	Yes	17215245
27	Mesoridazine	DRD2	antagonist	8	Yes	Yes	15357957
28	Minaprine	DRD2	agonist	5	Yes	No	17139284
29	Olanzapine	DRD2	antagonist	15	Yes	Yes	14575800
30	Paliperidone	DRD2	antagonist	12	Yes	Yes	11132243
31	Perphenazine	DRD2	antagonist	12	Yes	Yes	2573104
32	Pimozide	DRD2	antagonist	14	Yes	Yes	8301582
33	Pipotiazine	DRD2	antagonist	9	Yes	/	15694263
34	Promazine	DRD2	antagonist	6	Yes	Yes	17139284
35	Propiomazine	DRD2	antagonist	5	Yes	Yes	17139284
36	Remoxipride	DRD2	antagonist	7	Yes	No	8665533
37	Risperidone	DRD2	antagonist	13	Investigational	Yes	17059881
38	Rivanicline	CXCL8	antagonist	2	Investigational	No	16715250
39	Ropinirole	DRD2	agonist	11	Investigational	Yes	10446316
40	Rotigotine	DRD2	agonist	7	Yes	Yes	18691132
41	Siltuximab	IL6	inhibitor	4	Yes	Yes	8823310
42	Sodium tetradecyl sulfate	PROC	inhibitor	5	Yes	Yes	11752352
43	Tasosartan	AGTR2	antagonist	2	Yes	No	11683476
44	Thioproperazine	DRD2	antagonist	7	Yes	No	15694263
45	Thiothixene	DRD2	antagonist	9	Yes	Yes	15694263
46	Tinzaparin sodium	CXCL12	binder	2	Yes	Yes	18991783
47	Trifluprom azine	DRD2	antagonist	6	Yes	Yes	17139284
48	Velcalcetide	CASR	agonist	4	Investigational	No	24235081
49	Zuclopenthixol	DRD2	antagonist	8	Yes	Yes	17535043

Each individual instance of a drug-gene interaction was evaluated in the context of the gene's relationship to EMT-induced infertility and the drug's relationship to the gene, thus ensuring any putative drug would be expected to have the desired directional effect on the condition. Drugs and compounds which met the criteria of targeting one of the candidate genes by an appropriate interaction were collected in a final list.

*The score is the combined number of database sources and PubMed references supporting a given interaction.

aviroc, Menadione, Mesoridazine, Minaprine, Olanzapine, Paliperidone, Perphenazine, Pimozide, Pipotiazine, Promazine, Propiomazine, Remoxipride, Risperidone, Rivanicline, Ropinirole, Rotigotine, Siltuximab, Sodium tetradecyl sulfate, Tasosartan, Thioproperazine, Thiothixene, Tinzaparin sodium, Trifluprom azine, Velcalcetide and Zuclopenthixol.

Potential gene targets of the drugs in this list are DRD2 (37 drugs), PROC, IL6 and CASR (2 drugs each), POMC, F5, CXCL8, CXCL12, CCR5and AGTR2 (1 drug each). Common previously approved uses for these drugs include the treatment of hemostasis, nausea, vomit, mental disease, chronic kidney disease, Parkinson's disease, and Alzheimer's disease. A total of 25 drugs on the list are used for anti-mental disease therapy. Next, we verified whether the drugs identified by our analysis could target pathways associated with EMT-induced infertility.

4. Discussion

Our purposes were to explore the potential drugs through silico text-mining and pathway analysis tools to identify existing drugs with the potential for topical administration and treatment with patients with EMT-induced infertility. The cause by EMT-induced infertility may be the following reasons: (1) Changes in the normal anatomy of the pelvic cavity cause obstruction of the fallopian tubes, which affects conception. (2) abnormal immune function and autoimmune response, such as the cytokines, including IL-6, IL-8 and VEGF, Iwabe *et al.* [26] found that IL-6 may promote the formation of autoantibodies and has embryotoxicity and inhibits early embryo implantation, which can cause EMT-induced infertility. (3) endocrine abnormalities: including ovarian hormone abnormalities and insufficient luteal function. Currently, the treatment of EMT-induced infertility is mainly anticipatory, drug treatment, surgical treatment, combined drug and surgical treatment and assisted reproductive technology treatments. Now, the drugs used for treatment are OC, drugs that inhibit the gonadal axis from antagonizing sex hormones, including mifepristone, danazol, gestrinone capsules and Gonadotropin-releasing hormone agonists and medicines that promote ovulation. De Ziegler *et al.* [27] found that using OC 6–8 weeks before assisted reproduction can also increase the pregnancy rate of assisted reproductive technology. Clinical studies have proved that mifepristone is effective in treating EMT-induced infertility [28].

A Cochrane study of 16 cases of preoperative and post-operative use of hormonal drugs to treat EMT-induced infertility, there is insufficient evidence that the drug can improve pregnancy rates [29]. Therefore, it is particularly important to find other safe and effective therapeutic drugs to treat EMT-induced infertility. In this study, we identified 39 genes following the gene set enrichment analysis representing a network (Fig. 2) targetable by the 49 drugs, all of which have not yet been tested for EMT-induced infertility (Table 3). The majority of potential drugs identified by the drug-gene interaction search are known to target dopamine receptor D2 (DRD2). These drugs belong to treat mental disease. Besides, it also includes some drugs that target inflammatory factors, such as IL-6, CXCL8 and CXCL12.

It is reported that DRD2 is the main receptor for most antipsychotic drugs. Numerous documents have shown that DRD2 is essential for learning and memory, especially in the prefrontal cortex [30]. Activating DRD2 will also enable the corresponding downstream pathways, thereby mediating a series of downstream signaling effects such as the inhibition of inflammation and apoptosis [31]. Many scholars have pointed out that in various diseases, such as inflammatory bowel disease [32], luteinizing granular cells [33], and lung cancer [34], dopamine inhibit VEGF-mediated vascular permeability and angiogenesis through DRD2 to treat diseases or inhibit tumors. The possible mechanism is that dopamine can inhibit VEGF-mediated microvascular permeability and endothelial cell proliferation and migration [35]. Some scholars also pointed out that dopamine can block VEGF-induced focal adhesion kinase (FAK) and mitogen-activated protein kinase (MAPK) phosphorylation in endothelial cells [36]. Angiogenesis is of great significance to the formation of ectopic intima, and many factors regulate it. As we knew, endothelial growth factor (VEGF) is one of the most important factors in angiogenesis. The expression of VEGF in the peritoneal fluid, ectopic endometrium, and eutopic endometrium of patients with endometriosis was significantly higher than in the control group. Based on this, it can be considered that the high expression of VEGF in patients with EMs indicates that it promotes angiogenesis in the disease. And it plays an important role in occurrence and development in EMT [37]. Therefore, we suspect that DRD2 may be involved in the incident and development of EMT through VEGF.

Besides, the recruitment of inflammatory cells and the production of inflammatory factors, such as IL-6 and IL-8, play a key role in the formation of EMT. IL-6 mainly promotes cell growth, stimulates cell differentiation, and participates in acute inflammation. It induces local adhesion, fibrosis and immunological abnormalities in the pelvic cavity by mediating immune and inflammatory reactions, and promotes the formation and development of EMT [38]. What is more, it can increase the toxicity of early embryos and cause infertility [26]. IL-8 has angiogenic activity, increases the formation of microvessels in the abdominal cavity, and increases the acceptance of endometrial implants. It can promote the proliferation and adhesion of endometrial cells, leading to pelvic adhesion and fibrosis [39]. It can also increase the activity and infiltration capacity of matrix metallo proteinases (MMP) in endometrial stromal cells. It is a proteolytic enzyme that regulates the degradation and reconstruction of the extracellular matrix. It can make the endometrial fragments that flow back into the abdominal cavity with menstrual blood have a strong planting inva-

sive ability plays an important role in the pathogenesis of EMT [40].

This study has the following limitations: (1) The database used in the research may have limited information on the annotation of gene functions or pathways. The services or effects of some genes cannot be verified through experiments; (2) For a given drug, not all existing gene interactions are known. Therefore, potentially useful drugs for EMT-induced infertility may be missed or ignored. The gene interaction may not have been fully elucidated, or the drug-gene interaction is suspected of producing harmful effects. (3) all the results were based on online bioinformatics databases, and as such require validation experiments. (4) some of the drugs highlighted as possibly relevant may be toxic and as such safely data is required before any experiments are undertaken in humans.

5. Conclusions

In conclusion, we have reported a method that has founded the panel of candidate drugs that target the genes/pathways relevant to EMT-induced infertility. With the development and improvement of databases and analysis tools, such a method can be used regularly. Therefore, through this analysis, we have identified 49 drugs, which have not been used in EMT-induced infertility, which provides a basis for new trials and the development of novel targeted therapies as potential treatments for EMT-induced infertility.

Author Contributions

YYL, WZC and PJH designed the research study. NJF, JYQ and LX analyzed the data. YYL, WZC and PJH wrote the manuscript. LC and HL reviewed relevant literature and revised the manuscript. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics Approval and Consent to Participate

The article does not contain any studies with human participant or animal performed by any of the authors. This study was approved by the Ethics Committee of Fujian Provincial Maternity and Children Hospital (FMCH2018-155) and complied with the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

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