

Quorum Sensing-Based Interaction Network Construction for Drugs, Microbes, and Diseases

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Research

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Abstract

Background:

Various diseases and health are closely related to different gut microbes, which own complex interactions with diverse drugs, while the detailed targets for drug-microbe interactions are still limited and investigated separately. Quorum sensing (QS), a potential target for dealing with drug resistant, are yet to be further explored systematically for drug-microbe interactions. Furthermore, many existing studies have reported diverse casual associations among drugs, gut microbes, and diseases, which call for a systematic framework and repository to reveal their intricate interactions.

Results:

In this study, interactions between microbes and more than 8000 drugs have been systematically studied targeting on microbial quorum sensing receptors (LuxR, LasR, TraR, CviR, PqsR, QscR, YenR, SdiA, LsrB, LuxP, CckA) combined docking-based virtual screening technique and *in vitro* experimental validation. We have also illustrated the potential drug-microbe interaction network based on the predicted docking-based results to to have a more comprehensive illustration for the drug-microbe interactions, along with obtaining 14 possible potential broad-spectrum drugs for all of the 11 QS receptors. Furthermore, we have constructed a systematic framework including various connections for drugs, receptors, microbes, and diseases to form a comprehensive repository and network, which can give the QS-based underlying mechanisms for the reported causal associations between drugs and microbes at the phenotypic level. The framework, repository, and network will promote the understanding on personalized medicine and developing potential therapies for diverse diseases.

Conclusions: Taken together, we curated and predicted various interactions carefully for drugs, receptors, microbes, and diseases to form a comprehensive framework, repository, and network for QS-based drug-microbe-disease interactions. This work contributes to the paradigm for the construction of the more comprehensive molecule-receptor-microbe-disease interaction network for human health that may form one of the key knowledge maps of the precision medicine in the future.

Background

The human gut microbiome, a complex and diverse community consisting of a variety of genes in the gut [1], which regulates a variety of important physiological functions of the human body, such as metabolism [2], immunity [3], and host behavior [4]. Although the gut microbiota includes thousands of strains, it is mainly divided into four microbial phyla, namely Firmicutes, Bacteroidetes, Actinobacteria and Proteobacteria [5]. There is growing evidence indicates that the composition of gut microbiome will be influenced by exogenous substances to a large extent, such as drugs [6–8] and diet [9, 10]. It is important to investigate the diverse microbiome-relevant interactions, specifically as it relates to various drugs, while accounting for the significant variability between individuals.

Recently, researchers have reported diverse interactions between various drugs and gut microbiota [11–13]. For example, Jackson et al. [14] developed gut microbiota association analyses between diseases and medications based on 38 common diseases and 51 medications within the human cohort including more than 2700 members. The gut microbiome can directly affect the metabolism for a specific drug by altering the structure of an enzymatic transforming drug and changing its bioavailability, bioactivity or toxicity [15]. Javdan et al. [6] developed a quantitative experimental framework, named as Microbiome-Derived Metabolism (MDM)-Screen, to investigate the variable ability of the human gut microbiome for metabolizing diverse drugs. They found that drug-microbe interactions vary among individuals, indicating that differentiation of microbes should be considered in the process of drug development for personalized medicine [7]. Zimmermann et al. [16] also found that the microbiome in the gut can directly and significantly influence drug metabolism in the gut and throughout the body, resulting in different drug effects by mapping how 76 species of human gut bacteria metabolize 271 drugs. Furthermore, accumulating evidence verified that drugs can also affect the composition and function of the gut microbiota [17]. A recent study conducted by Raju et al. [18] revealed the long-term effects of commonly used antibiotics on the saliva microbiota of children. In all selected children, there were significant differences in the composition of the microbiota after lifetime use of azithromycin. Maier et al. [19] found that 24% of drugs targeting human body had inhibitory effects on microbes, especially antipsychotics, by comparing the effects of 1079 marketed drugs on representative gut symbiotic microbes. Proton pump inhibitors (PPIs), a widely used drug in stomach trouble, have been associated with changes in the composition of the gut microbiome, especially the increase in typically oral bacteria in the gut [20, 21]. The use of metformin, treating type 2 diabetes, has been shown to change the composition of gut microbiota and affect the production of metabolites in the gut microbiota, which in turn will affect the activity of this useful drug [22, 23]. Recent evidence suggests that gut microbiota can interact with anti-cancer drugs, affecting the efficacy and toxic side effects of cancer treatment [24]. By analyzing the gut metagenomic of 26 patients with different types of tumors, Heshiki et al. [25] found that the diversity, composition and function of gut microbiota in patients who responded to treatment were significantly different from those in patients who did not. A method named RapidAIM developed by Li et al. [26] was developed to rapidly determine the effects of drugs on the composition and function of individual microbiome.

In addition to most of the above studies focusing on the association between drugs and gut microbiota, researchers are gradually digging into the underlying mechanisms of these causal associations, such as searching for various human gut microbial targets [27]. For example, targeting quorum sensing (QS) as chemotherapy is one of the vital means to overcome bacterial disease resistance, which is less likely to generate resistance [28]. With QS systems of diverse pathogens being targeted for diverse therapies, more research is gradually focusing on these gut microbial targets to investigate and interpret complex microbial interactions [29]. Accumulating evidence indicates that drug molecules may competitively bind to QS receptors in human gut microbiome, thus blocking the QS regulation process of gut microbiome, and affecting some gut diseases. For instance, Singh et al. [30] found that Albendazole, a FDA approved clinical drug, would interacted with the LasR and CviR (Two typical QS receptors) of *Pseudomonas aeruginosa* and *Chromobacterium violaceum*. Abbas et al. [31] shown that metformin could be used to resist the infection of *P. aeruginosa* by binding to its QS receptor LasR and RhlR. Salicylic acid, nifuroxazide, and chlorzoxazone can also bind to LasR and show significant inhibition of QS-regulated gene expression [32]. In our previous study [33], we developed a pipeline including SMILES-based algorithms and docking-based verification to mine the potential QS interference molecules for typical microbial QS receptors.

While QS targets such as LasR, RhlR, and CviR have demonstrated their potential in binding with various FDA-approved drugs and resisting infections of pathogens, they have largely been investigated separately so far, which may limit our understanding of complex drug-microbe interactions and their scope of diverse applications. Systematic effects of multiple drugs on different microbes are yet to be further explored particularly for human gut microbiota. Besides, existing studies have often focused on the demonstration of casual associations between diverse drugs metabolism, gut microbiome, and various diseases [34–36]. A systematic framework, revealing various interactions among drugs, receptors, microbes, and diseases, are expected to be constructed to promote the understanding on personalized medicine and developing potential therapies for diverse diseases.

In this study, QS-relevant effects of various drugs on multiple microbes have been systematically studied combined docking-based virtual screening technique and *in vitro* experimental validation. We have first collected the existing cases, which have reported the binding of diverse drugs and QS receptors from different strains. We conducted the docking-based calculation for the above cases to decide the cutoff, which formed a basis for predicting potential binding of the other drugs and QS receptors. Then the analysis for docking results was developed by us to investigate the systematic QS-relevant interfering between eleven typical QS receptors (LuxR, LasR, TraR, CviR, PqsR, QscR, YenR, SdiA, LsrB, LuxP, CckA) from diverse microbes and more than 8000 drug molecules from the DrugBank database. Some drugs were validated by the surface plasmon resonance (SPR) experiment *in vitro*. We have also mapped the potential interaction network based on the predicted results between various drugs and QS receptors to have a more comprehensive illustration for various drug-microbe interactions. Furthermore, we have constructed a systematic framework and repository for various drugs, receptors, microbes, and diseases to form one of the key knowledge maps of the human gut microbiota. Overall, this study indicates new implications for drugs targeting gut microbial QS systems to develop novel potential therapies for various gut diseases in precision medicine.

Results

Reported QS-based drug-microbe interactions

Quorum sensing (QS), a means of microbial communication, regulates biological behaviors among microbes by synthesizing and releasing signaling molecules such as acyl-homoserine lactones (AHL), 2-heptyl-3-hydroxy-4-quinolone (PQS), and autoinducer-2 (AI-2) also named as autoinducers, which are received by diverse QS receptors [37]. Note that there are most of the reported QS receptors missing their crystal structures in the Protein Data Bank (PDB), except eleven QS receptors (SmcR, LasR, TraR, CviR, QscR, SdiA, YenR, PqsR, LuxP, LsrB, and CckA) (Table 1). Generally, QS systems including these receptors can be divided into four groups: AHL-type, PQS-type, AI-2-type, and two component system (TCS). TCS is a typical QS system which is consist of a histidine kinase receptor such as CckA and a response regulator partner [38]. As in our previous study [33], we also used the maximum homology SmcR from *Vibrio vulnificus* [39] to represent the common QS receptor LuxR from *Vibrio fischeri*, of which crystal structure is missed. Although hundreds of QS receptors were reported without crystal structures, the homology modeling of them can be also developed based on the above eleven typical QS receptors (Table 1).

Table 1. Details for various QS systems including eleven QS receptors.

QS	Ligand	Receptor	PDB	Binding sites	Organism	Refs
AHL	3OC6HSL	SmcR	3KZ9	Asn133, Gln137	<i>Vibrio vulnificus</i>	[39]
	3OC12HSL	LasR	2UV0	Tyr56, Trp60, Asp73, Thr75, Ser129	<i>Pseudomonas aeruginosa</i>	[40]
	3OC8HSL	TraR	1L3L	Tyr53, Trp57, Asp70	<i>Agrobacterium tumefaciens</i>	[41]
	C6HSL	CviR	3QP1	Tyr80, Trp84, Asp97, Ser155	<i>Chromobacterium violaceum</i>	[42]
	3OC12HSL	QscR	3SZT	Tyr58, Trp62, Asp75, Ser38	<i>Pseudomonas aeruginosa</i>	[43]
	3OC6HSL	SdiA	4Y15	Tyr63, Trp67, Asp80, Ser43	<i>Escherichia coli</i>	[44]
	3OC6HSL	YenR	5L09	Ser32, Try50, Trp54, Asp67	<i>Yersinia enterocolitica</i>	[45]
PQS	PQS	PqsR	4JVD	Ile149, Ile168, Leu207, Ile236, Thr265	<i>Pseudomonas aeruginosa</i>	[46]
AI-2	S-THMF-borate	LuxP	1JX6	Gln77, Ser79, Trp82, Asn159, Arg215, Thr266, Asp267, Trp289, Arg310	<i>Vibrio harveyi</i>	[47]
	R-THMF	LsrB	1TJY	Lys35, Asp116, Asp166, Gln167, Ala222, Pro220	<i>Salmonella typhimurium</i>	[48]
TCS	c-di-GMP	CckA	5IDJ	Tyr514, Lys518, Trp523	<i>Caulobacter crescentus</i>	[38]

We have collected examples of the reported binding of drugs to QS receptors. There are diverse drugs such as metformin, berberine, eugenol, salicylic acid, nifuroxazide, and chlorzoxazone can be bound to the QS receptor LasR [31, 49] [32, 50]. For example, compared with the positive control N-3-oxododecanoyl-homoserine lactone (3OC12HSL), there are highly similar binding sites (Tyr56, Trp60) for the berberine and 3OC12HSL when docking with LasR with AutoDock Vina (Figure 1A). With regard to the binding of drugs and another QS receptor CviR, there are same binding sites from Vina-based docking results (Tyr80) for positive control (N-Hexanoyl-L-Homoserine Lactone, C6HSL) and albendazole (Figure 1B). We conducted an analysis for the distribution of the free binding energies (FBE) of diverse QS receptors and various ligands, including original ligands (Figure 1C) and reported docking-validated drugs (Figure 1D). Combined with our previous study [33], we suggested that “-6 kcal/mol” can be also set as the cutoff to separate the binding and non-binding, which can be used to test the validity of Vina-based docking approach.

The set of the docking cutoff formed a good basis for predicting potential binding of the other drugs and QS receptors. Some other cases [16, 51] showed that drug molecules can influence the abundance of the specific microbe or the relevant pathways without pointing out the specific drug-microbe target. Results from docking-based prediction verified that commonly used drugs, such as proton pump inhibitors (Omeprazole, Esomeprazole, Pantoprazole and Rabeprazole), SSRI antidepressants antibiotics (Fluvoxamine, Fluoxetine, Paroxetine, Sertraline, Escitalopram and Citalopram), have some potential to bind to CckA, LasR, LuxR, PqsR and QscR proteins (Figure 1E). It indicates that various QS receptors may be one type of the important targets for drug-microbe interactions. Furthermore, we found that there is drug crosstalk for different QS receptors (Figure 1F). Taking the eleven common drugs from the reported cases (metformin, chlorzoxazone, eugenol, salicylic acid, nifuroxazide, berberine, indoramine, tiaprofenic acid, donepezil, albendazole, fluvoxamine), we developed a crosstalk investigation for the above 11 drugs and QS receptors (Figure 1F). As a result, drug-microbe interaction predictions illustrated in Figure 1F have been partially verified from other reported researches. For example, the salicylic acid (-6.7 kcal/mol) and tiaprofenic acid (-8.9 kcal/mol) were reported to bind to SdiA from *Salmonella enteritidis* [52]. There is a strongest binding between indoramine and QscR. Tiaprofenic acid has huge potential to bind to the above stated QS receptors except the LsrB. The free binding energies (FBEs) of three drugs (chlorzoxazone, eugenol and salicylic acid) and the eleven QS receptors were relatively close, which indicates the potential drugs crosstalk on different microbes. LsrB and LuxP have stronger specificity than other receptors and have less potential to bind to different drugs.

Predicted QS-based drug-microbe interactions

To have a better understanding for the QS-based drug-microbe interactions at a larger scale, we conducted a docking-based calculation for FBEs distribution of the above 11 QS receptors and more than 8,000 drugs from the DrugBank database (Figure 2). In order to make the FBE

distribution more detailed, we have set -8 kCal/mol, -10 kCal/mol, and -12 kCal/mol as three other cutoffs to rank the docking results in a certain gradient. Results shown that there are the most of drugs not binding to LsrB ($FBE \geq -6$ kCal/mol), followed by LuxP, YenR, CviR, TraR, SdiA, LasR, QscR, LuxR (SmcR), PqsR, and CckA. Most of FBEs are located in the range of -6~-8 kCal/mol, followed by -10~-12 kCal/mol and smaller than -12 kCal/mol (Figure 2A). Excluded the non-binding cases, we have analyzed docking-based results with FBEs smaller than -6 kCal/mol (Figure 2B). There are the least drugs and weakest binding to LsrB receptor, while the most cases and strongest binding to CckA. The FBEs of the strongest cases for LasR, QscR, SdiA and TraR, are all lower than -12 kCal/mol. The above results indicate that there are changeable drug-receptor interaction strengths among different drugs and microbes.

Furthermore, we have analyzed the strongest binding cases for the above 11 QS receptors (Figure 2C). Results shown that, LsrB, LuxP, YenR, TraR, SdiA, LasR, CckA, QscR, LuxR (SmcR), PqsR, and CviR have the corresponding strongest binding with Perflenapent (DB11625), 3-(5-amino-7-hydroxy-(1,2,3)triazolo(4,5-d)pyrimidin-2-yl)benzoic acid (DB01906), Flavone (DB07776), Indirubin (DB12379), alpha-Naphthoflavone (DB07453), Tecovirim (DB12020), 2-({[3-(3,4-dihydroisoquinolin-2(1H)ylsulfonyl) phenyl] carbonyl} amino) benzoic acid (DB07691), 2-aminoquinazoline 5 (DB06925), Phthalocyanine (DB12983), (3S)-1-cyclohexyl-N-(3,5-dichlorophenyl)-5-oxopyrrolidine-3-carboxamide (DB07188), and 3-(4-fluorophenyl)-5-phenyl-4H-1,2,4-triazole (DB08470), respectively. As illustrated in Figure 2D, there is highly similar binding site (Ala222) for the positive control (R-THMF) and Perflenapent when docking with LsrB. With respect to the SdiA receptor, there are same binding sites (Tyr63 and Asp80) for positive control (C6HSL) and alpha-Naphthoflavone. Excluded the LsrB receptor, ten other QS receptors would also bind to the other drugs to a certain extent, which also suggests that LsrB have the strongest specificity for various drugs (Figure 1F and 2C). Taking CviR, SdiA, PqsR, LuxP, and CckA as example, we have further analysed the drug crosstalk for the potential drugs with FBEs smaller than -6 kCal/mol (Figure 2E). Results shown that there is the strongest drug crosstalk for CckA (6,633), followed by PqsR (6,094), CviR (2,920), SdiA (3,729), LuxP (1,247). This indicates that the complex drug-microbe interactions entail multilayer drug crosstalk and diverse QS-based regulations including different QS receptors.

Experimental validations

Based on the docking-based results, we have verified some of them by surface plasmon resonance (SPR), which are commonly used to study the direct interaction between small molecules and proteins. Three drug molecules with similar structures, i.e., mandelic acid, aspirin, and salicylic acid were selected for subsequent SPR validation to verify their binding affinity to LsrB receptor from *S. typhimurium*. As shown in Figure 3A, there are hydrogen-binding intermolecular forces between drugs and receptors. All the binding sites of these three drugs are similar to the active pocket of LsrB for its positive control case, i.e., R-THMF (Table 1). Both of the docking-based and SPR-based results indicate the potential binding of these three drugs and LsrB (Figure 3A).

Another three drugs (alpha-naphthalene, sulfabenzamide, and progesterone) were selected to validate their interactions with SdiA protein from *E. coli* strain (Figure 3B). Docking results shown that FBEs of these three drugs to SdiA are -13, -10.4, -6.0 kCal/mol. Similarly, all the binding sites of (alpha-naphthalene, sulfabenzamide, progesterone) are similar to the active pocket of SdiA for its positive control case, i.e., 3OC6HSL (Table 1). SPR results shown that binding affinity (K_d) for them are 1.71×10^{-5} M, 5.23×10^{-5} M, 9.31×10^{-5} M, which verified the drug-SdiA interaction. To sum up, it is certain that various drugs can bind to diverse QS receptors to interference with the corresponding biological activities for microbes with the help of docking-based calculations and SPR-based validations.

Construction and analysis for the drug-receptor interaction network

As stated above, QS receptors are the potential targets for diverse drug-microbial interactions. Therefore, we have constructed a potential drug-receptor interaction network based on the above cases with $FBEs \leq -6$ kCal/mol, where the absolute value of FBEs were set to be the weight values (Figure S1 in the Supplementary material). This potential network visualizes the complex QS-based drug-receptor interactions. Different QS receptors are linked together through various drugs to be a QS-based drug-receptor interaction network, and the connections will be used to regulate the drug-based interactions among various QS receptors. The giant bipartite network would consist of 8,270 nodes connected via 42,785 edges. The largest degree in the giant network is 6,197 from CckA node, followed by PqsR (6,197), LuxR (5,663), QscR (5,216), LasR (4,671), SdiA (3,924), TraR (3,924), CviR (3,079), YenR (2,251), LuxP (1,411), and LsrB (309). This indicates that fewer of microbes with Al-2 bound receptors (LuxP and LsrB) and most of the microbes with CckA and LuxR-type QS receptors will be affected by diverse drugs.

To have a better understanding on the drug-receptor interactions, we have shrunken the comprehensive network (Figure S1) into a simplified network (Figure 4) with showing only common elements and specific elements like the flower for the 11 QS receptors. Note that each QS receptor has its own specific binding drug, except for the TraR receptor, and there are most of specific drugs for LuxR (73), followed by CckA (62), LuxP (54), LasR (44), PqsR (27), LsrB (26), QscR (15), SdiA (14), CviR (10), and YenR (7). Furthermore, there are 14 drugs that have potential to bind to all of the 11 QS receptors, and their details are listed in Table 2. When these 14 drug molecules are distributed *in vivo*, all of the 11 QS receptors will be targeted, thus affecting their corresponding microbes. Considering that these 11 receptors represent hundreds of microbes including pathogens and probiotics, it is better to have a systematic understanding of the interactions between these potential broad-spectrum drugs and microbes to prevent some undesirable effects in the treatment of diverse diseases.

Table 2. The potential broad-spectrum drugs for 11 QS receptors

Drugs ID	PubChemID	Name	LuxR	LasR	TraR	CviR	QscR	PqsR	SdiA	LuxP	LsrB	YenR	CckA
DB07992	10258	Indoxyl sulfate	-6.1	-8.1	-7.9	-7.7	-7.9	-7.3	-8.2	-6.4	-6.2	-8.3	-7.1
DB02070	161166	Kynurenine	-6.5	-8.1	-7.3	-7.0	-7.7	-6.8	-7.9	-6.6	-6.2	-7.7	-6.8
DB09531	9639	Perflexane	-8.5	-8.9	-7.7	-8.4	-8.8	-7.5	-8.6	-6.6	-7.3	-9.0	-7.0
DB01924	10313	Benzhydroxamic acid	-6.7	-7.7	-7.3	-7.5	-7.4	-6.4	-7.3	-6.2	-6.9	-7.6	-6.6
DB04029	445694	Phenylalanyl amide	-7.3	-7.6	-7.7	-7.6	-7.1	-6.3	-7.9	-6.7	-6.4	-7.6	-6.5
DB04236	6951149	Tryptophanol	-7.4	-7.5	-7.7	-7.3	-7.6	-7.1	-7.9	-6.1	-6.5	-8.0	-6.8
DB02494	444718	(S)-3-phenyllactic acid	-7.2	-7.5	-7.5	-7.6	-7.2	-6.4	-7.6	-6.5	-6.8	-7.5	-6.2
DB04476	449146	Trencam-3,2-hopo	-6.4	-7.4	-6.4	-6.3	-7.0	-6.1	-6.9	-6.3	-6.6	-7	-6.4
DB07673	5288102	(2S)-2-Methyl-3-phenylpropanoic acid	-7.1	-7.8	-7.9	-7.5	-7.1	-6.4	-7.6	-6.6	-6.9	-7.6	-6.3
DB04157	448926	N-[(Aminoxy) Carbonyl] Aniline	-6.2	-7.6	-7.1	-6.3	-7.4	-6.2	-7.3	-6.5	-6.9	-7.1	-6.1
DB00909	5734	Zonisamide	-6.2	-9.2	-8.2	-7.8	-7.6	-7.1	-8.5	-7.2	-6	-8.1	-7.1
DB01662	17754112	Trans-o-hydroxy-alpha-methyl cinnamate	-7.4	-7.5	-6.9	-7.2	-7.8	-6.7	-7.6	-6.7	-7.6	-7.8	-6.2
DB08327	780	Homogentisic acid	-6.5	-6.6	-6.3	-6.2	-6.8	-6.0	-7.1	-6.6	-7.5	-7.2	-6.3
DB02556	6919011	D-Phenylalanine	-7.3	-7.4	-7.9	-6.7	-7.4	-6.3	-7.9	-6.5	-6.5	-7.9	-6.1

Unit of FBEs, kCal/mol

Systematic framework construction for drugs, microbes and diseases

Drugs, microbes, and diseases are located in a complex system, where contains various drug-receptor, drug-microbe, drug-disease, receptor-microbe, and microbe-disease interactions. It is demonstrated that QS receptors can be used as potential targets for some commonly used drugs, not only affecting the efficacy of the drugs themselves, but also affecting certain diseases by affecting the abundance of specific microbes. Herein, we integrated various drugs, receptors, gut microbes, and diseases together to be a systematic framework (Figure 5A) to form a potential key knowledge map of the human gut microbiota to promote the understanding of personalized medicine and developing potential therapies for diverse diseases. Some research has also carefully collected the drug-diseases [53] and drug-microbe [54], and microbe-disease [55] causal connections, respectively. Combined with the data from the above databases and diverse lectures, we have curated various connections carefully for drugs, receptors, microbes, and diseases to form a repository of drug-based microbial interactions, which were listed in Table S1. Note that Table S1 does not include drug-disease connections, which have been collected and can be searched in the DrugBank database.

Take some cases as example, we have illustrated a schematic diagram for diverse connections among drugs, microbial QS receptors, corresponding microbes, and relevant diseases (Figure 5B). For example, Berberine and Metformin, which were commonly used to treat type 2 diabetes, have potential to bind to the LasR, thus interfering the curing of cystic fibrosis caused by *P. aeruginosa*. Salicylic acid and aspirin were verified by molecular docking and SPR experiments, and the results showed that they bind to LsrB, which may affect the treatment of diseases such as typhoid fever caused by *S. typhimurium* infection. Furthermore, proton pump inhibitors (PPIs), which are inhibitors of gastric acid production, have been reported to be associated with the increase of typical oral bacteria in the intestinal tract[20]. Docking-based results showed that some PPIs binding to CckA (omeprazole, esomeprazole) and QscR (pantoprazole, rabeprazole), which indicates that PPIs may be able to affect the composition of the corresponding microbes (*Faecalibacterium prausnitzii*, *Caulobacter crescentus*, and *P. aeruginosa*) through QS receptors, thus having an impact on relevant diseases (Breast cancer, Cystic fibrosis, Liver cirrhosis, Diarrhea, Atopic dermatitis, Type 2 diabetes, Septicemia, Crohn's disease (CD), and Inflammatory bowel disease (IBD)). To sum up, drugs used *in vivo* will bind to various receptors, some of them are relevant to diseases treating, and others are QS-based targets, which affecting the abundance and diversity of corresponding microbes, and then interfere the efficacy for specific diseases.

Discussion

Generally, chemical similarity is a basis for ligand-based drug discovery. As shown in Fig. 3A, there is high structure similarity for salicylic acid, aspirin, and mandelic acid, which have much potential in binding to LsrB receptor from *S. typhimurium*. We can speculate that all of them will affect microbial physiological activities by binding to LsrB receptor or its homologous protein. Aspirin and its primary metabolite salicylic acid have been approved to interference the function and composition of microbes in the treatment of colon tumorigenesis at the strain level [56], which agrees well with our above speculation. Similarly, three drugs listed in Fig. 3B are flavonoids, which can bind to SdiA receptor from *E. coli* strain. Both of the above SPR-validated cases for LsrB and SdiA indicate that similar drugs tent to binding to the same QS receptor, leading to similar QS-based drug-microbe interactions.

It is worth noting that the systematic framework shown in Fig. 5A illustrate diverse QS-based connections, which lacks the further interactions based on other receptors. By collecting and mining other receptors from gut microbes and human, there is potential to construct a more comprehensive network for drugs, receptors, microbes, and diseases. Recently, many researchers found that nutrients and non-nutrients in the diet can influence the composition of the gut microbiota, which in turn affects a range of metabolic, hormonal, and nervous system processes [57, 58]. Many studies have proved that the sensitivity of microorganisms to dietary fat composition [59, 60], fiber types [61, 62] and food additives [63, 64] are slightly different. Therefore, the systematic framework shown in Fig. 5A can be further extended to include more molecules, such as dietary goods. The reliable construction of the extended framework and even network including various molecules, receptors, microbes, and diseases still faces many challenges, such as the complex interleaved crosstalk, huge network scale, uncultured microbes, and different spatial distributions. Nevertheless, we expect that the construction of the further comprehensive molecule-receptor-microbe-disease network, which can be regarded as one of the key knowledge maps of the human, will receive increasing attention from future research which will be engaged in developing more therapies for various diseases.

Conclusion

Drugs, microbes, and diseases are inherently linked in human health. Therefore, constructing a comprehensive drug-microbe-disease repository and network for human microbial systems are highly desirable. In this work, we integrated docking-based virtual screening technique and *in vitro* experimental validation to study QS-based drug-microbe interactions systematically. Information gathering above were further illustrated in a proposed drug-microbe interaction network. Furthermore, we have also curated various connections carefully for drugs, receptors, microbes, and diseases to form a comprehensive repository of QS-based drug-disease interactions. This repository can give the QS-based underlying mechanisms for the reported causal associations between drugs and microbes at the phenotypic level. We believe that this work contributes to the construction of the more comprehensive molecule-receptor-microbe-disease interaction network for human health that may form one of the key knowledge maps of the personalize medicine in the future. Such a network or repository holds huge potential for improving our understanding of diverse side effects coming from various microbiota and for developing applications such as different potential therapies in precision medicine.

Methods

Data acquisition

Based on databases listed in Table 3, we have collected the all 11 QS receptor proteins with crystal structure from PDB, i.e., CviR, LsrB, LuxP, LasR, LuxR, PqsR, QscR, SdiA, TraR, CckA, YenR. The relevant detailed information of the above receptors were listed in Table 1, including synthetic genes, signal molecules, receptors of the quorum sensing system, and the protein sites for docking with Vina software [65]. DrugBank is a web-enabled database that provides highly detailed information across multiple topics including pharmacology, chemical structures, targets, metabolism, and toxicology [53]. More than 8,000 small molecules were collected from the DrugBank database, including approved small molecule drugs, approved biotech drugs and experimental drugs.

Table 3. Databases involved in the data acquisition.

Name	Website URL	Data acquisition	Refs
Drugbank	https://go.drugbank.com/	Drug structure	[53]
PubChem	https://pubchem.ncbi.nlm.nih.gov/	Drug structure	[66]
ZINC	https://www.zinc.org/	Drug structure	[67]
SigMol	https://bioinfo.imtech.res.in/manojk/sigmol	QS of Gram-negative bacteria	[68]
Quorumpeps	http://quorumpeps.ugent.be/	QS of Gram-positive bacteria	[69]
QSldb	http://qsldb.yhpjc.vip/index.jsp	QS interference	[33]
NCBI	https://www.ncbi.nlm.nih.gov/	Receptor sequence	[70]
UniPort	https://www.uniprot.org/	Receptor sequence	[71]
PDB	https://www.rcsb.org/	Receptor structure	[72]

Molecular docking by AutoDock Vina

Molecular docking is based on the "lock and key principle" of the interaction between ligands and receptors, which simulates the interaction between small molecule ligands and receptor biological macromolecules. Interaction between ligand and receptor is a process of molecular recognition, including electrostatic interaction, hydrogen bonding, hydrophobic interaction, van der Waals interaction and so on [73]. The scoring function of Autodock Vina is based on force field, which mainly calculates van der Waals force and Coulomb force [65]. After the data of quorum sensing receptor protein and drug molecule were pretreated, AutoDock Vina software was used for molecular docking, and the detailed binding sites for QS receptors were listed in Table 1.

K_D (equilibrium dissociation constant) is usually used to express the strength of mutual binding between a single biomolecule (such as a protein or DNA) and its ligand/binding partner (such as a drug or inhibitor) [74]. The binding affinity is influenced by interactions between non-covalent molecules, such as hydrogen bonding, electrostatic interactions, hydrophobicity between two molecules, and van der Waals forces. The smaller the K_D value, the greater the binding affinity of the ligand for its target.

Surface Plasmon Resonance technology

Surface plasmon resonance (SPR), which is used to detect the interaction between ligands and analytes on biosensor chip, is widely used in the fields of therapeutics, pharmaceuticals, food safety, environmental monitoring and homeland security [75, 76]. As a rapid, label-free and real-time technique, SPR can be used to study the binding between ligands and membrane proteins, which is the main molecular target for the discovery of verified drugs and current and foreseeable drugs [75, 77]. In order to detect the binding between analyte molecules and receptor molecules, the receptor molecules are first bonded to the biosensor surface, and then a solution containing another biomolecule that can interact with the target molecules is injected and flows through the biosensor surface. The binding of biomolecules leads to an increase in the surface mass of the biosensor, resulting in an increase in the refraction index in the same proportion, and the change in the reaction between biomolecules can be detected. The reaction is measured by the reaction unit RU, and the kinetic constant can be determined by fitting the reaction curve with the combined interaction model. In this study, a Biacore T200 optical biosensor (Cytiva, USA) was used for the surface plasmon resonance (SPR) experiment. In brief, experiments were performed at 25 °C in PBS-P + with 5% DMSO buffer (20 M phosphate buffer with 2.7 mM KCl, 137mM NaCl and 0.05% Surfactant P20). The protein was immobilized on CM5 chips by amine coupling, then the diluted ligand (0–200 μ M) was flowed through the chips at 30 μ L/ min. The solvent correction was performed at the same time, and the data were collected and analysed in the BIACore T200 Evaluation Software (version 3.2).

Abbreviations

PPIs: Proton pump inhibitors, QS: Quorum sensing, SPR: Surface plasmon resonance, AHL: Acyl-homoserine lactones, PQS: 2-heptyl-3-hydroxy-4-quinolone, AI-2: Autoinducer-2, 3OC12HSL: N-3-oxododecanoyl-homoserine lactone, C6HSL: N-Hexanoyl-L-Homoserine Lactone, FBE: Free binding energies, CD: Crohn's disease, IBD: Inflammatory bowel disease.

Declarations

Supplementary information

Supplementary Data will be available online.

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Authors' contributions

JQ and FG conceived, organized, and supervised the project. SW and SY conducted data curation, experimental design, and interpreted the results. MW and HW contributed to experimental validations. YL and CL contributed to analyzing docking results. SW and SY wrote the manuscript. CL, YL, FG, and JQ commented and edited the manuscript. All authors read and approved the final version of the manuscript before submission.

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Availability of data and materials

Various interactions among drugs, QS receptors, corresponding microbes, and relevant diseases are listed in Table S1.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing financial interests.

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Figures

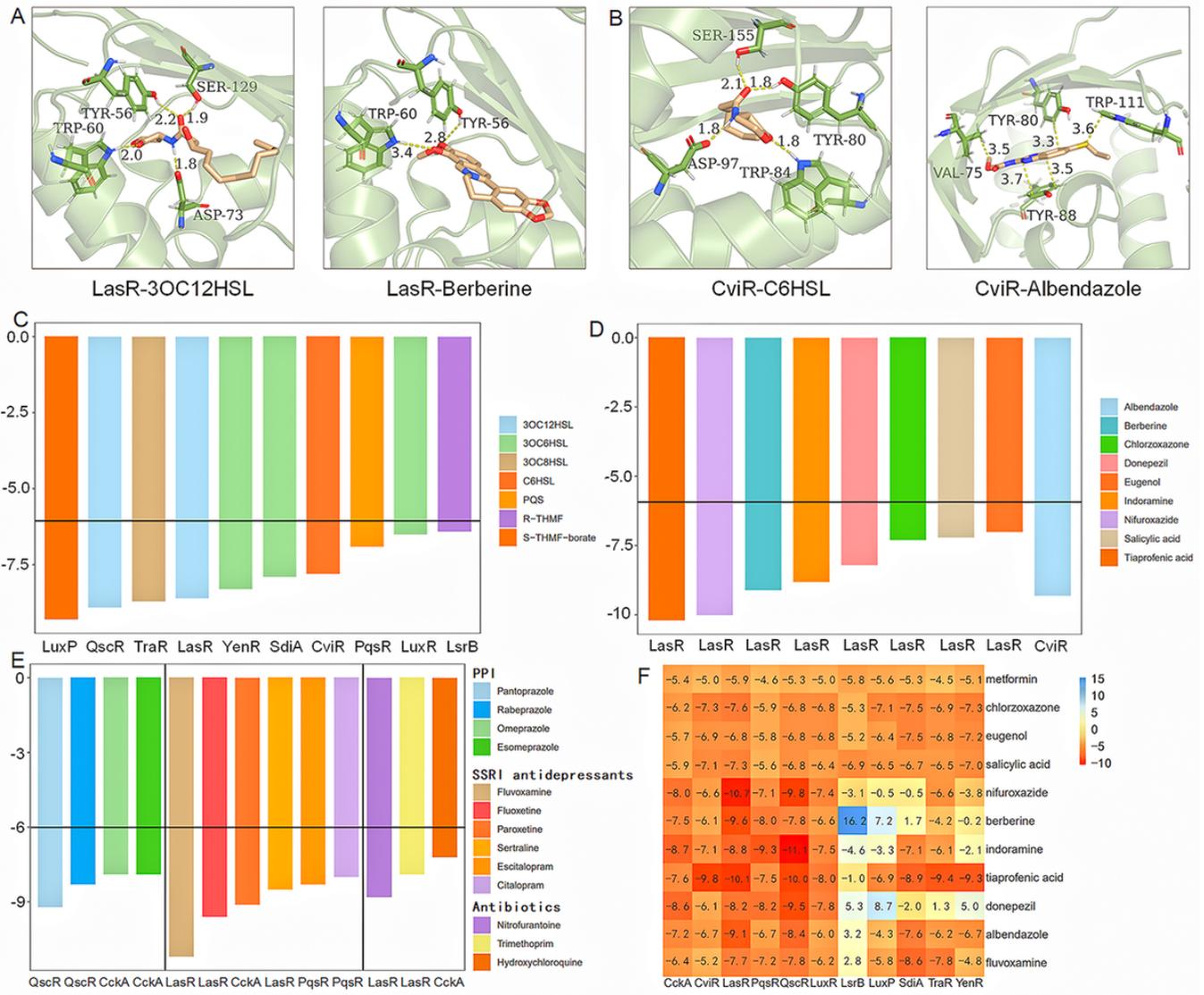


Figure 1

Analysis for the reported QS-based drug-microbe interactions. A. Binding illustration for 3OC12HSL-LasR and berberine-LasR, B. Binding illustration for C6HSL-CviR and albendazole-CviR, C-D. FBE results for the original ligands (C) and common drugs (D) binding to corresponding QS receptors, E. FBE results for the reported cases without pointing out the targets, F. Crosstalk analysis for different drug-receptor combinations.

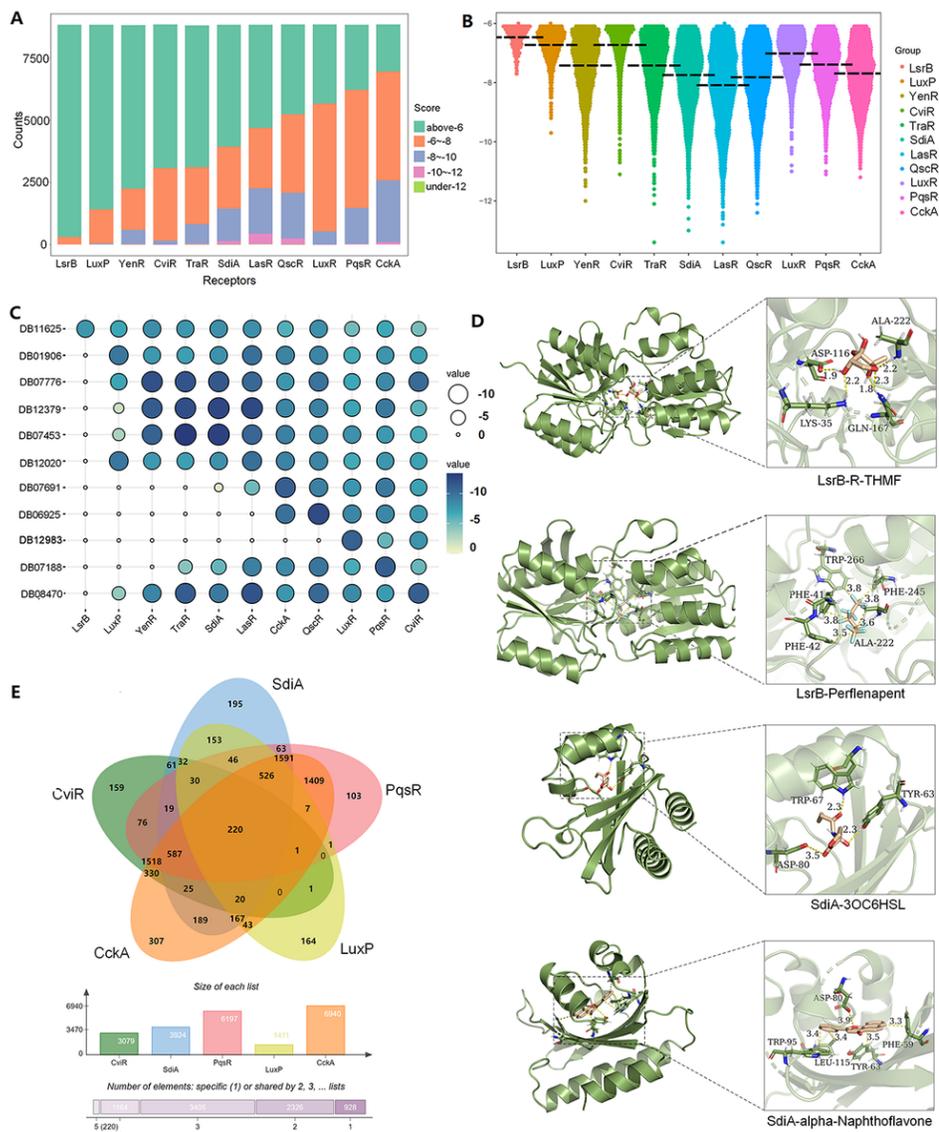


Figure 2

Analysis for various predicted drug-receptor interactions. A. Docking results distribution of 11 QS receptors and more than 8000 drug molecules, B. Docking results distribution for FBE below -6 kcal/mol, C. FBE results of the strongest binding for the screened eleven ligands and QS receptors, D. Illustration for Perflenapent and alpha-Naphthoflavone bind to LsrB and SdiA, respectively, E. Drug crosstalk results for CviR, SdiA, PqsR, LuxP, and CckA.

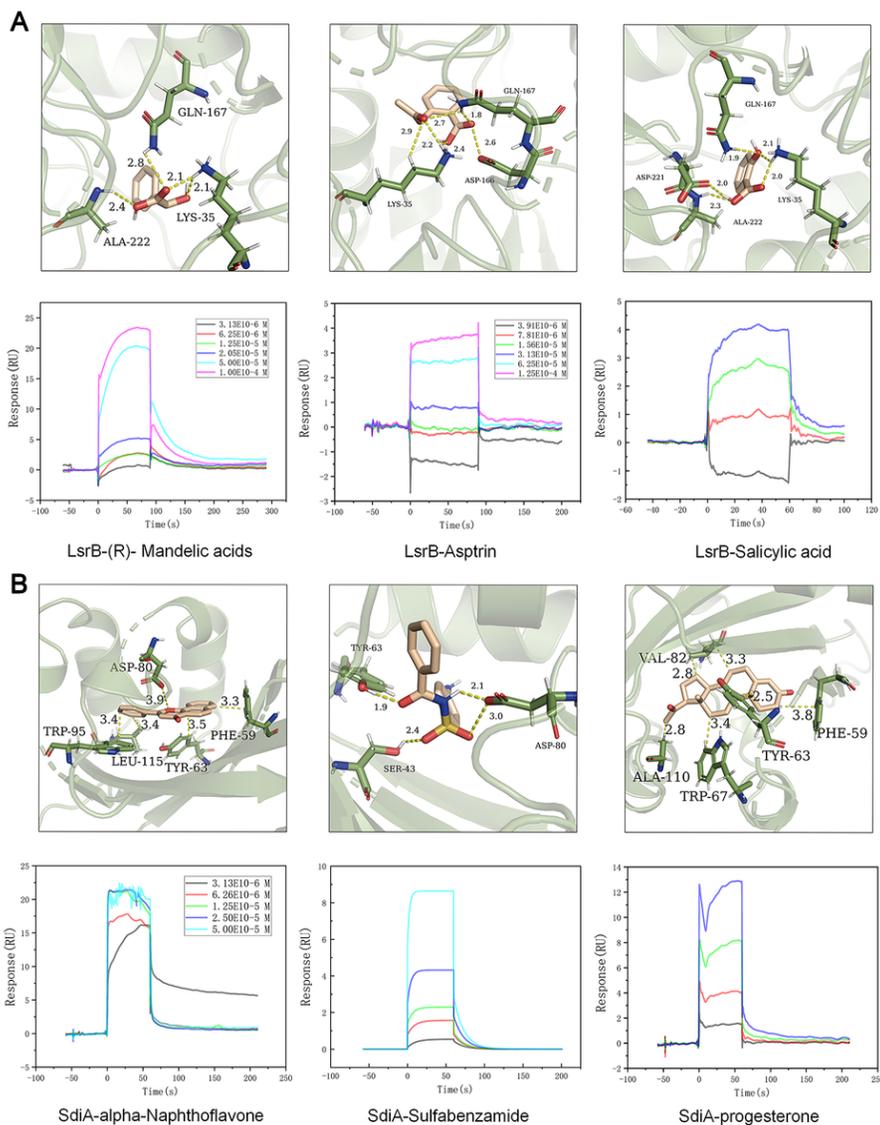


Figure 3

Experimental validations for docking-based results of LsrB and SdiA QS receptors. A. Validations for docking-based results of LsrB and three drugs (mandelic acid, aspirin, salicylic acid). B. Validations for docking-based results of SdiA and other three drugs (alpha-naphthalene, sulfabenzamide, and progesterone).

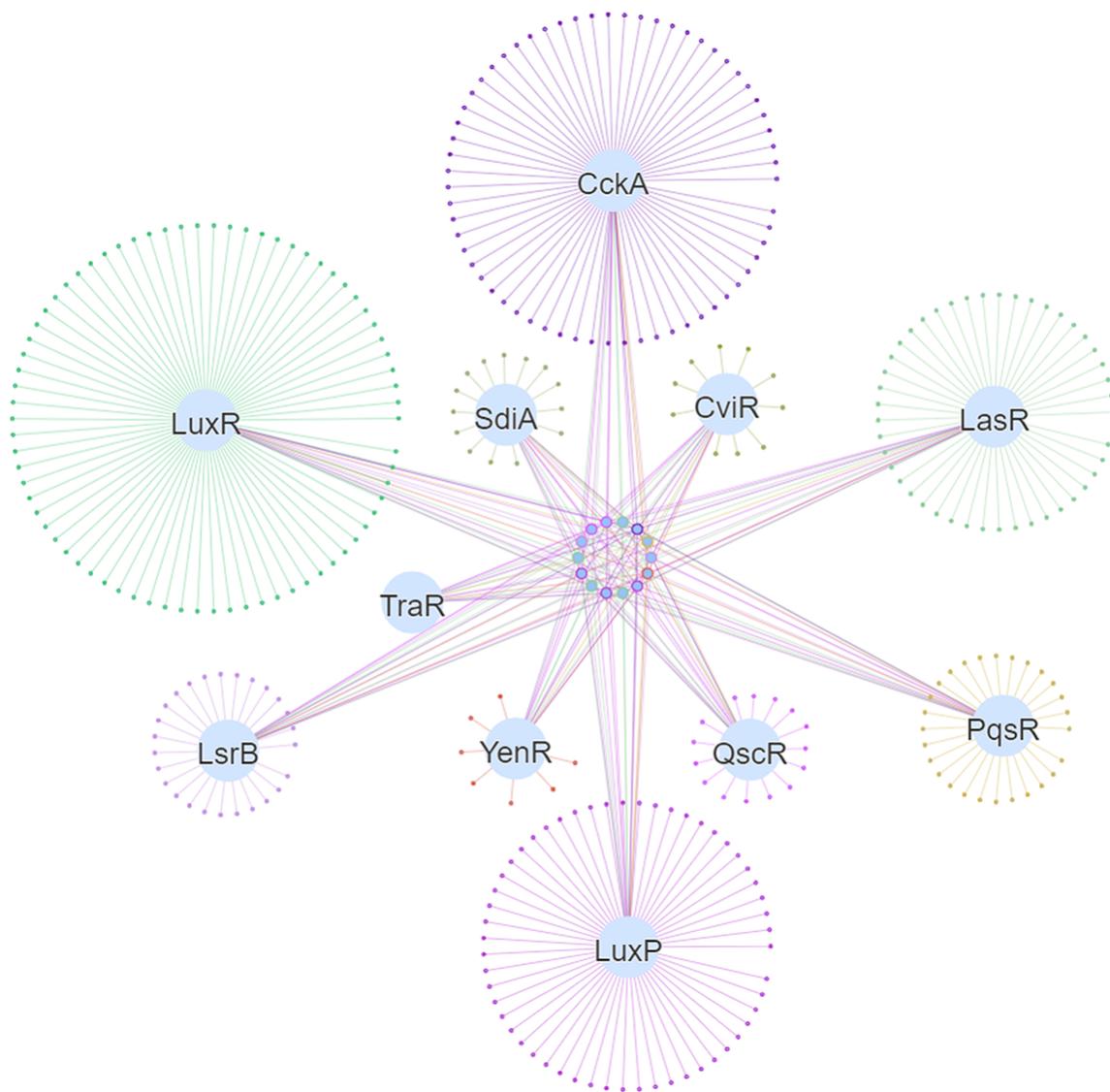


Figure 4

Illustration for the shrunken drug-receptor interaction network, which was generated using EVenn (<http://www.ehbio.com/test/venn>).

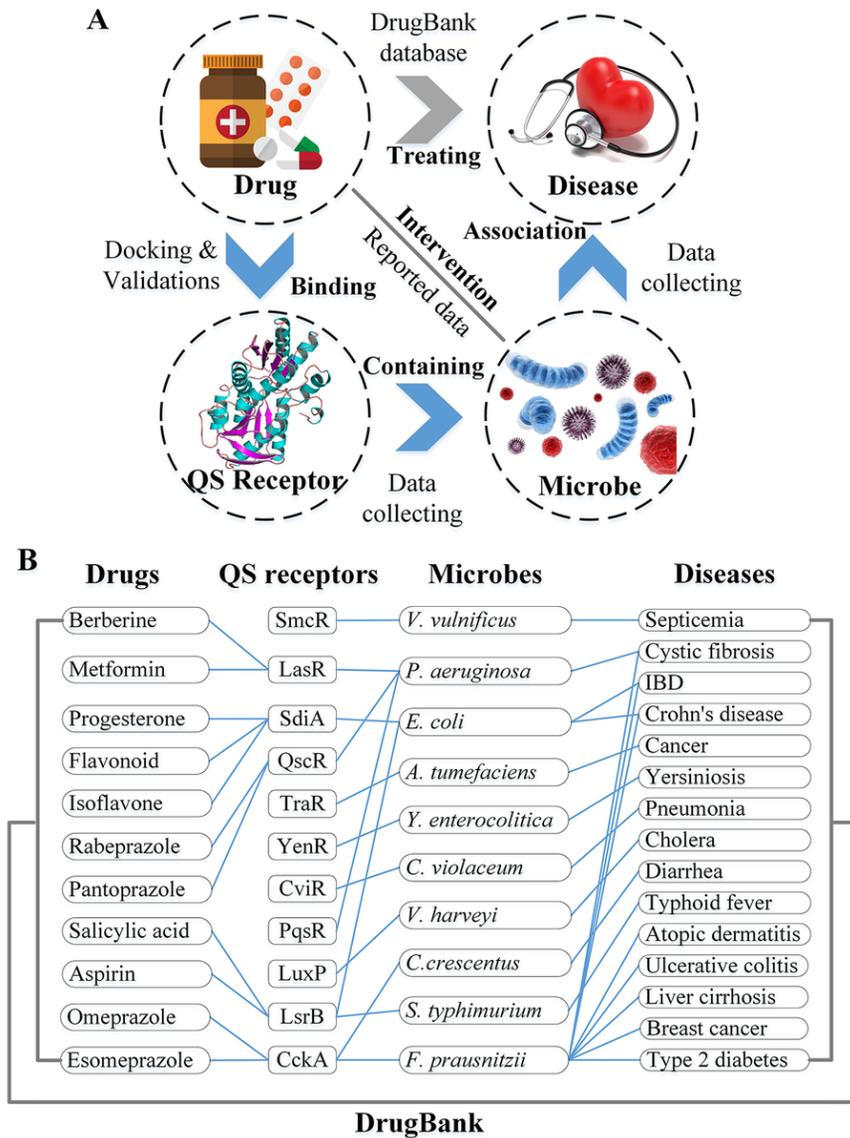


Figure 5

Systematic framework and repository construction for drugs, microbes and diseases. A. Schematic diagram of the systematic framework, B. Cases for circle interactions among drugs, QS receptors, corresponding microbes, and relevant diseases. Note that blue lines represent various interactions, the grey line represents the abbreviated interactions, which can be searched in DrugBank database.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplementarymaterial.docx](#)
- [TableS1.xlsx](#)