Recent advances in antibacterial drugs

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Abstract

The incidence of antimicrobial resistance is on continued rise with a threat to return to the "pre-antibiotic" era. This has led to emergence of such bacterial infections which are essentially untreatable by the current armamentarium of available treatment options. Various efforts have been made to develop the newer antimicrobials with novel modes of action which can act against these multi-drug resistant strains. This review aims to focus on these newly available and investigational antibacterials approved after year 2000, their mechanism of actions/resistance, and spectrum of activity and their phases of clinical trials. Newer unexploited targets and strategies for the next generation of antimicrobial drugs for combating the drug resistance and emerging pathogens in the 21st century have also been reviewed in the present article.

Key words: Biopotentiators, *clostridium difficile* infection, doripenem, pleuromutilin, virulence inhibitors

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Introduction

Serious infections caused by microorganisms resistant to commonly used antimicrobials have become a major healthcare problem worldwide in the 21st century. This is responsible for the significant increase in morbidity and mortality, longer hospitalization and increased health care costs. Keeping in view the seriousness of this problem, the World Health Organization (WHO) has selected "Antimicrobial resistance: No action today no cure tomorrow" as the theme for World Health Day 2011 as a preventive measure.

In recent years, the number of availability of new antimicrobials for human use across the globe has been lower than in the recent past. No new classes of antimicrobials were developed in the thirty seven years between the introduction of nalidixic acid (1962) and linezolid (2000) and all antimicrobials that entered the market during this time period were modifications of the existing molecules. The development of new antimicrobial agent is very expensive and time consuming, leading to diminishing interest of pharmaceutical industries in it. On an average, research and development of anti-infective drugs takes around 15-20 years, and can cost more than $1000 million.[1] The cost of bringing a new product to the market is increasing at a rate of 10% per annum. The majority of large pharmaceutical companies have terminated their anti-infective research programs altogether.

In the present review, all new antibacterial agents which have been approved after the year 2000 have been described along with their mechanism of action, development of resistance, spectrum of activity and the stage of developmental in case of yet to be approved drugs. Some newer unexploited targets and strategies for combating drug resistance have also been reviewed.

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Recently marketed antimicrobial agents and agents in clinical development

Many new antimicrobial agents with new targets have been marketed recently, while few are still awaiting Food and Drug Administration (FDA) approval. Some of the new agents are in clinical development phase [Table 1].

Macrocyclic antibiotic

Fidaxomicin

It is the first drug in this new class of antimicrobial agents

Table 1: Newer antibacterial agents

Name of drug	Class of drug	Year of FDA approval/Phase of trial	Spectrum of activity
Marketed agents			
Daptomycin	Lipopeptide	2003	Gram+ve bacteria
Telithromycin	Ketolide	2004	Gram+ve and –ve
Tigecycline	Glycylcycline	2005	Gram+ve and –ve
Doripenem	Carbapenems	2007	Gram+ve and +ve
Retapamulin	Pleuromutilin	2007	Gram+ve
Telavancin	Glycopeptides	2009	Gram+ve
Ceftaroline	Cephalosporins	2010	Gram+ve
Fidaxomicin	Macrocyclic	2011	Gram+ve
Awaiting FDA approval			
Ceftobiprole	Cephalosporin	Approval awaited	Gram+ve
Iclaprim	DHFR inhibitor	Approval awaited	Gram+ve
Agents in clinical development			
Torezolid	Oxazolidinones	Phase II	Gram+ve
Radezolid	Oxazolidinones	Phase II	Gram+ve
Cethromycin	Ketolides	Phase III	Gram+ve
Solithromycin	Ketolides	Phase II	Gram+ve
Oritavancin	Glycopepetide	Phase III	Gram+ve
Dalbavancin	Glycopepetide	Phase III	Gram+ve

DHFR: Dihydrofolate reductase; FDA=Food and Drug Administration

which shows narrow spectrum of activity. It is active against Clostridium difficile infection (CDI) and show limited activity against normal intestinal flora.[2] This drug acts by inhibiting the bacterial enzyme RNA polymerase.[3]

It is an alternative to the currently used treatment regimens of vancomycin and metronidazole against CDI. In a phase III trial (n = 1000), fidaxomicin 200 mg (twice a day) was found to be non-inferior to vancomycin 125 mg (four times a day) for the treatment of initial or first recurrences of CDI. Recurrence rates of CDI with fidaxomicin were significantly lower (13%) as compared to vancomycin (25%).[4] It is available as oral formulation with recommended dose of 200 mg twice daily.

Newer cephalosporins

Ceftaroline

Ceftaroline fosamil is a prodrug of Ceftaroline. It is a novel broad-spectrum antibiotic effective against Methicillin Resistant *Staphylococcus aureus* (MRSA), penicillin and cephalosporin resistant *S. pneumoniae*, vancomycin-intermediate *S. aureus* (VISA), and vancomycin-resistant *S. aureus* (VRSA).[5] It is also active against many gram-negative pathogens but inactive against extended-spectrum β-lactamase (ESBL) producing bacteria. It has been approved for the treatment of community acquired pneumonia (CAP) and cSSSTIs. Ceftaroline was developed by modifying the structure of the fourth-generation cephalosporin cefozopran.[6]

Ceftaroline acts by binding to penicillin binding proteins 1-4 (PBPs 1-4). It shows high affinity for PBP2a present in *Staphloccocus aureus*, which is responsible for methicillin resistance. In *S. pneumonia*, ceftaroline can bind to all six PBPs identified (PBP1A, 1B, 2x, 2A/B, and 3).[7]

Inside the blood circulation, ceftaroline fosamil (prodrug) is rapidly converted to ceftaroline (active form) by phosphatase enzymes. It exhibits linear pharmacokinetics and has a serum half-life (t½) of 1.6 hr (for a single dose) to 2.7 hr (following multiple doses). Volume of distribution (20 l) of ceftaroline is similar to that of other parenteral cephalosporins with plasma protein binding of 20%. Ceftaroline is metabolized by hydrolysis of its β-lactam ring which results into the formation of an inactive, open-ring metabolite called as ceftaroline M-1. It has a low potential for drug interactions because of insignificant metabolism by CYP_{450} enzymes.

It is given as 600 mg intravenous dose, every 12 hourly.[8] Dose adjustment is required in patients with renal impairment as it is primarily eliminated by the kidneys. The most common side effects observed during cSSSI clinical trials were nausea, dysgeusia and caramel-like taste disturbances, vomiting, diarhoea and headache.

Ceftobiprole

It is another newer cephalosporin which has completed its trial in 2007 and is awaiting FDA approval due to additional safety data being demanded by FDA. It is the broad-spectrum antibiotic which shows good spectrum of activity against MRSA, penicillin-resistant *S. pneumoniae*, *P. aeruginosa* and *Enterococci*.[9] Ceftobiprole shows strong affinity for PBP2a of MRSA and PBP2x of *S. pneumoniae*.[10]

It is given as 1 hr IV infusion of 500 mg every 12 hrs for gram-positive infection and a 2 hr infusion of 500mg every 8 hrs for gram-negative. Dose adjustment is needed in patients with renal impairment.[11] It is well tolerated with most common side effects being nausea and dysgeusia.

Newer glycopeptides

Due to emergence of vancomycin resistant strains, interest has been focused on the development of three newer derivatives of glycopeptides – oritavancin, dalbavancin, and telavancin. Of these, oritavancin and dalbavancin are still in developmental phases while telavancin have been approved by FDA for the treatment of cSSTIs in adults. All three newer glycopeptides are much more potent with lesser potential for development of resistance in comparison to vancomycin. They show rapid bactericidal activity against Vancomycin Resistant *Enteroccoci* (VRE) and VRSA, unlike vancomycin which is bacteriostatic.

The newer glycopeptides act by inhibiting transglycosylation and transpeptidation reactions of peptidoglycan biosynthesis. Both oritavancin and telavancin shows additional mode of action.They disrupt the membrane potential and thus increase cell permeability causing rapid bactericidal activity.[12]

Dalbavancin, oritavancin, and telavancin have been well tolerated in clinical trials.[13-15] Their half lives in humans are approximately 7 days, 15 days, and 7.5 hrs respectively.[16,17] This allows longer dosing intervals for dalbavancin and oritavancin. The side effect profile of telavancin includes nausea, vomiting, taste disturbances, QT prolongation, and infusion-related reactions (red-person syndrome).

Mechanism of resistance to vancomycin includes the synthesis of low-affinity precursors by bacteria in which C-terminal D-alanine residue is replaced by D-lactate (D-Lac) or by D-serine (D-Ser).[18] This mechanism of resistance have been overcome by newer glycopeptides by having high binding affinity to both the precursor substrates (D-Ala-D-Lac and D-Ala-D-Ser) due to presence of hydrophobic side chains in the drug.

Newer carbapenems

Doripenem

It is the newer parenteral carbapenem approved for the treatment of complicated urinary tract infections and intra-abdominal infections. The drug acts by binding to PBPs and thus inhibiting cross-linking of the peptidoglycan structure. The high binding affinity of doripenem to PBP-2 and -3 may enhance its activity against drug-resistant *P.* aeruginosa. Thus, it is a suitable alternative to currently available anti-pseudomonal carbapenems (i.e, imipenem, meropenem).[19] Doripenem has a unique spectrum of activity. It shows activity against gram-positive cocci like imipenem and activity against gram-negative bacilli like meropenem.[20] Doripenem, like other carbapenems, is stable to ESBLs produced by *E. coli* and Klebsiella species and to AmpC β-lactamases enzymes; but it is vulnerable to certain acquired β-lactamases like class B metallo-β-lactamases produced by some P. aeruginosa isolates and carbapenemases produced by some Enterobacteriaceae and Acinetobacter species.[21]

Recommended dose of doripenem is 500 mg IV every 8 hr. Doripenem exhibits linear pharmacokinetics with volume of distribution of 16.8 l. Protein binding is low (8.1%) and is independent of concentrations of drug in the plasma. The estimated elimination half-life of doripenem is 0.95 hr, and 75% of the drug is excreted unchanged in the urine, requiring dosage adjustment in patients with renal impairment.[22] The most common ADRs are headache, nausea, diarrhea, rash, and phlebitis. Postmarketing reports have also identified Stevens-Johnson syndrome, toxic epidermal necrolysis, interstitial pneumonia, and seizures as adverse drug reactions.

Razupenem (PZ-601)

It is another novel carbapenem active against multi drug-resistant gram positive and gram-negative (ESBL producers) bacteria and is currently in trials for cSSSI.[23]

Pleuromutilin

Retapamulin

It is a novel topical antibiotic and the first approved member in this new class. It is approved for the treatment of skin and soft tissue infections caused by *S. pyogenes* and *S. aureus* which are resistant to the most commonly used topical antibiotics. It is ineffective against gram-negative organisms.[24] Retapamulin is a semisynthetic pleuromutilin derivative isolated from *Clitopilus scyphoides* (an edible mushroom). It is a protein synthesis inhibitor which acts by binding to 50-S subunit of bacterial ribosomes.

Plasma protein binding of Retapamulin is 94% and it is metabolized mainly in liver by CYP_{3A4} to numerous metabolites.[25] The most common adverse effect is pruritus at the application site.

Glycylcyclines

Glycylcyclines is a new class of antimicrobials that are chemical derivatives of minocycline.

Tigecycline

It is the first glycylcycline approved by FDA for cSSTIs, intra abdominal infections and CAP.[26] It has been designed to overcome two common mechanisms of tetracycline resistance i.e. resistance mediated by acquired efflux pumps and by ribosomal protection. It acts by binding to 30-S subunit of ribosome, thus inhibiting protein synthesis which is 20 fold more efficient than tetracycline.

Tigecycline has a broader spectrum of activity against aerobic and anaerobic gram-negative and positive pathogens. *In vitro* data shows that tigecycline has very good antibacterial activity against ESBL as well. It is not active against *P. aeruginosa,* which is an important gap in its antimicrobial spectrum.[27]

Tigecycline, formulated for parenteral use only, is given as 100 mg loading dose followed by a maintenance dose of 50 mg every 12 hr. As with all tetracyclines, tissue and intracellular penetration is excellent with large volume of distribution. Protein binding for tigecycline is 71% to 89%.[28] It has a long terminal elimination half-life of about 36 hr which allows for twice-daily dose administration. Its pharmacokinetics is unaffected by food, age, race, and renal disease.[29] Primary route of elimination is the biliary excretion so dose adjustment is recommended in

hepatic disease.[30] The side effect profile includes mild GIT disturbances like diarhoea, nausea and vomiting.

Ketolides

Ketolides are the new class of macrolides designed particularly for the treatment of respiratory tract pathogens that have acquired resistance to macrolide antibiotics. Ketolides are semi-synthetic derivatives of the 14-membered macrolide, erythromycin. They are synthesized by substituting a keto- function for the α, L-cladinose moiety at position 3 of the 14-membered erythronolide A ring. Carbonyl group at C3 position is responsible for sensitivity to macrolide resistant strains.[31]

Telithromycin

It is the first ketolide to enter clinical use for the treatment of CAP, chronic bronchitis and acute sinusitis. Other ketolides are under clinical development phase [Table 1]. Telithromycin is a protein synthesis inhibitor that blocks the progression of the growing polypeptide chain by binding to 50-S subunit of the bacterial ribosome. Telithromycin exhibits 10 times higher affinity to the subunit 50-S than erythromycin. In addition, telithromycin strongly bind simultaneously to two domains of 23-S RNA of the 50-S ribosomal subunit, where as older macrolides bind strongly only to one domain and weakly to the second domain [Figure 1].

Telithromycin is more active *in vitro* against *S. pneumoniae* compared with clarithromycin and azithromycin and maintains activity against macrolide resistant strains (*S. pneumoniae, S. pyogenes*).[32]

Telithromycin is formulated as 400 mg tablet for oral administration. It is well absorbed orally with 60% bioavailability. Peak plasma concentration of 2.27 mg/l and a terminal half-life of 9.81 hr is achieved with a single 800 mg daily oral dose.[33] Telithromycin achieves high tissue concentrations in respiratory fluids and tissues including saliva, alveolar macrophages, epithelial lining fluid, and bronchial mucosa.[34] Telithromycin is 66-89% bound to serum protein, principally albumin. Drug is cleared primarily by hepatic metabolism, 50% by CYP_{3A4} and 50% by CYP independent metabolism. No dose adjustment is required for patients of hepatic failure or mild to moderate renal disease.

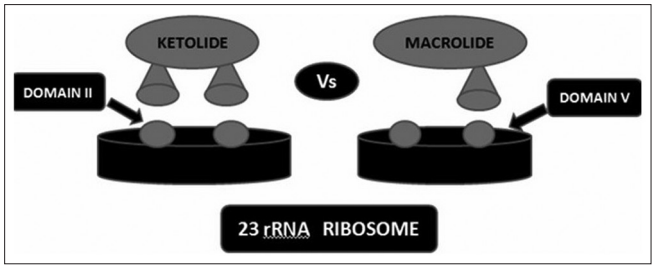

Figure 1: Mechanism of action of ketolide that overcome resistance

Approval of telithromycin was controversial due to trial irregularities, non-inferiority study designs, and the use of foreign safety data. On 12 February 2007, FDA withdrew two of its indications with CAP as the only remaining indication, with a black-box warning issued due to its safety concerns involving hepatotoxicity, myasthenia gravis exacerbation, and visual disturbances.[35]

Lipopeptides

Daptomycin

Daptomycin is a cyclic lipopeptide antibiotic derived from *Streptomyces roseosporus* and is the first member of this new class of antimicrobials. It was approved by FDA in 2003 for the treatment of SSTIs and approved in 2006 for the treatment of blood stream infections. It shows the unique mechanism of action by inserting its lipophilic tail into the cell membrane of gram-positive organisms without entering the bacterial cytoplasm. This calcium dependent process leads to the formation of channels from which intracellular potassium is lost disrupting the bacterial cell membrane potential and causing cell death.[36]

Daptomycin is bactericidal against *Methicillin resistant staphylococcus aureus* (MRSA), *Methicillin-resistant Staphylococcus epidermidis* and VRE inclusive of linezolid-resistant isolates. It is inactive against gram negative pathogens because of its inability to penetrate its outer membrane. It is poorly absorbed orally, thus administered by intravenous route only. It is highly bound to plasma protein with serum half life of 8-9 hr. Approximately 80% of the administered dose is recovered in urine and only a small amount is excreted in faeces. In July 2010, a warning was issued by FDA about the potential of daptomycin to cause life threatening complication i.e., eosinophilic pneumonia. Seven cases of eosinophilic pneumonia were identified between 2004 and 2010.[37]

Novel dihydrofolate reductase inhibitors

Iclaprim

Iclaprim is a synthetic diaminopyrimidine, a selective inhibitor of the enzyme dihydrofolate reductase, which is similar to trimethoprim. Iclaprim is particularly potent against *S. pneumoniae* and *S. aureus*, including trimethoprim-resistant isolates. In contrast to trimethoprim which is most frequently used in combination with sulfamethoxazole, iclaprim is being developed for administration as a single agent, though highly synergistic activity was demonstrated with the sulfonamides like sulfamethoxazole, and sulfadiazine.[38]

Iclaprim displays linear pharmacokinetics. The protein binding of iclaprim is 92%-94% and half-life is 2-4 hr.[39] A NDA for iclaprim in the treatment of cSSSIs was submitted to the FDA based on data from two phase III studies (ASSIST-1 and-2). These studies showed that iclaprim 0.8 mg/kg every 12 hr

was non-inferior to linezolid.[40] However, FDA demanded additional clinical data in January 2009 to demonstrate its clinical efficacy for gaining approval.[41]

Oxazolidinones

Torezolid and radezolid

In the past three decades, oxazolidinones are considered to be the first truly new class of antibacterial drugs. As of the year 2009, linezolid is the only oxazolidinone available in the market for the treatment of gram-positive infections, including those caused by MRSA or VRE. Newer oxazolidinones with improved potency, aqueous solubility and reduced toxicity have been developed by modifications of A, B and C rings of linezolid.[42] Torezolid and radezolid are two novel oxazolidinones being under research for the treatment of cSSSI and uSSSI respectively, and both have completed phase II clinical trials. Their mechanism of action is similar to linezolid i.e., to prevent the initiation of translation of proteins by binding to the 23-S portion of the 50-S ribosomal subunit.

Torezolid is the active moiety of the prodrug, torezolid phosphate, which has 4-16 fold greater potency than linezolid against gram-positive species including MRSA.[43] Radezolid is another novel oxazolidinone with increased and broader spectrum of activity as compared to linezolid. In a phase II clinical trial ($n = 150$) for uSSSIs, a similar cure rate of 97.4% was achieved with 450 mg (once a day) radezolid as compared to 600 mg linezolid (twice a day) against gram positive pathogens.[44] Resistance to linezolid results from mutations in ribosomal RNA (rRNA) that has been overcome by newer oxazolidinones by additional hydrogen bond interactions with 23-S rRNA.

Newer targets for the next generation antimicrobials for combating drug resistance

There are a number of good clinically efficacious antibiotics in use today; however, the development of bacterial resistance has rendered almost all of them less effective. Most of these are bacteriostatic, and act by either protein or cell wall synthesis inhibition. This critical situation necessitates the designing of novel antibacterial agents with new targets.

Target bacterial proteins

Antibiotics can act to target novel bacterial proteins like inhibiting β-ketoacyl-acyl-carrier-protein synthase I/II enzyme required for fatty acid biosynthesis. Platensimycin is one such drug in preclinical trials which acts by blocking these enzymes involved in the condensation steps in fatty acid biosynthesis.[45]

Target the virulence factors for rapid clearance of infecting organisms

Virulence inhibitors could target - toxin function e.g., *B. anthracis* lethal factor catalytic activity; toxin delivery by inhibiting various bacterial systems such as type II or type III secretion; virulence gene regulation that control virulence gene expression; and bacterial adhesion to host cells e.g., inhibition of the formation of pili by pilicides.[46]

Modulating the host response pathways

Toll-like receptor activators and modulators could potentially have an antimicrobial role by producing antimicrobial peptides that activates the adaptive immune response to combat the infection.[47]

Therapeutic use of bacteriophages to treat pathogenic bacterial infections

Small, acid-soluble protein (SASPs) genes can be delivered to *S. aureus* via a *S. aureus*-specific delivery bacteriophage, resulting in the production of SASPs which can bind to and inactivate bacterial DNA.[48] These proteins have been shown to be rapidly bactericidal and active against a range of *S. aureus* strains, irrespective of existing antibiotic resistances.

Combining β-lactamase enzyme with β-lactam antibacterial drug

It can significantly reduce emergence of resistant microbes by taking advantage of the natural phenomenon of inactivation of antibacterial drugs by enzymatic hydrolysis.[49]

In a Phase II study ($n = 112$) for the treatment of serious respiratory infections, fifty four patients treated with P1A (β-lactamase product) and ampicillin had a 20% change in gut microflora compared to 50% change in patients treated with ampicillin alone. The β-lactamase would inactivate any unused β-lactam antibacterial drug in the GI tract, thus maintaining the gut microflora. Emergence of ampicillin resistance was also 7-fold lower in patients treated with the enzyme/lactam combination compared to antibacterial drug alone.

Combination of antibiotics with bioenhancers

A bioenhancer is an agent capable of enhancing the bioavailability and efficacy of a drug with which it is co-administered, without any pharmacological activity of its own at the therapeutic dose used.[50] Bioenhancers can be used to increase the efficacy of commonly used antibiotics, like combining antibiotic tetracycline with non-antibiotic drug loperamide tend to enhance the efficacy of tetracycline by increasing its permeability;[51] Cow urine distillate (CUD) can act as a potential therapeutic target to enhance the activity of antibacterial agents. CUD when combined with rifampicin increased the activity of drug by about 5-7 times against *Escherichia coli* and 3-11 times against gram-positive bacteria.[50]

Newer strategies for antibacterial drug discovery

Most of the current antibacterial drugs were discovered by means of traditional approaches, which are now saturated. This has led to the emergence of drug resistance as well as the

emergence of new pathogens, requiring the development and exploration of newer strategies in antibacterial drug discovery.

Antimicrobial peptides derived from vertebrates, invertebrates and microorganisms

These act by interfering with metabolism, targeting cytoplasmic components and disrupting cell membranes. They may also enhance the immunity by functioning as immunomodulators, thus can serve as a novel potential therapeutic target. Examples are dermaseptin derived from frog skin, defensin and crustin from crustacean family and bacteriocin derived from bacteria.[52] Drugs in the pipeline are omiganan and pexiganan both of which are under clinical trials.

Engineer a prodrug that gets converted into highly potent drug within a microbe

Using prodrug form of a drug, which is converted into highly potent drug within a microbe so that common resistance mechanisms could be bypassed, can be another strategy for new drug discovery.

Engineer hybrid antibacterial drugs for high potency against two targets

Simultaneously two targets can be covered like Mutilin- quinolone hybrid AM-3005 is a Type II topoisomerase inhibitor and also a protein synthesis inhibitor.[53]

Alternative form of drug delivery methods

Unconventional form of drug delivery methods can be used like inhaled amikacin available as nanoscale liposomal formulation showing potential for treatment of chronic *P. aeruginosa* lung infections in cystic fibrosis patients by offering advantages such as biofilm penetration and sustained release from liposomes.[54]

Herbal derivatives as lead molecules

Even herbal drugs, certain plant-derived compounds, their essential oils and medicinal smoke from sublimating the *havana sámagri* (mixture of wood and odoriferous and medicinal herbs) can serve as lead molecules and play a significant role in drug discovery and development process [Table 2].

A study was done by Nautiyala *et al.* in which it was observed that 1 hr treatment with medicinal smoke, released by burning wood and mixture of odoriferous and medicinal herbs, lead to 94% reduction of bacterial counts by 60 min. Absence of pathogenic bacteria (*Corynebacterium urealyticum, Enterobacter aerogenes, Enterobacter aerogenes, Klebsiella mobilis, Kocuria rosea, Pseudomonas syringae pv. persicae, Staphylococcus lentus)* in the open room even after 30 days is indicative of the bactericidal potential of the medicinal smoke treatment.[60] Medicinal smoke from natural herbal products have a potential for use as a smoke/inhalational form of drug delivery.

Table 2: Herbal drugs and drugs from other natural sources with antibacterial potential

Common name (Botanical name)	Spectrum of activity	References
Chakvad (*Cassia tora*)	*S. aureus*	Roopashree TS, 2008[55]
Pot marigold (*Calendula officinalis*)	*B. subtilis, P. aeruginosa*	Roopashree TS, 2008[55]
Karela (*Momordica charantia*)	*E. coli*	Roopashree TS, 2008[55]
Peppermint (Mentha piperita)	*E. coli*	Schelz Z *et al.*, 2010[56]
St. John's wort (*Hypericum perforatum*)	MRSA	Schelz Z *et al.*, 2010[56]
Honey	*S. aureus, E. coli, S. faecalis, P. aeruginosa, P. mirabilis, Salmonella typhi*	Chute RK, 2010[57]
Cow urine distillate	*B. subtilis, P. aeruginosa, Klebsiella pneumonia, Salmonella typhi*	Sathasivam AK, 2010[58]
Mineral leachates - clay mineral mixtures	MRSA, *E. coli*	Otto *et al.*, 2010[59]

MRSA: Methicillin resistant *staphylococcus aureus*

Conclusion

At the beginning of 21st century, the widespread emergence of antimicrobial resistance has lead to the ineffectiveness of large number of the current antimicrobials in use. Various efforts have been made to combat this resistance so that newer targets can be identified and next generation of effective antimicrobials be produced.

It is notable that few of the drugs described in this paper are in various phases of clinical trial and some awaiting final regulatory approvals. We can expect these antibacterials to be soon present in market for the treatment of resistant strains once they gain the FDA approval. The post marketing surveillance of these newer drugs in clinical trials is must, once the drug is in the market, as rare adverse events often go un-noticed during trials due to enrollment of selected and limited number of patients. There is urgent need for complete understanding of the various aspects of drug resistance in microbes which can help in the choice of good targets, vital for discovery of new antibacterial drugs. In the near future, the next challenge will be to identify newer agents for the treatment of multidrug-resistant Gram-negative pathogens which are emerging at a rapid rate.

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