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A Review on Efflux Pump Inhibitors of Gram-Positive and Gram-Negative Bacteria from Plant Sources

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A B S T R A C T

Resistance of bacteria to most of the classes of antibiotics is a big problem now days. The component responsible for resistance in both the gram positive and gram negative bacteria are classified as multidrug resistant efflux pumps. In recent years a huge number of efflux pumps are identified in both gram- positive and gram-negative bacteria and these efflux pumps are responsible for the intrinsic resistance of bacteria to most of the antibiotics. Efflux pump inhibitors are the compounds which inhibit the activity of efflux pumps and they have the potential to restore the activity of standard antibiotics. In recent years, there are many classes of efflux pump inhibitors has been reported. Some of these efflux pump inhibitors are synthetic while some of them are natural inhibitors. Efflux pump inhibitors derived from chemical sources have drawbacks as they shows toxic effect at high concentrations in which they can be used. Some plants show potential EPI activity along with some antibiotics and shows effect on many efflux pumps. This review focuses on the use of efflux pump inhibitors from natural sources for blocking the activity of efflux pumps in case of both gram positive and gram negative bacteria.

Introduction

Antimicrobial drug resistance becomes a major challenge in spread of infectious diseases[1]. Efflux pumps are known as transport proteins which have the ability to expel out toxic substances including clinically relevant antibiotics from the cells to the external environment[2]. Efflux pumps are reported in both gram positive and gram negative bacteria and as well as in eukaryotic organisms. Active efflux is known to be major component of resistance in bacteria to most of the antibiotics.

The mechanism of active efflux is mediated by efflux pumps.[3,4,5] Some of the bacterial efflux pumps are selective for only one substrate while some of them are not. The non- selective efflux pumps are involved in transport of wide range of compounds and different classes of antibiotics and confer a multiple drug resistance phenotype.[4,5,6,7,8] Some bacteria have developed resistance against multiple antibiotics and the infections caused by these bacteria are very effective and impossible to treat. In case of

gram negative pathogen, there are many species of gram negative bacteria which developed resistance to almost all good antibiotics. So there is a need of new antimicrobial agents to control multi drug resistant gram negative bacteria[9]. Efflux pump inhibitors are the compounds which have the ability to reduce the intrinsic resistance of bacteria to antibiotics. Efflux pump inhibitors have been classified as additives which enhances the activity of traditional antibiotics. Efflux pump inhibitors are the compounds which reduce the bacterial virulence in vivo. Efflux pump inhibitors are used as new weapon against virulent strains of bacteria and reduce the survival of bacteria in vivo[5]. In general, efflux pump inhibitors are classified as small molecule inhibitors and polymeric inhibitors[10,11]. Efflux pump inhibitors have the ability to reverse the acquired resistance and also reduce the frequency of prevalence of new resistant strains[5].

Efflux Systems in Bacteria

Phylogenetically, bacterial efflux pumps belongs to five major super families(fig.1) which are classified as: primary transporters and secondary transporters.[4,5,6,7,8,12-15]

Primary Transporters

The primary transporters of bacterial efflux pump are also known as ATP binding cassette (ABC) transporters. These ABC transporters are well classified in both prokaryotes and eukaryotes and these transporters are ubiquitous membrane systems.[16] P-glycoprotein 1 is the ABC transporter which is studied more in case of humans, it confers resistance to cytotoxic compounds which are used in cancer chemotherapy.[17] These ABC transporters have two hydrophobic transmembrane domains and two cytoplasmic domains which are involved in ATP binding. In bacteria, the ABC transporters acquired high specificity for substrates, like antibiotics, vitamins, amino acids and sugars.[16,18] The ABC transporters are also reported in gram-positive bacteria, where these transporter confers resistance to macrolide and bacitracin.[19,20]

Secondary Transporters

Bacterial efflux systems which is classified as secondary transporters includes the following super families: MFS (the major facilitator super family), RND (the resistance nodulation division super family), SMR (the small multidrug resistance super family) , MATE (the multidrug and toxic compound extrusion super family). [4-8,12-15]
Out of these efflux pump families RND and MFS efflux pumps are ubiquitous systems.[21,22]

Efflux Pump inhibitors

Efflux pump inhibitors are classified as compounds which blocks the activity of efflux pumps. Efflux pump inhibitors blocks the activity of efflux pumps by competitive manner or by non competitive manner with the substrates. There is a series of efflux pump inhibitors reported such as naturally occurring inhibitors and synthetic efflux pump inhibitors.

Synthetic Efflux Pump inhibitors

Synthetic compounds have been classified as major efflux pump inhibitors.

L-phenylalanyl-L-arginyl-b-naphthylamide (PAβN): This efflux pump inhibitor is characterized as dipeptide amide compound MC -207 110. This epi compound increases the effect of levofloxacin against *P.aeruginosa* strains.[23] This MC-207 110

EPI involved in lowering the frequency of evolution of levofloxacin – resistant *P.aeruginosa* strains.[24] This efflux pump inhibitor shows inhibitory activity against AcrAB-TolC efflux pump of gram-negative bacteria such as *E.coli, K. pneumoniae* and *E. aerogenes* by combining with fluoroquinolones.[25-29]

Arylpiperidines and arypiperazines: Some members of this family of efflux pump inhibitors have the ability to reduce the multidrug resistance in case of RND efflux pump of *E.coli* bacteria. [30]

Nocardamines: These efflux pump inhibitors are known as iron chelator and they inhibit the activity of TetB and TetK efflux pumps of *Staphylococcus aureus*.[31]

Arylated benzothiophenes and tiophenes: Efflux pump inhibitor of this group shows inhibitory activity against NorA efflux pump of *Staphylococcus aureus*.[32]

Quinoline derivatives: Quinoline compound shows a great inhibitory activity against multidrug resistant *Enterobacter aerogenes* isolates. Different quinoline compounds subsequently expand the intracellular concentration of chloramphenicol and therefore inhibit the transportation of drug by AcrAB – TolC.[33]

Indole derivatives: INF- 55 and INF-271 derivatives of indole shows efflux pump inhibitory activity against NorA efflux pump of *Staphylococcus aureus*.[34] 3-amino-6-carboxyl- indole and nitro-6-amino-indole enhances the antimicrobial effect of tetracycline, ciprofloxacin, chloramphenicol and erythromycin against *E.coli*.[35]

Amide derivatives: 5, 9- dimethyl- deca-2,4,8- trienoic acid amides and 9- formyl-5-methyl- deca-2,4,8- trienoic acid are two compounds of amide family and they potentiate the activity of ciprofloxacin against *Staphylococcus aureus*.[36]

Sodium orthovanadate: Sodium orthovanadate proves as a promising inhibitor of ABC efflux pump of *Streptococcus pneumonia*.[37]

Phenothiazines: Thioridazine a efflux pump inhibitor belongs to phenothiazines which is a neuroleptic drug. Thioridazine shows efflux pump inhibitory activity against multidrug resistant bacteria such as *M. tuberculosis, S. aureus, E.coli, P. aeruginosa and S. typhimurium*.[38-41]

Carbonyl cyanide m-chlorophenylhydrazone (CCCP): CCCP subsequently affects the energy level of membrane CCCP posses high toxicity for the cells, beside its toxicity it is classified as a substrate for bacterial efflux pumps.[42-43] CCCP has efflux pump inhibitory activity against *Mycobacterium smegmatis* by the inhibition of MFS efflux pump.[44-45]

Alkoxyquinolone derivatives: 2,8-dimethyl- 4- (2' pyrrolidinoethyl) oxyquinolone, are the derivatives of Alkoxyquinolone and it inhibits the activity of efflux pump in case of *E. aerogenes* and *K. pneumonia*. This efflux pump inhibitor increases the effect of chloramphenicol, norfloxacin and tetracycline up to 8 fold.[46]

Substituted polyamines: These compounds shows efflux pump inhibitory activity against *Haemophilus influenza*.[36]

Verapamil: Verapmil is a drug which is used for the treatment of hypertension and cluster headaches. It shows efflux pump inhibitory activity against *Mycobacterium tuberculosis*. It also intensify the activity of isoniazid and rifampin.[47] Verapamil also shows EPI activity in case of *Lactococcus lactis*.[48]

Bacterial efflux pumps of some important pathogens[2,50,51]

Efflux pump family	Nature of substrate	Antibiotics used	Organisms
RND	Aphiphilic, charged substrates	Tetracycline, fluoroquinolone, erythromycin, rifampicin, β – lactam, fusidic acid, chloramphenicol, aminoglycosides	*E.coli*, *P. aeruginosa*
MATE	Low molecular weight cationic substrates	Norfloxacin, fluoroquinolone, amioglycosides	*Staphylococcus aureus, Escherichia coli and vibrio parahaemolyticus*
ABC	Amphiphilic neutral or cationic substrates	Tetracycline, fluoroquinolones, macrolides, lincosamides, rifanpicin, chloramphenicol,aminoglcosides	*Staphylococcus aureus and Lactococcus lactis*
MFS	Amphiphilic, mono or dicationic substrates	Tetracycline, fluoroquinolone, erythromycin, lincosamides, rifampicin, pristinamycin, chloramphenicol, aminoglycosides	*Staphylococcus aureus and Escherichia coli*
SMR	Lipophilic, multicationic substrates	Tetracycline, erythromycin, sulfadiazine	*Staphylococcus aureus, Acinetobacter baumannii*

Bacteria	EPI	Antibiotic	Efflux pump	Plant source	Reference
E.coli	Baicalein	Tetracycline	TetK	*Thymus vulgaris*	53
Klebsiella pneumoniae	Theobromine	Ciprofloxacin	AcrAB-TolC	*Theobroma cacao*	55
Salmonella typhimurium	Theobromine	Ciprofloxacin	AcrAB-TolC	*Theobroma cacao*	55
Salmonella typhimurium	Cathinone	Ciprofloxacin	AcrAB-TolC	*Catha edulis*	55
Pseudomonas aeruginosa	Pheophorbide a	Ciprofloxacin	MexAB-OprM	*Berberis aetnensis*	73
Enterobacter cloacae	Theobromine	Ciprofloxacin	AcrAB-TolC	*Theobroma cacao*	55
Enterococcus faecalis	Caeffeoylquinic acid	Berberine	NorA	*Artemisia absinthium*	74
Enterococcus faecalis	Karavilagenin C	Ethidium bromide	Rv1258c	*Momordica balsamina*	75
Mycobacterium spp	Fernasol	Ethidium bromide	TetK	*Cymbopogon citratus*	72
Mycobacterium spp	Myricetin	Isoniazid	TetK	*Allium cepa*	76
Mycobacterium spp	Quercetin	Isoniazid	TetK	*Allium cepa*	76
Mycobacterium spp	Rutin	Isoniazid	TetK	*Dimorphandra mollis*	76
Mycobacterium spp	Taxifolin	Isoniazid	TetK	*Sophora japonica*	76
Mycobacterium spp	Isorhamnetin	Isoniazid	TetK	*Tagetes lucida*	76
Mycobacterium spp	Kaempferol	Isoniazid	TetK	*Camellia sinensis*	76
Mycobacterium spp	Baicalein biochanin A	Ethidium bromide	TetK	*Oroxylum indicum*	77
Mycobacterium spp	Epicatechin	Isoniazid	TetK	*Camellia sinensis*	78
Mycobacterium spp	Genistein	Ethidium bromide	TetK	*Glycine max*	77
Mycobacterium spp	Resveratrol	Ethidium bromide	TetK	*Fallopia japonica*	77

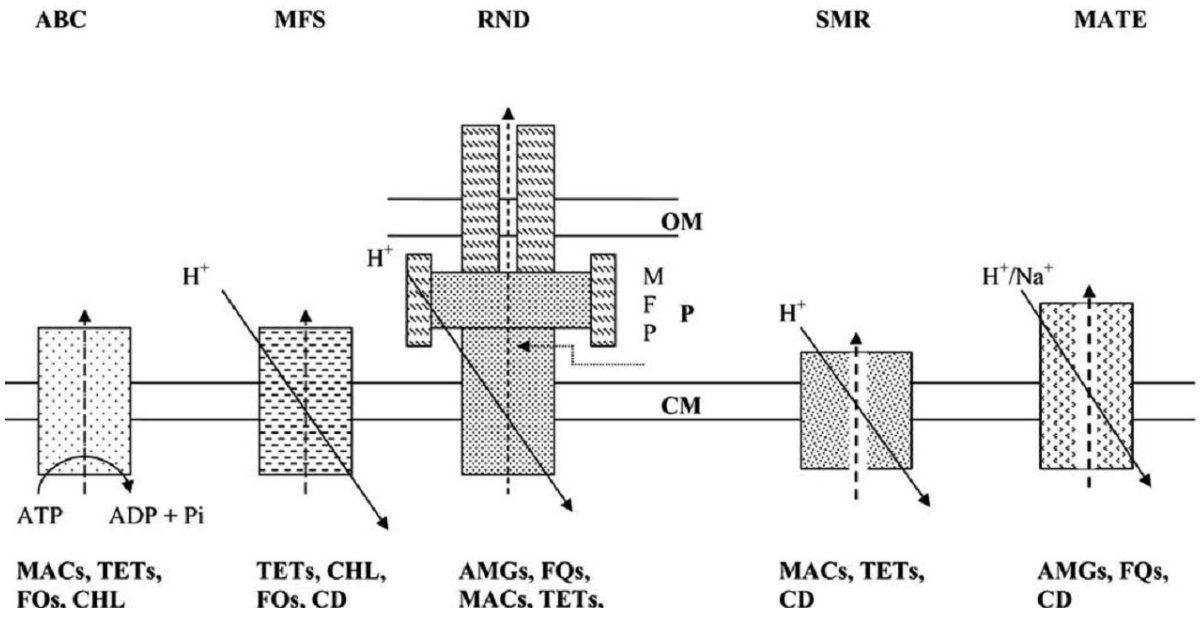
Mycobacterium spp	Piperine	Ethidium bromide	Rv 1258c	Piper nigrum, Piper longum	**80**
Bacillus subtilis	Reserpine	Tetracycline	Bmr	Rauwolfia vomitoria	4,42
Bacillus cereus	Chalcone	Berberine, erythromycin and tetracycline	NorA	Nicotiana tobacum	80
Streptococcus pneumoniae	Reserpine	Ciprofloxacin	NorA	Rauwolfia vomitoria	81,82,83
Staphylococcus aureus	Reserpine	Norfloxacin, Tetracycline	TetK,NorA	Rauwolfia vomitoria	81,82,83,84
Staphylococcus aureus	Porphyrin,Pheophorbide	Ciprofloxacin,Norfloxacin	NorA	Berberis aetnensis	85,86
Staphylococcus aureus	Polyacylated neohesperidosides	Ciprofloxacin, norfloxacin, rhein, berberine	NorA	Geranium caespitosum	87, 88
Staphylococcus aureus	Carnosic acid, carnosol	Tetracycline, Erythromycin	TetK, MsrA	Rosmarius officinalis	55,89
Staphylococcus aureus	Chalcone	Berberine, erythromycin and tetracycline	NorA	Dalea versicolor	90
Staphylococcus aureus	Epicatechin gallate and epigallocatechin gallate	Norfloxacin	NorA	Camellia sinensis	91,92,93
Staphylococcus aureus	Baicalein	Tetracycline	tetK	Thymus vulgaris	53
Staphylococcus aureus	Citropten and furocoumarins	Norfloxacin	NorA, ermA, ermB	Citrus paradise	94
Staphylococcus aureus	Orizabin	Norfloxacin	NorA	Ipomoea violacea	95

Staphylococcus aureus	Piperine	Ciprofloxacin	MdeA and NorA	Piper nigrum, Piper longum	96
Staphylococcus aureus	Salicylic acid	Ciprofloxacin, Ethidium bromide	SarA	Salix alba	97
Staphylococcus aureus	Balsaminol, Balsaminagenin, karavilagenin	AcrAB-TolC	NorA	Momordica balsamnia	75
Staphylococcus aureus	Isopimaric acid	AcrAB – TolC	Nor A	Pinus nigra	98
Staphylococcus aureus	Crysoplenol and crysoplenetin	Berberine, Fluoroquinolones, Norfloxacin	NorA	Artemisia annua	99
Staphylococcus aureus	Murucoidins	Norfloxacin	NorA	Ipomoea murucoides	100
Staphylococcus aureus	Kaempferol glycoside, tiliroside	Ciprofloxacin	NorA	Herissantia tiubae	101
Staphylococcus aureus	Genistein , orobol, Biochanin	Norfloxacin, Berberine	NorA	Lupinus argenteus	102
Staphylococcus aureus	Galbanic acid	Ciprofloxacin, Ethidium bromide	NorA	Ferula szowitsiana	103
Staphylococcus aureus	Chrysosplenol - D	Berberine	NorA	Artemisia annua	99
Staphylococcus aureus	Orobol	Berberine	NorA	Lupinus argenteus	79
Staphylococcus aureus	Biochanin	Berberine	NorA	Lupinus argenteus	79
Staphylococcus aureus	Bonducillin	Berberine	NorA	Caesolpinia digyana	79
Staphylococcus aureus	Acetoxycavicolacetate	Ethidium bromide	NorA	Alpinia galangal	79

Staphylococcus aureus	Totarol	Ethidium bromide	NorA	Chamaecyparis nootkatensis	104
Staphylococcus aureus	Ferruginol	Norfloxacin, Oxacillin	NorA	Chamaecypar lawsoniana	105
Staphylococcus aureus	Olaanolic acid, ulvaol	Norfloxacin, Oxacillin	NorA	Carpobrotus edulis	106
Staphylococcus aureus	Harmaline	Ethidium bromide	NorA	Peganum harmala	107
Staphylococcus aureus	Ergotamine	Norfloxacin	NorA	Claviceps purpurea	108
Staphylococcus aureus	Julifloridine, juliflorine and juliprosine	Norfloxacin	NorA	Prosopis juliflora	6
Staphylococcus aureus	Indoles , Indirubicin	Ciprofloxacin	NorA	Wrightia tinctoria	109
Staphylococcus aureus	Pterocarpan	Berberine	NorA	Dalea spinosa	79
Staphylococcus aureus	Reserpine	Berberine	LmrA	Rauwolfia vomitoria	66,67
Staphylococcus aureus	Caffeoylquinic acid	Berberine	NorA	Artemisia absinthium	74
Mycobacterium spp	Sandaracopimeric acid	Isoniazid	TetK	Juniperus procera	78
Mycobacterium spp	Totarol	Isoniazid	TetK	Juniperus procera	78
Mycobacterium spp	Ferruginol	Isoniazid	TetK	Juniperus procera	78

Diagramatic representation of efflux pump families[110]

Fig.1: Bacterial efflux pumps. The figure shows diagrammatic representation of the five superfamilies of bacterial efflux pumps. ABC: ATB-binding cassettes, MFS: major facilitator superfamily, RND: resistance- nodulation- division, SMR: small multidrug resistance, MATE: multidrug and toxic compound extrusion, OM: outer membrane, P: periplasm, CM: cytoplasmic membrane, MFP: membrane fusion protein, MACs: macrolides, TETs: tetracyclines, FQs: fluoroquinolones, CHL: chloramphenicol, CD: cationic drugs, AMGs: aminoglycosides, BLAs: beta-lactams.



GG918, biricodar (vx – 710) and timcodar (vx – 853)

These two compounds shows efflux pump inhibitory activity against *S. aureus, S. pneumonia* and *E. faecallis* with fluoroquinolones and they also reduce the mic of etbr.[49]

EPIs derived from plants against different bacteria

Many cytotoxic compounds are produced from plants which have the ability to protect the plants from pathogenic bacteria because of these cytotoxic compounds the plants are safe from infective diseases. [6]

Gram- negative bacteria

Multidrug resistance among gram – negative bacteria is very common problem. So far very less efflux pump inhibitors has been detected against Gram - negative bacteria , this is due the efflux pumps present in gram – negative bacteria are comprises of an inner membrane pump, an outer- membrane channel, and periplasmic adaptor protein, which helps in transportation of structurally unrelated drugs.[15] It is important to search new compounds which have the ability to make the reuse of previous antibiotics against gram negative bacteria, as there is a slight decrease in number of new agents and development of antibiotics. Very few compounds has been discovered so far which shows efflux pump inhibitory activity against gram-negative bacteria.[52]

Baicalein, a well known efflux pump inhibitor which shows the activity against efflux pump of *E.coli*. Baicalein is isolated from Thymus vulgaris.[53] Derivatives of isopimarane shows efflux pump inhibitory activity against efflux pumps of *Enterobacter aerogenes*.[54] The obromine which is a bitter alkaloid which shows synergistic activity with ciprofloxacin against RND efflux pump of different gram – negative bacteria such as, *Klebsiella pneumonia*, *Salmonella typhimurium* and *Pseudomonas aeruginosa*. Cathinone, is a monoamine alkaloid which shows efflux pump inhibitory activity against *Salmonella Typhimurium* alongwith ciprofloxacin.[55] Only few plants have reported so far which shows efflux pump inhibitory activity against gram – negative bacteria in combination with different antibiotics. The plants which shows Epi activity against gram – negative bacteria are, Helichrysum italicum, Thymus maroccanus, Thymus broussonetii and Callistemon citrinus, Commiphora molmol, Centella asiatica, Daucus carota,Citrus aurantium and Glycyrrhiza glabra. Extracts of these plants shows EPi activity against *Pseudomonas aeruginosa* and *Salmonella enteric*.[5,56,57] The extract of Berberis aetnensis along with ciprofloxacin shows efflux pump inhibitory activity against *E.coli.* The ethanolic extracts of Vernonia adoenis, Mangifera indica and Callistemon citrinus shows efflux pump inhibitory activity against *Pseudomonas aeruginosa* and *E.coli*.[58]

Gram positive bacteria

In recent years, multidrug resistant gram positive bacteria becomes a major public health concern.[59] Gram positive bacteria are prime cause of nosocomial and community acquired infections. These bacteria subsequently shows high resistance to antimicrobials.[60]

Staphylococcus

Staphylococcus aureus is one of the vital cause of community and hospital acquired infections.[61,62] *Staphylococcus aureus* has the ability to attain resistance to almost all the antibiotics which are currently present in the market.[63] Many plant derived

compounds acts as efflux pump inhibitor against *Staphylococcus aureus*.

Lactococcus

Lactococcus lactis is commonly classified as non- pathogenic, but pathogenicity can be emerged.[64] There are two types of efflux pumps present in *Lactococcus lactis* and responsible for its multidrug resistance.[65] Reserpine has the ability to inhibit Lmra efflux of *Lactococcus lactis*.[66,67]

Bacillus

Bacillus cereus responsible for food born infections such as, vomiting and diarrhoea etc.[68] In immune compromised patients diseases are caused by *B.subtilis*. Drug resistance due to efflux is a familier problem in Bacillus. Reserpine has the ability to block the activity of Bmr- mediated multidrug resistance in *Bacillus subtillis*.[69]

Mycobacterium

Mycobacterium tuberculosis is one of the ancient and the most familier source of infection and death in the world. *Mycobacterium* is the major cause of blood infection in AIDS patients. *Mycobacterium smegmatis* is also characterized as an opportunistic pathogen. The active multidrug efflux pump is the major factor responsible for natural drug resistance of Mycobacteria.[70] Piperine an alkaloid compound shows efflux pump inhibitory activity against *Mycobacterium tuberculosis*.[71] Farnesol a colourless organic compound shows efflux pump inhibitory activity against efflux pumps of *Mycobacteria*.[72]

In conclusion, the present review accentuates a numerous efflux pump inhibitors which are mainly derived from plant sources and some of them are synthetic inhibitors. The activity shown by some of these natural efflux pump inhibitors against gram positive bacteria is appreciable. Some of the natural compounds described in the present review possess both antibacterial and potentiating activity. Most of the efflux pump inhibitors show activity against gram positive bacteria mostly against *Staphylococcus aureus* as compare to gram negative bacteria. The gram negative bacteria such as *Pseudomonas, E.coli* and *Acinetobacter* are one of the most problematic bacteria. These organisms possess intrinsic resistance because of the presence of lipophilic membranes. The study of literature of secondary metabolites of plants suggest that they show the activity only against gram positive bacteria and show no activity against gram negative bacteria because of the factor that gram negative bacteria possess effective barriers against all antibiotics and other compounds. Gram positive bacteria are comprises of single membrane so the antimicrobial compounds are easily passed through that membrane while in case of gram negative bacteria there is an extra membrane present which blocks the entry of antimicrobial agents or compounds. So there is need of discovery of new efflux pump inhibitors against gram negative bacteria.[112] from study of literature it has been concluded that compounds derived from plants can easily evade multi drug resistance mechanisms and can be developed in broad spectrum antibiotics.

So far there has been no efflux pump inhibitor reported which can be used in the treatment of infections caused by bacteria in humans or animals. One efflux pump inhibitor compound MC-601, 205 in combination with ciprofloxacin has been used as a trial in case of humans for the treatment of pulmonary exacerbations in cystic fibrosis patients.[110] In case of this

disease the symptoms are seen in lungs, which increases the chances of infection by bacteria such as *B. Cepacia, P. aeruginosa* and *S. aureus*.[111] The study of literature of secondary metabolites of plants suggest that they show the activity only against gram positive bacteria and show no activity against gram negative bacteria because of the factor that gram negative bacteria possess effective barriers against all antibiotics and other compounds. Gram positive bacteria are comprises of single membrane so the antimicrobial compounds are easily passed through that membrane while in case of gram negative bacteria there is an extra membrane present which blocks the entry of antimicrobial agents or compounds. So there is need of discovery of new efflux pump inhibitors against gram negative bacteria.[112]

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