The use of the Heter-LP algorithm to reposition antibiotics for managing E. coli mastitis in dairy cattle

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Research article

Keywords: Drug repositioning, Drug target, E. coli mastitis, Gene regulator, Heter-LP algorithm, semi-supervised learning

Posted Date: July 17th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-36172/v1

Abstract

Mastitis, a disease with high incidence worldwide, is the most prevalent and costly disease in the dairy industry. Environmental mastitis pathogens, such as Escherichia coli (*E. coli*), are major etiological agents of bovine mastitis in well-managed dairy farms. However, there is still a need to develop more efficient, safe, and economical treatments for mastitis. In the current research, Heter-LP, a new system biology-based method of drug repositioning, was applied to potentially identify novel therapeutic avenues for the treatment of *E. coli* mastitis. On-line data repositories relevant to known diseases, drugs, and gene targets along with other specialized biological information for *E. coli* mastitis, including key genes with robust bio-signatures, drugs and related diseases were used as input data for analysis with the Heter-LP algorithm. Our analyses identified novel drugs such as Glibenclamide, Ipratropium, Salbutamol, and Carbidopa as possible therapeutics that could be used against *E. coli* mastitis. Predicted relationships can be used by pharmaceutical scientists or veterinarians to find commercially efficacious medicines or combination of two or more active compounds to treat mastitis.

1. Introduction

Clinical mastitis, an ongoing problem for dairy producers, results in considerable economic losses and has led to increased risk of culling and death in dairy cows [4–6]. Mastitis control programs with impact on prevalence of contagious mastitis pathogens, led to a reduction in the incidence of *Staphylococcus aureus* and *Streptococcus agalactiae* mastitis, and as a result the increase in the relative impact of environmental mastitis pathogens such as *Escherichia coli* (*E. coli)* [6–9]. *E. coli* infection can cause either subclinical infection of the mammary gland or a severe systemic disease. Although, intramammary *E. coli* infections with acute inflammation may be self-healing by spontaneously eradicated by host defenses, however in extreme case it can be fatal [6, 10–12]. Unfortunately, self-care is often associated with significant economic damage due to the longer duration of infection, lower milk yield, and the potential for pathological changes to the mammary gland [6, 13]. The rate of clearance of bacterial pathogens that may be goverend by mammary gland responses within hours of initial infection, is a key determinant of the outcome of intra-mammary gland infection [6, 14].

The therapeutic success of bovine mastitis depends mainly on accurate diagnosis of kind of pathogen, it will contribute to improvement of clinical and microbiological efficacy and helps to prevent of emergence and spread of resistant microorganisms. Despite the development prospects for bovine mastitis diagnosis with a focus on specific pathogens at an early stage fast together with the efficient devices can offer a “cow-side” and “on-site” with high sensitivity and specificity [1, 6, 15–17]; the most efficient, safe, and economical treatments for mastitis are still topics of scientific debate [6, 18, 19]. Generally, narrow and/or broad spectrum antibiotics are generally used for the treatment of *E. coli* mastitis, but treatment studies have shown controversial results. Given the problems associated with antibiotic therapy, including emergence of antibiotic-resistant strains, and the concern about antibiotics entering the food chain, efforts are being made to substitute the alternative strategies for new antimicrobial agents including bacteriophage, vaccination, nanoparticles, cytokines, homeopathy, natural compounds from

plants, animals, and bacteria or the discovery of new drugs that are effective against mastitis pathogens [6, 20–22].

Novel computational systems biology tools, such as meta-analysis, the pathways analysis, data mining and machine learning have provided good opportunities to understand the molecular mechanisms associated with diseases [23–27]. Currently, the first step to drug development is the use of previously known drugs; this is known as drug repositioning. This approach has attracted a lot of interest in recent years because of the increased speed of this process, drug safety concerns, and its lower cost. The integration of drug, disease and gene target information, in addition to how they affect and function in the body, can have a significant impact on drug repositioning and the possible identification of disease treatments.

The primary goal of this research was to identify some drugs that might be used for the treatment of *E. coli* mastitis (most prevalent agent in clinical cases). We used a recently introduced computational approach to facilitate drug repositioning, called Heter-LP [3]. Heter-LP is a systems biology approaches that integrate different types of data at different levels. Its ability to detect drug-disease relation has been proven by various analyses [3]. Heter-LP was selected because of some more of its advantages such as accuracy, no need to negative samples, its ability to predict trivial and non-trivial relationships between drugs, diseases and protein targets, and also its ability to use heterogenous data. Data resources in the public repository relevant to diseases, drugs, and gene targets along with other specialize biological information for *E. coli* mastitis were used as input data network to Heter-LP algorithm. Key genes with robust bio-signatures achieved from our recent meta-analysis work, related disease constructed by Pathway Studio web tool and drugs extracted from the literature review were used as complementary biological information to add to dataset gathered from the public repository.

2. Material And Methods

Our approach consisted of two steps. The first step was to construct a heterogeneous network by using input data including different kinds of nodes and edges. There were three types of nodes in the proposed heterogeneous network: targets, drugs and diseases. There were six different kinds of edges with represented one type of similarity or association: target similarity, drug similarity, disease similarity, known drug–target interaction, known drug-disease association, and known disease-target interaction. Then, at the second step, we tried to predict important links which were not identified in the input data by using of Heter-LP. As we used the Heter-LP for the second step, we had to arrange our network (step 1) according to its input structures, which consisted of six separate matrices: (1) drug similarities, (2) disease similarities, (3) targets similarities, (4) drug-target relations, (5) disease-target relations and (6) drug-disease relations [3].

We tried to find a specialized dataset for mastitis to integrate with the aforementioned data. Unfortunately, no dataset is publically available. It seems that all available data and information related to animal diseases, genes targets, and drugs are only embedding in the publication and there are no

comprehensive datasets or repositories for them. Lack of access to this data however did not negatively impact the current analysis because of the generality of the input datasets due to the similarity of this disease in humans and other animals. To specialize the results for *E. coli* mastitis we added three parts of information to our generated datasets (cases 2 to 4 in the following).

Based on the above descriptions, data sets that were used to construct the input data network for Heter-LP algorithm included:

1. Previously known drugs information gathered by public repositories.
2. Key genes that had a robust bio-signature in response to mastitis specially in *E. coli* infection. These genes are the results of our recent research findings based on meta-analyses to detect up/down regulated genes by utilizing machine learning algorithms [1] and network analysis [2, 28],
3. Functionally related diseases or biological processes related to bovine mastitis illustrated by Pathway Studio web tool.
4. Relevant drugs and antibiotics to *E. coli* mastitis gathered by literature analysis.

Finally, by the integration of these data a heterogeneous network is constructed and used as input for the Heter-LP algorithm.

A brief description and the data preparation methods of each part are presented in next subsections (Fig. 1). Different parts of this workflow were described in its caption and in more details in sub-Sect. 2.1 to 2.5.

2.1 Previously known drugs information

As mentioned before six different kinds of data including (1) Drug similarity, (2) Disease similarity, (3) Target similarity, (4) Known drug-disease associations, (5) Known drug–target interactions, and (6) Known disease-target associations, were necessary as input data to develop the network for Heter-LP. The base of these data was gathered previously [3], from some important databases. The data resources are summarized in the Table 1. In order to have an updated version of these data, the last version of data resources to generate the six matrices are provided according to the methods described at GitHub (https://github.com/MLotfiSH/Heter-LP) and DKR site (http://dkr.iut.ac.ir/projects) and in detail in our previously published research [3].

Table 1
Resources of data related to each sub-network and the number of nodes in each one.

Sub-network	Using criterion	Resource	Number of nodes	
			In each resource	In total
Drugs	Chemical substructures similarities	PubChem[1]	1103	5089
	Side effect similarities	SIDER[2]	888	
	Anatomical Therapeutic Chemical (ATC) code similarities	KEGG[3]	4867	
Diseases	Disease genes similarities	DisGeNET[4]	3295	9886
	The similarity based on ICD-10 classification[5]	KEGG	1366	
	Semantic similarity based on Disease Ontology (DO)[6]	DOSE[7] package in R	6560	
	Semantic similarities based on GO[8]	GOSemSim[9] package in R	1550	
Targets	Semantic similarities based on HPO[10]	HPOSim[11] package in R	979	2940
	Semantic similarities based on DO	DOSE package in R	1092	
	Similarities based on KEGG	KEGG	1132	
Drug-disease		Therapeutic Target Database (TTD)[12]	Drugs: 6931	Drugs: 7382
			Diseases: 1418	
		KEGG	Drugs: 1052	Diseases: 1970
			Diseases: 592	
Drug-target		DrugBank[13]	Drugs:1521	Drugs:3350
			Targets:1346	
		KEGG	Drugs:2440	Targets:1415
			Targets:335	
Disease-target		DiGeNet	Diseases:577	Diseases:1838
			Targets:2403	

	KEGG	Diseases:1271	Targets:4066
		Targets:2563	

[1] https://pubchem.ncbi.nlm.nih.gov/score_matrix/score_matrix.cgi

[2] http://sideeffects.embl.de/

[3] Kyoto Encyclopedia of Genes and Genomes ((http://www.kegg.jp)

[4] http://www.disgenet.org

[5] International Statistical Classification of Diseases and Related Health Problems-10

[6] http://disease-ontology.org/

[7] Disease Ontology Semantic and Enrichment analysis (https://bioconductor.org/packages/release/bioc/html/DOSE.html)

[8] Gene Ontology (http://www.geneontology.org/)

[9] https://bioconductor.org/packages/release/bioc/html/GOSemSim.html

[10] Human Phenotype Ontology, https://hpo.jax.org/ (http://human-phenotype-ontology.github.io/)

[11] https://mran.microsoft.com/snapshot/2014-10-20/web/packages/HPOSim/index.html

[12] http://bidd.nus.edu.sg/group/cjttd/

[13] http://drugbank.ca

2.2 Disease genes

Previously we identify differentially expressed genes in response to *E. coli* mastitis [1, 2, 28]. These genes have a robust bio-signature and thereby may be useful biomarker or therapeutic target candidates in mastitis [1, 2]. These genes/proteins are listed in Table 2 and added to the disease-gene relation part of the dataset shown in Table 1.

Table 2

The key genes or regulators with robust bio-signature in response to *E. coli* mastitis reported to our previous meta-analysis based microarray studies [1, 2]

Row	Gene symbol	Functional group	Gene name (alias)
1	*CXCL2*	Ligand	*Chemokine (C-X-C motif) ligand 2 (GRO3)*
2	*CXCL8*	Ligand	*C-X-C motif chemokine ligand 8 (IL-8, IL8)*
3	*GRO1*	Ligand	*Chemokine (C-X-C motif) ligand 1 (CXCL1, MGSA)*
4	*CFB*		*Complement factor B (BF)*
5	*ZC3H12A*		*Zinc finger CCCH-type containing 12A*
6	*CCL20*	Ligand	*C-C motif chemokine ligand 20*
7	*NFKBIZ*		*NFKB inhibitor zeta (MAIL)*
8	*S100A9*	Ligand	*S100 calcium binding protein A9*
9	*S100A8*	Ligand	*S100 calcium binding protein A8*
10	*PDE4B*		*Phosphodiesterase 4B*
11	*CASP4*		*Caspase 4, apoptosis-related cysteine peptidase (CASP13)*
12	*HP*	Ligand	*Haptoglobin*
13	*MAPK1*	Protein kinase	Mitogen-activated protein kinase
14	*TP53 (p53)*	Transcription factor	Tumor protein p53
15	*SP1*	Transcription factor	Sp1 transcription factor
16	*MAPK14*	Protein kinase	Mitogen-activated protein kinase 14
17	*INS*	Ligand	Insulin
18	*EGF*	Ligand	Epidermal growth factor
19	*AKT1*	Protein kinase	AKT serine/threonine kinase 1
20	*IFNG*	Ligand	Interferon gamma
21	*MAPK3*	Protein kinase	Mitogen-activated protein kinase 3
22	*MAPK8*	Protein kinase	Mitogen-activated protein kinase 8
23	*VEGFA*	Ligand	Vascular endothelial growth factor A
24	*MMP2*		Matrix metallopeptidase 2

Row	Gene symbol	Functional group	Gene name (alias)
25	*BCL2*		BCL2, apoptosis regulator
26	*IL10*	Ligand	Interleukin 10

2.3 Disease similarity data

One of the problems that arises when examining diseases is the use of different names or identifiers for the same disease. In the case of the disease in the current research, bovine mastitis was used for dairy cattle, and mastitis was used for human and other mammals in the literature. The Pathway Studio web tool 12.0.1.5 was used to construct a network of disease or cell processes that were functionally associated with mastitis or bovine mastitis. Pathway Studio as a pathway analysis tool incorporates some commercial and public databases such as BIND [29], KEGG [30], and GO [30] that utilizes the ResNet Mammal database. Moreover, it also uses the powerful text-mining tool MedScan to seek the latest information from PubMed and other public sources (Elsevier-Ariadne Genomics, Rockville, MD) [31]. For more confidence, all relationships which were reported by more than two references were selected. All relations between mastitis or bovine mastitis with other diseases or cell process are indicated in Table 3. Additional details and references are provided in Additional file 1. As shown, most of the cases related to mastitis or bovine mastitis are the same and demonstrated the similarity of this disease in all mammals. This information has been added to disease similarity part of dataset shown in Table 1.

Table 3
Known disease or cell process related to mastitis or bovine mastitis by using Pathway Studio web tool (based on at list two references)

		Related disease to mastitis or Bovine mastitis		Related disease to mastitis (continue)		Related disease to mastitis (continue)
1	Bovine mastitis	bacterial infection	34	injury	67	innate immune response
2		cellular immune response	35	metabolic disorder	68	ketosis
3		cryptococcosis	36	obesity	69	lactation
4		Escherichia coli infection	37	pain	70	life span
5		fever	38	sepsis	71	lipid degradation
6		fibrosis	39	skin disease	72	lupus erythematosus profundus
7		infection	40	swelling	73	maedi
8		inflammation	41	systemic lupus erythematosus	74	milk production
9		inflammatory disease	42	tuberculosis	75	MRSA infection
10		protothecosis	43	type 1 diabetes	76	mumps
11		staphylococcal infection	44	apoptosis	77	neoplasm
12		milk production	45	breast cancer	78	neutrophil recruitment
13	Mastitis	abscess	46	breast pain	79	nipple discharge
14		angiogenesis	47	breast-feeding	80	ovarian follicle development
15		autoimmune disease	48	contagious agalactia	81	ovary function
16		bacterial infection	49	diabetes mellitus	82	ovulation
17		benign breast disease	50	endemic disease	83	parity
18		breast abscess	51	energy homeostasis	84	parturient paresis

	Related disease to mastitis or Bovine mastitis		Related disease to mastitis (continue)		Related disease to mastitis (continue)
19	cancer	52	fat necrosis	85	parturition
20	candidiasis	53	fatty liver	86	pregnancy
21	cattle disease	54	fertilization	87	proteolysis
22	cell count	55	fibrosis	88	pseudotuberculosis
23	death	56	galactorrhea	89	respiratory tract infection
24	edema	57	Gram-negative bacterial infection	90	retained placenta
25	endotoxemia	58	granulomatous mastitis	91	smoking
26	Escherichia coli infection	59	hypocalcemia	92	staphylococcal infection
27	fever	60	IgG4-related disease	93	subfertility
28	hyperemia	61	immune response	94	virulence
29	immunity	62	immune system activation	95	virus infection
30	immunopathology	63	immune system function	96	weaning
31	infection	64	inbreeding	97	wounds and injuries
32	inflammation	65	infectious disease		
33	inflammatory disease	66	inflammatory response		

2.4 Drugs disease

With a review of the literature, we were able to develop a comprehensive list of drugs or antibiotics that have been used to treat *E. coli* mastitis (see Table 4). This information has been added to drug-disease relation part of dataset shown in Table 1.

Table 4
List of known drugs or antibiotics reported in literature to treat *E. coli* mastitis

	Drug or Antibiotic	Reference
1	Ampicillin	[32]
2	Aspirin	[33]
3	Ceftazidime	[32]
4	Cephalexin	[32]
5	Cephapirin (Cefoperazone, Ceftiofur, Cefquinome)	[34]
6	Chloramphenicol	[35]
7	Cinoxacin	[36]
8	Ciprofloxacin	[32, 36]
9	Dexamethasone	[37]
10	DHS (dihy- drostreptomycin sesquisulfate sa)	[32]
11	Flunixin meglumine	[38]
12	Fluoroquinolones (enrofloxacin, danofloxacin, marbofloxacin)	[34]
13	Gentamicin	[32, 35]
14	Isoflupredone acetate	[33]
15	Ketoprofen	[32]
16	Meloxicam	[39]
17	Oxytetracycline	[40]
18	Penethamate hydriodide	[39]
19	Polymixin	[41]
20	Prednisolone	[42]
21	Tetracycline	[32]
22	Trimethoprim	[32]
23	Sulfadoxine	[40]
24	Sulfamethoxazole	[35]
25	Sulfadiazine	[32]

2.5 Integration of data

The final heterogeneous network model was constructed by integration of these four mentioned data which were discussed in previous sections. It is necessary to mention that Heter-LP input data could be incoincident in different parts of the heterogeneous network. This means that a complete list of drugs, diseases and proteins/genes (as targets) will be achieved by union of similar typed items in each sub-network.

3. Results

The repositioning of antibiotics for managing *E. coli* mastitis in dairy cattle is the main findings of this study. Based on Heter-LP categorization, there are two kinds of predictions, known and novel [3]. The 30 top predicted drugs and antibiotics associated with *E. coli* mastitis are presented in Table 5. Most of the drugs listed in Table 4 have been reported in literature as treatments for *E. coli* mastitis. These results demonstrate that Heter-LP could identify known relations correctly, which indicates that the novel compounds may be realistic predictions. All predicted results of Heter-LP are presented in Additional file 2.

Table 5
30 top predicted drugs associated with *E. coli* mastitis by the Heter-LP algorithm

	Drug	Ranking Score	Verification
1	Cefoperazone	0.005000691	known drug
2	Meloxicam	0.004998696	known drug
3	Cephapirin	0.003363298	known drug
4	Cephalexin	0.003362269	known drug
5	Oxytetracycline	0.003352667	known drug
6	Cinoxacin	0.003351841	known drug
7	Ketoprofen	0.003350183	known drug
8	Aspirin	0.002526886	known drug
9	Ampicillin	0.001301824	known drug
10	Ceftazidime	0.001164398	known drug
11	Tetracycline	0.001162658	known drug
12	Chloramphenicol	0.000958009	known drug
13	Gentamicin	0.000937666	known drug
14	Ciprofloxacin	0.000680685	known drug
15	Dexamethasone	0.000618516	known drug
16	Prednisolone	0.000513524	known drug
17	Penicillin G	8.63E-05	New drug
18	Leucovorin	8.19E-05	New drug
19	Rifampicin	7.91E-05	New drug
20	Cefprozil	7.87E-05	New drug
21	Ipratropium	7.81E-05	New drug
22	Cefadroxil	7.77E-05	New drug
23	Clidinium	7.66E-05	New drug
24	Lopinavir	7.64E-05	New drug
25	Glibenclamide	7.61E-05	New drug
26	Thyroxine	7.57E-05	New drug

	Drug	Ranking Score	Verification
27	Salbutamol	7.55E-05	New drug
28	Carbidopa	7.51E-05	New drug
29	Benzquinamide	7.50E-05	New drug
30	Diethylpropion	7.49E-05	New drug

4. Discussion

The efficacy of antibiotic and/or anti-inflammatory drugs/compounds in the treatment of mastitis disease is not fully specified. Given the problems associated with antibiotic therapy, including emergence of antibiotic-resistant strains, and the concern about antibiotics entering the food chain, efforts are being made to substitute the alternative strategies for new antimicrobial agents including bacteriophage, vaccination, nanoparticles, cytokines, homeopathy and natural compounds from plants and animals, and bacteria or the discovery of new drugs that are effective against mastitis pathogens [6, 20–22].

While the pharmaceutical industry has explored the use of drug repositioning to identify novel treatments for diseases, this work has been hampered by a lack of a fundamental and systematic approach. In the current research, the biological algorithm Heter-LP was used to reposition antibiotics for managing *E. coli* mastitis in dairy cattle. The utility of Heter-LP, to discover new drug repositioning to rare diseases in human have been explored previously [43]. Data that was available in the public repositories along with other specialize biological information for *E. coli* mastitis including crucial genes, antibiotic or drugs used for treatment of *E. coli* mastitis, and its association with other disease or cell processes were used as input data for the Heter-LP algorithm. By using Heter-LP, we were able to introduce a list of most likely candidate drugs that could be used as therapeutic strategies against the *E. coli* infection. It is noteworthy that these drugs have been suggested among more than 11000 different drugs, which could help to accelerate and facilitate the drug identification process. Certainly, this list of suggested drugs is valubale for pharmaceutical scientists or veterinarians in order to find a commercial and efficacious medicine or combinations of two or more active compounds. In the following, we have tried to validate and confirm most of these new predictions by review of available scientific literature.

Penicillin G (also known as Benzylpenicillin), Rifampicin, Cefprozil and Cefadroxil are antibiotic drugs. Recent research has shown that Rifampicin could be used as a solo medical therapy in humans for chronic mastitis [44]. Cefprozil, a second-generation cephalosporins antibiotic, is approved worldwide strictly for the treatment of mastitis disease in dairy cattle. Cefadroxil, a broad-spectrum cephalosporins, is a first-generation cephalosporin antibacterial drug that is effective against gram-positive and gram-negative bacterial infections. It is the para-hydroxy derivative of cefalexin that is a bactericidal antibiotic and is used in the treatment of mild to moderate susceptible infections. Lipopoly sacharrides on the the outer membrane of the gram-negative bacteria such as *E. coli* are an important barrier that provides protection against toxic compounds, which include antibiotics and host innate immune molecules such

as cationic antimicrobial peptides. These bacteria use a wide variety of mechanisms to resist antimicrobials [45, 46].

Glibenclamide is an antidiabetic drug in a class of medications known as sulfonylureas, closely related to sulfonamide antibiotics. Sulfonamides are also occasionally used to treat septicemia caused by coliform mastitis in dairy cattle [47]. It has been investigated that, effects of inflammation markers (TNFα and NFκB), and activation of cell injury or cell death markers (IgG endocytosis and caspase-3), significantly reducing with glibenclamide [48].

In the case of Ipratropium, it has been shown that partially protect the lungs against inflammation by reducing neutrophilic infiltration. This protective effect is associated with a reduction in the MMP-9 activity, which is known to play an important pro-inflammatory role in the acute inflammatory process [49].

It has been demonstrated that hypothyroidism is associated with signs of low-grade inflammation (raised C-reactive protein levels) which may be elicited by the raised level of triglyceride or be an independent effect of an intracellular hypometabolic state or of a combination of them [50]. Also, other research has shown that l-thyroxine treatment of patients with subclinical hypothyroidism can reduce inflammation [51]

Salbutamol, the other predicted drug listed in Table 5, has been shown to decrease acute and chronic inflammation, decrease myeloperoxidase (MPO) activity and lipid peroxidation (LPO) level and increased the activity of superoxide dismutase (SOD) and level of glutathione (GSH) during the acute phase of inflammation possibly through the stimulation of β-2 adrenergic receptors [52].

Carbidopa has been used as a treatment for Parkinson's disease. New research has demonstrated that it inhibits early events in T cell activation and promotes the development of anti-inflammatory effects. Thus, it has been suggested as apotential therapeutic for the management and/or treatment inflammatory and autoimmune disorders in humans [53].

Based on these results, it can be concluded that the Heter-LP has successfully predicted drugs/compounds that can be used as suitable alternatives for the treatment of *E. coli* mastitis.

5. Conclusions

In the current study, has been shown that the system biology-based algorithm, Heter-LP, can be used to identify repositioned drugs that may be useful for the treatment of important disease. Integration of the biological data and using the Heter-LP algorithm enabled us to introduce novel drugs relevant to *E. coli* mastitis. Our results provide valuable information for pharmaceutical scientists or veterinarians in the dairy industry to find a commercial and efficacious medicine or a combination of two or more active compounds.

Declarations

Ethics approval and consent to participate:

Not applicable

Consent for publication:

Not applicable

Competing interests:

The authors declare that they have no competing interests

Funding:

The authors received no specific funding for this work.

Authors' contributions:

Somayeh Sharifi and Maryam Lotfi Shahreza wrote the main manuscript text, Abbas Pakdel and Esmaeil Ebrahimie are supervisor, James M. Reecy and Nasser Ghadiri are advisors of this manuscript. All authors reviewed the manuscript.

I can confirm I have included a statement regarding data and material availability in the declaration section of my manuscript.

Acknowledgement

We are grateful to Dr. Peng Liu from Iowa State University and Dr. Mahmoud Arabi for their generous help.

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Figures

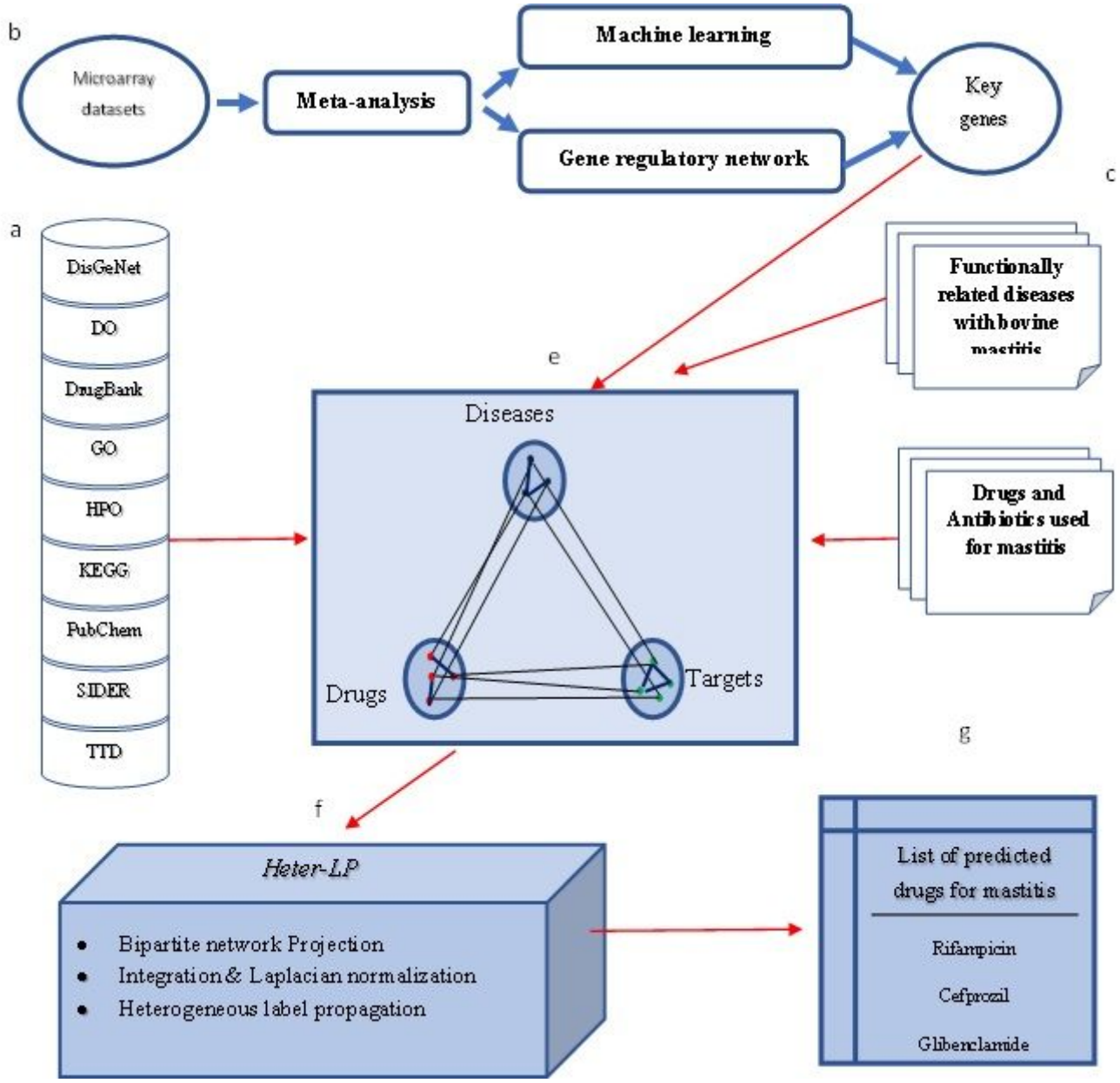

Figure 1

The workflow of this research. (a) Data related to diseases, drugs and their targets are gathered from different data sources (described in sub-section 2.1). (b) Key genes with robust biosignatures and key regulatory effects in response to E. coli mastitis were identified by meta-analysis to identify up-/down-regulated genes followed by the application of machine learning algorithms [1] and conduction of network analyses [2] (described in sub-section 2.2). (c) Functionally related diseases or biological processes to mastitis by using the Pathway Studio web tool. (described in sub-section 2.3). (d) Relevant drugs and antibiotics to E. coli mastitis gathered by literature mining (described in sub-section 2.4) (e) A suitable heterogeneous network model is constructed by integration of achieved data from parts A, B, C, D (described in sub-section 2.5). (f) Running the Heter-LP algorithm [3] on constructed network to predict some more important relations of mastitis. (g) Predicted drugs acording to their score computed by Heter-LP

Supplementary Files

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- Additionalfile2.xlsx
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