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KOMBAT: Knowledgebase of Microbes' Battling Agents for Therapeutics

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Abstract

Antimicrobial resistance (AMR) is one of the top 10 threats affecting global health. AMR defeats the effective prevention and treatment of infections caused by microbial pathogens including bacteria, parasites, viruses and fungi (WHO). Microbial pathogens have natural tendency to evolve and mutate over time resulting in AMR strains. The set of genes involved in antibiotic resistance also termed as "antibiotic resistance genes" (ARGs) spread through species by lateral gene transfer thereby causing global dissemination. While this biological mechanism is prevalent in the spread of AMR, human methods also augment through various mechanisms such as over prescription, incomplete treatment, environmental waste etc.

A considerable portion of scientific community is engrossed in AMR related work trying to discover novel therapeutic solutions for tackling resistant pathogens. Comprehensive inspection of the literature shows that diverse therapeutic strategies have evolved over recent years. Collectively, these therapeutic strategies include novel small molecules, newly identified antimicrobial peptides, bacteriophages, phytochemicals, nanocomposites, novel phototherapy against bacteria, fungi and virus.

In this work we have developed a comprehensive knowledgebase by collecting alternative antimicrobial therapeutic strategies from literature data. We have used subjective approach for

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datamining new strategies resulting in broad coverage of entities and subsequently add objective data like entity name, potency, safety information etc. The extracted data was organized KOMBAT (Knowledgebase Of Microbes' Battling Agents for Therapeutics). A lot of these data are tested against AMR pathogens. We envision that this database will be noteworthy for developing future therapeutics against resistant pathogens. The database can be accessed through http://kombat.igib.res.in/.

Keywords: Antibiotic resistance, text mining, therapy, database

1. Introduction

Antimicrobial resistance (AMR) is one of the top 10 threats affecting global health (1). AMR defeats the effective prevention and treatment of infections caused by microbial pathogens including bacteria, parasites, viruses and fungi (1). Microbial pathogens have natural tendency to evolve and mutate over time resulting in AMR strains (2). The set of genes involved in antibiotic resistance also termed as "antibiotic resistance genes" (ARGs) spread through species by lateral gene transfer thereby causing global dissemination (3). Not only this biological mechanism is prevalent in the spread of AMR, but also human noncompliance to use of antibiotics aggravate this scourge. Notable among the latter are mechanisms such as inappropriate use (under-dosing and over-prescribing) in humans, livestock and agriculture, misuse of antibiotics (for viral infections where they are ineffective) (4,5). The antibiotics in effluent water also add to the prevalence of AMR (6). Due to antibiotic resistance, 700,000 people die worldwide every year and this number is expected to rise to 10 million by 2050 (7). The health catastrophe due to AMR impacts on world's GDP and it is expected to cause $100.2 trillion GDP loss by 2050 (7). CDC's (Centers for Disease Control and Prevention) 2019 antimicrobial resistance threats report lists 18 antibiotic-resistant bacteria and fungi as either urgent, serious or concerning (8). Notably the Carbapenem-resistant *Acinetobacter, Enterobacterales*, and *Clostridioides difficile*, drug-resistant *Neisseria gonorrhoeae* and *Candida auris* are included in the urgent threats category.

The answer to this crisis is to develop novel effective antibiotics. However, it takes 10-15 years from discovery of a novel compound to development of new drug through pre-clinical and clinical testing

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(9). The average cost from research and development to a new medicine is approximately $4 billion, and could exceed to $10 billion in some cases (10). Undoubtedly, the antimicrobial discovery pipeline needs rejuvenation with modern technologies.

Comprehensive inspection of the literature shows that diverse therapeutic strategies have evolved over recent years. Collectively, these therapeutic strategies include novel small molecules, newly identified antimicrobial peptides, bacteriophages, phytochemicals against bacteria, fungi and virus. There are several antimicrobial therapeutic databases, such as database of antimicrobial peptides, of chemical compounds. For example, AntibioticDB (11) is a database of antibacterial compounds under development belonging to different phases of clinical trials including discontinued compounds, APD (12) is a resource for Antibacterial, antifungal, antiviral and antitumor peptides retrieved from literature. A comprehensive list of different antimicrobial databases is displayed in Supplementary Table1.

To the best of our knowledge there is no encyclopaedically recorded site for newly discovered antimicrobial strategies comprising of novel molecules, AMPs, bacteriophages, probiotics, phytochemicals, photodynamic therapy, nanocomposites. Our goal in KOMBAT was to develop an integrated resource of newly identified chemotherapeutic strategies against microbial pathogens from scientific literature. Many of these strategies are tested against AMR pathogens. Currently the available antimicrobial databases belong to 2 major domains, one focussing on the problem of AMR with the resources for ARGs and their sequences (eg: CARD (13), MEGARes (14), ARDB (15), PATRIC (16)); the second focussing on the solution to the AMR problem, (eg: AntibioticDB (11), ASDCD (17)). Overwhelmingly, these databases focus on bacterial pathogens and include one type of anti-microbial agent. Also, a large fraction of data from these databases are part of PubChem (18), instead of collection from primary sources. Some databases are either not regularly updated or not accessible (eg ACD (19), AMDD (20)).

Here we report KOMBAT (Knowledgebase of Microbes Battling Agents for Therapeutics). We have used a comprehensive method to overcome the discussed limitations by collecting text data from PubMed and organizing them in a user-friendly manner. We have used text mining (21) and natural

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language processing (22) for data curation, classification and developed a protocol for regular updates. KOMBAT contains alternative antimicrobial strategies against bacteria, virus, fungi and parasites. Our approach is focussed in

1. Data collection from primary sources
2. Manual curation to remove false positive
3. Subjective sentiment-based approach for datamining new strategies resulting in broad coverage of entities and subsequently add objective data
4. Including all the microbes namely bacteria, virus, fungi and parasites.
5. Tested strategies on AMR species.

2. Methods:

All text mining work was carried out using CRAN package pubmed.mineR (23). pubmed.mineR is a R package for analysis of PubMed literature texts. Infographics for detailed work flow is displayed in Figure 1.

2.1 Data collection and classification

1,42,205 abstracts were collected from PubMed using keywords “antimicrobial resistance” and “antibiotic resistance” using the “All fields” option. Abstracts were classified into 4 categories, (1) antibacterial using the keywords: bacteria, bacterial, antibacterial, (2) antiviral using keywords: virus, viral, antiviral, (3) antifungal using keywords: fungi, fungal, antifungal and (4) antiparasitic using the keywords: parasite, parasitic, antiparasitic in case insensitive search mode.

2.2 Subjective (Sentimental) text mining approach

For data retrieval, initially a couple of seed terms ‘therapy’ and ‘therapeutic’ were selected and vocabulary of associated keywords were made. Due to high diversity in the nomenclature of new entities, we required anchor terms for data mining. In order to extract entities like ‘Phage ZZ1’ or ‘ZZ1’, ‘1,4-naphthoquinones ', ‘compound6a’, we sought to locate ‘anchor’ terms expressing the sentiments of authors about their discoveries. Thus, we located 7 adjectives or adverbs namely,

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'therapeutic', 'promising', 'new', 'next', 'potent', 'alternative' and 'novel'. Additionally, we located anchor nouns: 'therapy', 'strategy' and verbs: 'prevent', 'alternate'. Subsequently, we extracted the left associated and right associated words of these conserved terms. Associated words appearing as pronouns and prepositions were not considered. These combinations were used to extract co-occurring sentences described in the next section. The word_associations() function of pubmed.mineR was used for collecting associated vocabulary of 11 anchor terms. The collected vocabularies are listed in supplementary Table2. Using natural language processing, the terms were automatically categorized in correspondence to part-of-speech (POS). Natural Language Toolkit (NLTK) library of python was used for POS tagging(24). Inclusively, we have collected 128 adjectives, 397 nouns, 48 verbs and 4 adverbs. The temporal trends of these terms were analysed by using BWI (buzzword index) function of pubmed.mineR reveals trends patterns over a period of time (25).

2.3 Data retrieval

For data retrieval, co_occurrence_fn() of pubmed.mineR package was used. This function extracts sentences with co-occurrence of 2 sets of given terms. One of the terms were among the 11 anchor terms and the other term was from the associated vocabularies. The sentences were then manually curated and only positive evidences were considered.

2.4 Objective text mining approach

The sentiment approach provided a conserved set of terms serving as anchors for extracting the new strategies. This resulted in obtaining the landing sentences from the abstracts. However, users and peers would require objective data devoid of sentiments for their own assessments. Therefore, we used the lateral movement approach in the same abstract using different set of terms to extract objective data including name of the entity (IUPAC name in case of chemicals), MIC, IC50, EC50, target species tested, safety and toxicity data. The full list of Terms and their corresponding part of speech tagging used for the objective data extraction are displayed in Table 1. The diversity of terms in the objective approach is also noteworthy. Sentences from the abstracts containing the given terms

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extracted were further curated manually. Whenever data was not available through this method in the abstracts, we used the same approach on full paper texts available from PubMed Central.

Table 1: Vocabularies and their POS used in objective approach

NOUN*	ADJECTIVE	PREPOSITION
'aim', 'goal', 'design', 'synthes', 'purpose', 'stud', 'test', 'evaluat', 'investigat', 'examin', 'explor', 'compar', 'effic', 'log[1234]', 'MIC', 'dos', 'cidal', 'fold', 'reduc', 'muta', 'resist', 'concentra', 'multipli', 'MOI', 'days', 'inhibit', 'CFU', 'kill', 'effect', '[ ]heal[eis]', 'eradicat', 'decoloniz', 'tolerat', 'advers', 'side effect', 'sever', '[a-z-]toxic', 'reaction', 'discomfort', 'complian'	'active', 'daily', 'clear', 'safe'	'as well as'

*Words are stemmed

2.5 Web interface development

The web interface of KOMBAT was developed using PHP 8.0.2 and HTML. The consolidated data were entered in MariaDB 10.4.17 tables using XAMPP (v3.2.4). XAMPP is an open-source cross platform package including MariaDB (database), Apache 2.4.46 (server application) and PHP (scripting language).

2.6 Database structure and content

KOMBAT contains newly identified potential therapeutic strategies against microbial pathogens and in many cases tested on AMR pathogens. Broadly the data can be classified in 4 categories: antibacterial therapeutic strategies, antiviral therapeutic strategies, antifungal therapeutic strategies and antiparasitic therapeutic strategies. Microbial species names were annotated using PubTator Central (26). The strategies were classified as (1) Antimicrobial Peptides, (2) Small Molecules, (3) Phage therapy, (4) Photodynamic Therapy, (5) Nano compounds and combinations, (6) Phytochemicals. Collected evidences were reported along with specific information containing data

 doi:10.20944/preprints202110.0033.v1

on potency (MIC, IC50, EC50), safety (toxicity) and on species tested was retrieved using objective approach.

Results and Discussion:

3.1 Data collection:

Antimicrobial research has increased substantially in recent years since 2001 with about 95% increase in the number of abstracts in PubMed articles. Searches revealed 43509 abstracts in bacteria (68%), 14418 abstracts in virus (23%), 5354 in fungi (8%) and 908 abstracts in parasite (1%) category. These sub-corpuses were used for text mining in the later stage.

3.2 KOMBAT user interface

KOMBAT has a very user-friendly web interface and it can be accessed through http://kombat.igib.res.in/.

Home: In this section, features of the database are displayed through which the user can enter into its desirable section. Separate web pages for bacteria, virus, fungi and parasites were created and user can switch between these pages. At the bottom we have added links for some relevant and complementary information. The “Related Database” link directs user to the list of antimicrobial databases. It contains resources along with their name, focus, weblink and PMID. Another tab acknowledging major events of antibiotic and post antibiotic era is added, which can be accessed through “Related Links”.

About: Includes the rationale behind developing KOMBAT, categories and sub-categories of included data.

Contact: Contact details of the authors are given in this section for query and suggestions.

Help: Guide for using different features of KOMBAT database were given here.

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KOMBAT Community: Significance of this database can be appreciated when this is updated regularly with inclusion of most recent therapeutic strategies. Therefore, we created KOMBAT community and encourage students to join.

3.3 Trend analysis of terms

The Trends analysis over last 30 years revealing importance of the terms displayed in Figure 2. The terms ‘therapy’ and ‘new’ go hand-in-hand importance over the years. The terms ‘novel’, ‘therapeutic’, ‘strategy’, ‘prevent’, ‘potent’, ‘alternative’ and ‘promising’ shows and overall increase in BWI values. The word ‘next’ shows a similar pattern with an exception of significant drop in BWI in 1994. The term ‘alternate’ shows a fluctuating trend with highest value (BWI = 14.48981) in 1991, followed by sudden drop (BWI = 0) in some years. However, over the last 15 years there is a rising trend in importance of this term.

3.4 Data in KOMBAT

3.4.1 Phage therapy

Bacteriophages infect and multiply inside bacteria. The Phage therapy concept is the use of phage as antibacterial agents by exploiting the property of phages to recognize specifically, bind and multiply within bacterial host cells (27). Phage lysin enzymes are responsible for bacterial cell wall lysis and also have the ability to disrupt biofilms (28). Lytic bacteriophages are known as potential antibacterial agent (29). Phage therapy is yet not included in mainstream treatment despite having advantages of high specificity towards bacteria (29). Though it has gained immense interest in last few years. For example, clinical trials are going for evaluating safety and efficacy of phage therapy to treat patients with urinary tract infection due to *E. coli* and *K. pneumoniae* (30) and for patients with ventricular assist devices (VAD) developing *Staphylococcus aureus* infections (31).

In KOMBAT database, we have reported 22 manually curated phage therapy strategies. This includes lytic phage, phage lysin enzymes and also different phage cocktails. For example, T4-Like Phage Bp7 (32), PhageTPR7 (33), lytic phage EcSw (34) are some potential bacteriophage therapies against hospital isolated drug resistant strains of *E. coli*. Jin et al., 2012 had reported the activity of phage

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ZZ1 against different clinically isolated strains of *Acinetobacter baumannii* namely AB09V, AB0902, and AB0901 (35). In the database, the "phage ZZ1" is included under 'ENTITY' column, target species and latent period that is the time required by the phage to reproduce inside infected cell is included under 'POTENCY' column. Additionally, we have included the proof of association in the 'EVIDENCE' column and link to PubMed site in the 'PMID' column. Another example of lytic phage cocktail included in KOMBAT is the combination of φkm18p, φTZ1 and φ314 having activity against extensively drug resistant *Acinetobacter baumannii* (36). Among the included lysins, CHAP(K) was tested against pathogenic *Staphylococci* including MRSA (37), combination therapy of bacteriophage lysin enzyme CF-301 with antibiotics was reported to be superior to traditional antibiotic monotherapy against several drug resistant and sensitive stains of *S. aureus* (38). HydH5 is another hydrolase with lytic activity as alternatives for anti-staphylococcal therapy (39).

3.4.2 Antimicrobial peptide

In the quest of new therapeutic strategies for tackling AMR, antimicrobial peptides (AMPs) or host defense peptides have gained enormous interest. These are bioactive polypeptides comprising 12-50 cationic and hydrophobic amino acid residues (40,41). The antimicrobial nature includes activity against bacteria, virus, fungi and parasites (42). These peptides interact directly with cell membranes via electrostatic and hydrophobic forces and self-assemble after reaching certain concentration (43). They further interact with the lipid bilayer and disrupt it. These interactions can be explained by transmembrane pore and non-pore models (44). Additionally, AMPs perform immunomodulatory activity by recruitment and activation of immune cells, which result in enhanced microbial killing (45). In KOMBAT database, 69 antimicrobial peptides having therapeutic potential are reported. Novel antimicrobial peptides and combinatorial therapeutic strategies of AMPs with photosensitizer or existing antibiotics are reported here. For example, the peptide KLKLLLLLKLK-NH2 and its D-enantiomer showed in-vivo activity against MRSA infected mice with drop of relative bacterial growth from 100% to almost negligible(46), Hominicin purified from *Staphylococcus hominis* MBBL 2-9 displayed potent antibacterial activity against different drug resistant and sensitive strains of *S. aureus* (47). Thionin Thi2.1 extracted from *Arabidopsis thaliana* is a potent AMP having activity

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against *S. aureus* isolated from cow's milk with subclinical mastitis (48). Many AMPs have been reported to have broad spectrum activity. TSG-8-1 (WWSYVRRWRSR-amide) is a potent 11-mer peptide with antibacterial activities against *E. coli* and *S. aureus* (49). Investigators have reported that this peptide showed very little hemolytic activity in human erythrocytes and this information is included in the 'SAFETY INFORMATION' head of KOMBAT. Brevinin-2Ta (B-2Ta) is another broad-spectrum AMP isolated and purified from *Pelophylax kl. esculentus* (European frog) showing in-vitro activities against *S. aureus*, *E. coli* and *C. albicans* (50). Further B-2Ta showed anti-inflammatory activity against *Klebsiella* infected rats. MICs displayed in 'POTENCY' column as 64 mg/L against *S. aureus* and *C. albicans*, 32 mg/L against *E. coli*. Histone H5 purified from chicken erythrocytes, has broad spectrum antibacterial properties against Gram-positive and Gram-negative planktonic bacteria including resistant strains (51). Alongside having therapeutic efficacies, AMPs can also be used as adjuvants to enhance the immune response. Liu et al., 2012 had reported antimicrobial peptide YI13WF (YVLWKRKRKFCFI-Amide) and its photodynamic inactivation of different Gram-negative bacterial strains(52). Here peptide was used as an adjuvant to enhance the binding to cell wall, which can be disrupted using white light source for 2, 5, and 10 min. Dimeric PpIX-YI13WF conjugates show strong photoinactivation of *Escherichia col*i DH5a, *S. enterica*, antibiotic-resistant *E. coli* BL21 *and K. pneumoniae* epidermicin. The peptide CSpK14 synergistically enhances the activity of β-lactams against vancomycin resistant strains of *Staphylococcus* and *Enterococci* (53). NI01 is a cationic, hydrophobic antimicrobial peptide discovered and purified by Sandiford et al., 2011 having antimicrobial activity against methicillin-resistant *Staphylococcus aureus* (MRSA), *Enterococci*, and biofilm-forming *S. epidermidis* strains (54). C(12)K-2β(12) is a oligo-acyl-lysyl (OAK) antimicrobial peptidomimetic, with anti-*H. pylori* activities (55). Overall, AMPs are promising therapeutic options for tackling various microbial infections.

3.4.3 Natural products

Phytochemicals have been used as part of traditional medicine. Their antimicrobial actions include diverse mechanisms like damage to cell membrane, suppression of virulence factors, enzymatic inhibition. In KOMBAT, we have included 88 different therapeutic strategies that use extracts from

 doi:10.20944/preprints202110.0033.v1

natural products. For example, tea tree oil (TTO) has potent antimicrobial and anti-inflammatory activities (56). Loughlin et al., 2008 had compared the antimicrobial activity of TTO and terpinen-4-ol against different isolates of *Staphylococci* including drug resistant strains (57). Liposome encapsulated TTO with silver ions Ag (+) has strong therapeutic potential due to the controlled release and thereby causing reduced cytotoxicity and lower chance of developing resistance in long term (58). Epigallocatehin-3-Gallate, which is abundantly present in green tea extracts has potent antimicrobial activity against hospital isolated *Pseudomonas aeruginosa* and *Escherichia coli* (59). It has potent antibiofilm activity and therefore can be used as adjuvant in antibiotic therapy (60). Antimicrobial property of honey has been extensively studied from different geographical regions against several Gram-positive, Gram-negative and fungal skin and wound infections (61,62). The combination therapy of honey and antibiotic has immense advantage due to synergistic enhancement in antimicrobial activity and reduction of developing AMR (63). Essential oils were part of traditional medicines and are used in modern medicine also. For example, essential oils extracted from *Origanum heracleoticum L* (64), *Lippia gracilis Schauer* leaves (65), *Hyptis martiusii Benth* leaves (66) were studied against different pathogenic microorganisms and showed considerable antimicrobial activities. Kwiatkowski et al., 2017 had studied the therapeutic potency of fennel essential oil in combination with antibiotics against drug resistant Staphylococcus (67).

Terpenes are plant secondary metabolites that are well known for antimicrobial activities. In KOMBAT, we have included monoterpenes, diterpenes and sesquiterpenes. For example, nerol (monoterpene) was proven as adjuvant with antibiotic therapy against multi-drug resistant Staphylococcus infection (68) and Totarol (diterpenoid) isolated from the bark of *Podocarpus nagi* showed activity against several Gram-positive and Gram-negative bacteria (69). Consumption of foods having antimicrobial activity is one alternative strategy for controlling the emergence of resistant microorganisms. The in-vitro and in-vivo activity of cranberry juice for treating drug resistant and sensitive strains of *Escherichia coli* in recurrent urinary tract infection was studied by Lavigne et al., 2008 (70). In another study, in-vitro observation showed the effectiveness of apple juice against *Enterococcus feacalis* and *Streptococcus mutans* (71). In KOMBAT, we have

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accommodated more such examples of natural products and their therapeutic efficacies. Although, these require clinical testing, but phytochemicals can be outstanding starting materials towards the discovery of new chemotherapeutic molecules.

3.4.4 Nanocomposites

Nanoparticles have been getting rising attentions due to their antimicrobial properties (72). Nanoparticles allow targeted drug delivery owing to a narrow therapeutic window or lower bioavailability and thus potentiate drug efficacy (73). They exhibit antimicrobial properties through a vast range of mechanisms like cell wall biosynthesis inhibition, disruption of electron transport chain, generation of toxic ROS, photocatalysis, enzymatic inhibition, reduced DNA production (74).

In KOMBAT, we have included 47 different nanoparticle combinations against bacterial pathogens. It includes different metal or metallic compounds nanoparticles such as that of silver, gold, zinc oxide, Tungsten, selenium, titanium and iron oxide. Also, various hybrid therapy comprising nanoparticles with herbal extracts, photodynamic therapy and conventional antibiotics are included.

Li et al, 2013 had first reported the effectiveness of silver nanoparticles against *Neisseria* gonorrhoeae at MIC: 12.5 µg/ml. They have also observed that 120 nm Ag NPs form conjugates with cefmetazole and produced additive effects against multidrug resistant strains (75). Antistaphylococcol activity of AgNPs in combination with visible blue light was investigated to reduce rapidly emerging multidrug resistant strains (76). In another study, Scandorieiro et al., had demonstrated the combinatorial effect of *Origanum vulgare* (Oregano) essential oil and Biological Silver Nanoparticles (bio-AgNP) against Multidrug-Resistant Bacterial Strains (77). The inhibitory activity against different bacterial species was mentioned in the ‘POTENCY’ column with MIC against OEO in the range 0.298 to 1.193 mg/mL and MIC against bio-AgNP in the range 62.5 to 250 µM. Zhang et al., had come across a combination therapy using β-carboxyphthalocyanine zinc photosensitizer, lanthanide-doped up conversion nanoparticles and polyvinylpyrrolidone (78). This showed promising antibacterial and antifungal properties including drug resistant pathogens like growth inhibition of MRSA by 4.7 log10 fold and MDR *E. coli* by 2.1 log10 fols . Hybrid technologies comprising antibiotics and

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nanoparticles offer useful resources for the elimination of drug resistant pathogens. One such technology using nanocomposite structure included in KOMBAT is Tobramycin mediated silver nanospheres tested against ampicillin and chloramphenicol resistant resistant *E. coli* (BL21 DE3) (79).

3.4.5 Photodynamic therapy

Antimicrobial Photodynamic therapy (aPDT) has emerged in recent years for treating infections caused by bacteria, fungi, and viruses (80). aPDT mainly uses a photosensitizer (PS) molecule that gets excited by light source to generate reactive oxygen species (81). PDT is site-specific and the PSs are only toxic when irradiated by light so no resistance is developed against antimicrobial (82). Diverse combinations of PS and light source are being reported in the literature.

In KOMBAT, 39 strategies for photodynamic inactivation of bacterial pathogens have been included. Among them, various strains of *E. coli*, *Staphylococcus*, *Pseudomonas*, *Acinetobacter*, *Enterococcus*, *Helicobacter*, *Clostridium*, *Propionibacterium*, *Klebsiella* are covered. Data retrieved from literature also includes combination therapeutic strategy of light source with antibiotics, herbal extracts and metal ions. Photodynamic inactivation strategy of different methicillin-susceptible and resistant strains of *Staphylococcus* was included namely using hypericin and LED light (83), photosensitizer 5,10,15,20-tetrakis(1-methylpyridinium-4-yl) porphyrin tetra-iodide (Tetra-Py(+)-Me) (84), benzylidene cyclopentanone PSs (85). Another example included in KOMBAT is a broad-spectrum combinatorial therapy of Porphyrin-cellulose nanocrystals against multidrug-resistant *Acinetobacter baumannii* (MDRAB) and MRSA. Choi et al. had observed that antibacterial activity of tetracycline for treating *Clostridium difficile* infection was bolstered in combination with chitosan and ultraviolet A (UVA) light (86).

These data suggest that there is a scope for extensive use of phototherapy to control drug resistant pathogens. This not only creates new therapeutic avenues but also enhances the efficacy of conventional antibiotics.

3.5.6 Chemical compounds

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Chemical compounds have always been the part of cause and solution to antimicrobial resistance problem. A considerable part of scientific research has been concentrated on developing novel small molecule inhibitors, which also includes derivatives of available antimicrobials. Chemical compounds follow diverse mechanisms to inhibit microbial growth like inhibition of cell wall or membrane, inevitable biochemical processes for cell proliferation like microbial replication, transcription and translation. They generally bind to specific enzymes and disrupt its function thereby inhibiting cell growth.

Amidst the data retrieved from literature for this work, chemical compounds occupy the highest share. In KOMBAT, we have included 387 newly discovered antibacterial compounds. This includes compounds derived by modifying antibiotics like derivatives of carbapenem, quinolone, cephalosporins, penicillin, β-lactams, oxazolidinones, erythromycins. For example, a novel pyrrolidinyl-thio carbapenem, CW-270033 was synthesized by Kim et al., which showed broad spectrum activity against different drug resistant and sensitive pathogens like *E. coli*, *Pseudomonas aeruginosa* and *Staphylococcus aureus* (87). This information is added in the list of antibacterial chemical compound table of KOMBAT.

Overall, the data retrieved showed a clear focus on novel therapeutic molecules for tackling AMR.

Conclusion

AMR is a major public health concern. A considerable portion of scientific community is engrossed in AMR related work trying to discover novel therapeutic solutions for tackling resistant pathogens. In this work we have developed a comprehensive knowledgebase by collecting alternative antimicrobial therapeutic strategies from literature data. Overwhelmingly, the retrieved data are comprised of novel chemical compounds, antimicrobial peptides, photodynamic therapy, phage therapy, nanocomposites and phytochemicals. We have organized the extracted data into KOMBAT. A lot of these data are tested against AMR pathogens. We envision that this database will be noteworthy for developing future therapeutics against resistant pathogens.

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References

1. Antimicrobial resistance [Internet]. [cited 2021 Sep 30]. Available from: https://www.who.int/westernpacific/health-topics/antimicrobial-resistance

2. Reygaert WC. An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiol. 2018 Jun 26;4(3):482–501.

3. Sun D, Jeannot K, Xiao Y, Knapp CW. Editorial: Horizontal Gene Transfer Mediated Bacterial Antibiotic Resistance. Front Microbiol. 2019;10:1933.

4. Buchy P, Ascioglu S, Buisson Y, Datta S, Nissen M, Tambyah PA, et al. Impact of vaccines on antimicrobial resistance. Int J Infect Dis IJID Off Publ Int Soc Infect Dis. 2020 Jan;90:188–96.

5. Huan Y, Kong Q, Mou H, Yi H. Antimicrobial Peptides: Classification, Design, Application and Research Progress in Multiple Fields. Front Microbiol [Internet]. 2020 [cited 2021 Aug 6];0. Available from: https://www.frontiersin.org/articles/10.3389/fmicb.2020.582779/full?utm_source=researcher_app&utm_medium=referral&utm_campaign=RESR_MRKT_Researcher_inbound

6. Amador PP, Fernandes RM, Prudêncio MC, Barreto MP, Duarte IM. Antibiotic resistance in wastewater: occurrence and fate of Enterobacteriaceae producers of class A and class C β-lactamases. J Environ Sci Health Part A Tox Hazard Subst Environ Eng. 2015;50(1):26–39.

7. Antimicrobial resistance : tackling a crisis for the health and wealth of nations / the Review on Antimicrobial Resistance chaired by Jim O'Neill. [Internet]. Wellcome Collection. [cited 2021 Aug 5]. Available from: https://wellcomecollection.org/works/rdpck35v

8. CDC. Antibiotic-resistant Germs: New Threats [Internet]. Centers for Disease Control and Prevention. 2021 [cited 2021 Sep 22]. Available from: https://www.cdc.gov/drugresistance/biggest-threats.html

9. Securing new drugs for future generations : the pipeline of antibiotics / the Review on Antimicrobial Resistance chaired by Jim O'Neill. [Internet]. Wellcome Collection. [cited 2021 Jul 29]. Available from: https://wellcomecollection.org/works/zqv86kgr

10. Team TI. Average Research and Development Costs for Pharmaceutical Companies [Internet]. Investopedia. [cited 2021 Aug 5]. Available from: https://www.investopedia.com/ask/answers/060115/how-much-drug-companys-spending-allocated-research-and-development-average.asp

11. Farrell LJ, Lo R, Wanford JJ, Jenkins A, Maxwell A, Piddock LJV. Revitalizing the drug pipeline: AntibioticDB, an open access database to aid antibacterial research and development. J Antimicrob Chemother. 2018 Sep 1;73(9):2284–97.

12. Wang Z, Wang G. APD: the Antimicrobial Peptide Database. Nucleic Acids Res. 2004 Jan 1;32(Database issue):D590-592.

13. McArthur AG, Waglechner N, Nizam F, Yan A, Azad MA, Baylay AJ, et al. The comprehensive antibiotic resistance database. Antimicrob Agents Chemother. 2013 Jul;57(7):3348–57.

14. Lakin SM, Dean C, Noyes NR, Dettenwanger A, Ross AS, Doster E, et al. MEGARes: an antimicrobial resistance database for high throughput sequencing. Nucleic Acids Res. 2017 Jan 4;45(Database issue):D574–80.

15. Liu B, Pop M. ARDB--Antibiotic Resistance Genes Database. Nucleic Acids Res. 2009 Jan;37(Database issue):D443-447.

16. Wattam AR, Abraham D, Dalay O, Disz TL, Driscoll T, Gabbard JL, et al. PATRIC, the bacterial bioinformatics database and analysis resource. Nucleic Acids Res. 2014 Jan 1;42(Database issue):D581–91.

17. Chen X, Ren B, Chen M, Liu M-X, Ren W, Wang Q-X, et al. ASDCD: Antifungal Synergistic Drug Combination Database. PLoS ONE. 2014 Jan 24;9(1):e86499.

18. Wang Y, Xiao J, Suzek TO, Zhang J, Wang J, Bryant SH. PubChem: a public information system for analyzing bioactivities of small molecules. Nucleic Acids Res. 2009 Jul;37(Web Server issue):W623-633.

19. Azam MW, Kumar A, Khan AU. ACD: Antimicrobial chemotherapeutics database. PLOS ONE. 2020 Jun 25;15(6):e0235193.

20. Danishuddin M, Kaushal L, Hassan Baig M, Khan AU. AMDD: antimicrobial drug database. Genomics Proteomics Bioinformatics. 2012 Dec;10(6):360–3.

21. Gong L. Application of Biomedical Text Mining [Internet]. Artificial Intelligence - Emerging Trends and Applications. IntechOpen; 2018 [cited 2021 Sep 23]. Available from: https://www.intechopen.com/chapters/60491

22. Chowdhury GG. Natural language processing. Annu Rev Inf Sci Technol. 2003;37(1):51–89.

23. Rani J, Shah ABR, Ramachandran S. pubmed.mineR: an R package with text-mining algorithms to analyse PubMed abstracts. J Biosci. 2015 Oct;40(4):671–82.

24. Bird S, Klein E, Loper E. Natural Language Processing with Python: Analyzing Text with the Natural Language Toolkit. O'Reilly Media, Inc.; 2009. 506 p.

25. Jensen LJ, Saric J, Bork P. Literature mining for the biologist: from information retrieval to biological discovery. Nat Rev Genet. 2006 Feb;7(2):119–29.

26. Wei C-H, Kao H-Y, Lu Z. PubTator: a web-based text mining tool for assisting biocuration. Nucleic Acids Res. 2013 Jul;41(Web Server issue):W518-522.

27. Burrowes B, Harper DR, Anderson J, McConville M, Enright MC. Bacteriophage therapy: potential uses in the control of antibiotic-resistant pathogens. Expert Rev Anti Infect Ther. 2011 Sep;9(9):775–85.

28. Broncano-Lavado A, Santamaría-Corral G, Esteban J, García-Quintanilla M. Advances in Bacteriophage Therapy against Relevant MultiDrug-Resistant Pathogens. Antibiot Basel Switz. 2021 Jun 4;10(6):672.

29. Liu D, Van Belleghem JD, de Vries CR, Burgener E, Chen Q, Manasherob R, et al. The Safety and Toxicity of Phage Therapy: A Review of Animal and Clinical Studies. Viruses. 2021 Jun 29;13(7):1268.

30. Adaptive Phage Therapeutics, Inc. A Phase I/II Study of Bacteriophage Therapy to Evaluate Safety, Tolerability, and Efficacy of Targeted "Personalized" Bacteriophage Treatments in Patients With Bacterial Infection of the Urinary Tract [Internet]. clinicaltrials.gov; 2021 Jan [cited 2021 Sep 28]. Report No.: NCT04287478. Available from: https://clinicaltrials.gov/ct2/show/NCT04287478

31. Voelker R. FDA Approves Bacteriophage Trial. JAMA. 2019 Feb 19;321(7):638.

32. Zhang C, Li W, Liu W, Zou L, Yan C, Lu K, et al. T4-like phage Bp7, a potential antimicrobial agent for controlling drug-resistant Escherichia coli in chickens. Appl Environ Microbiol. 2013 Sep;79(18):5559–65.

33. Rahmani R, Zarrini G, Sheikhzadeh F, Aghamohammadzadeh N. Effective Phages as Green Antimicrobial Agents Against Antibiotic-Resistant Hospital Escherichia coli. Jundishapur J Microbiol. 2015 Feb;8(2):e17744.

34. Easwaran M, Paudel S, De Zoysa M, Shin H-J. Functional characterization of a novel lytic phage EcSw isolated from Sus scrofa domesticus and its potential for phage therapy. Mol Cell Probes. 2015 Jun;29(3):151–7.

35. Jin J, Li Z-J, Wang S-W, Wang S-M, Huang D-H, Li Y-H, et al. Isolation and characterization of ZZ1, a novel lytic phage that infects Acinetobacter baumannii clinical isolates. BMC Microbiol. 2012 Jul 28;12:156.

36. Shen G-H, Wang J-L, Wen F-S, Chang K-M, Kuo C-F, Lin C-H, et al. Isolation and characterization of φkm18p, a novel lytic phage with therapeutic potential against extensively drug resistant Acinetobacter baumannii. PloS One. 2012;7(10):e46537.

37. Fenton M, Ross RP, McAuliffe O, O'Mahony J, Coffey A. Characterization of the staphylococcal bacteriophage lysin CHAP(K). J Appl Microbiol. 2011 Oct;111(4):1025–35.

38. Schuch R, Lee HM, Schneider BC, Sauve KL, Law C, Khan BK, et al. Combination therapy with lysin CF-301 and antibiotic is superior to antibiotic alone for treating methicillin-resistant Staphylococcus aureus-induced murine bacteremia. J Infect Dis. 2014 May 1;209(9):1469–78.

39. Rodríguez L, Martínez B, Zhou Y, Rodríguez A, Donovan DM, García P. Lytic activity of the virion-associated peptidoglycan hydrolase HydH5 of Staphylococcus aureus bacteriophage vB_SauS-phiIPLA88. BMC Microbiol. 2011 Jun 17;11:138.

40. Raheem N, Straus SK. Mechanisms of Action for Antimicrobial Peptides With Antibacterial and Antibiofilm Functions. Front Microbiol. 2019;10:2866.

41. Wu Q, Patočka J, Kuča K. Insect Antimicrobial Peptides, a Mini Review. Toxins. 2018 Nov 8;10(11):E461.

42. Moretta A, Scieuzo C, Petrone AM, Salvia R, Manniello MD, Franco A, et al. Antimicrobial Peptides: A New Hope in Biomedical and Pharmaceutical Fields. Front Cell Infect Microbiol. 2021;11:668632.

43. Epand RM, Walker C, Epand RF, Magarvey NA. Molecular mechanisms of membrane targeting antibiotics. Biochim Biophys Acta. 2016 May;1858(5):980–7.

44. Kumar P, Kizhakkedathu JN, Straus SK. Antimicrobial Peptides: Diversity, Mechanism of Action and Strategies to Improve the Activity and Biocompatibility In Vivo. Biomolecules. 2018 Jan 19;8(1):4.

45. Hilchie AL, Wuerth K, Hancock REW. Immune modulation by multifaceted cationic host defense (antimicrobial) peptides. Nat Chem Biol. 2013 Dec;9(12):761–8.

46. Nakajima Y, Alvarez-Bravo J, Cho J, Homma K, Kanegasaki S, Natori S. Chemotherapeutic activity of synthetic antimicrobial peptides: correlation between chemotherapeutic activity and neutrophil-activating activity. FEBS Lett. 1997 Sep 22;415(1):64–6.

47. Kim PI, Sohng JK, Sung C, Joo H-S, Kim E-M, Yamaguchi T, et al. Characterization and structure identification of an antimicrobial peptide, hominicin, produced by Staphylococcus hominis MBBL 2-9. Biochem Biophys Res Commun. 2010 Aug 20;399(2):133–8.

48. Ochoa-Zarzosa A, Loeza-Angeles H, Sagrero-Cisneros E, Villagómez-Gómez E, Lara-Zárate L, López-Meza JE. Antibacterial activity of thionin Thi2.1 from Arabidopsis thaliana expressed by bovine endothelial cells against Staphylococcus aureus isolates from bovine mastitis. Vet Microbiol. 2008 Mar 18;127(3–4):425–30.

49. Wu Y-S, Liao Z-J, Wang K-S, Lung F-DT. Structure-activity relationship of potent antimicrobial peptide analogs of Ixosin-B amide. Bioorg Med Chem Lett. 2013 May 15;23(10):2929–32.

50. Liu S, Long Q, Xu Y, Wang J, Xu Z, Wang L, et al. Assessment of antimicrobial and wound healing effects of Brevinin-2Ta against the bacterium Klebsiella pneumoniae in dermally-wounded rats. Oncotarget. 2017 Dec 19;8(67):111369–85.

51. Jodoin J, Hincke MT. Histone H5 is a potent Antimicrobial Agent and a template for novel Antimicrobial Peptides. Sci Rep. 2018 Feb 5;8(1):2411.

52. Liu F, Soh Yan Ni A, Lim Y, Mohanram H, Bhattacharjya S, Xing B. Lipopolysaccharide neutralizing peptide-porphyrin conjugates for effective photoinactivation and intracellular imaging of gram-negative bacteria strains. Bioconjug Chem. 2012 Aug 15;23(8):1639–47.

53. Regmi S, Choi YH, Choi YS, Kim MR, Yoo JC. Antimicrobial peptide isolated from Bacillus amyloliquefaciens K14 revitalizes its use in combinatorial drug therapy. Folia Microbiol (Praha). 2017 Mar;62(2):127–38.

54. Sandiford S, Upton M. Identification, characterization, and recombinant expression of epidermicin NI01, a novel unmodified bacteriocin produced by Staphylococcus epidermidis that displays potent activity against Staphylococci. Antimicrob Agents Chemother. 2012 Mar;56(3):1539–47.

55. Mo M, H G, Bm C, Dp M, Ds M. The oligo-acyl lysyl antimicrobial peptide C_{12}K-2β_{12} exhibits a dual mechanism of action and demonstrates strong in vivo efficacy against Helicobacter pylori. Antimicrob Agents Chemother [Internet]. 2012 Jan [cited 2021 Jul 23];56(1). Available from: https://pubmed.ncbi.nlm.nih.gov/22064541/

56. Halcón L, Milkus K. Staphylococcus aureus and wounds: a review of tea tree oil as a promising antimicrobial. Am J Infect Control. 2004 Nov;32(7):402–8.

57. Loughlin R, Gilmore BF, McCarron PA, Tunney MM. Comparison of the cidal activity of tea tree oil and terpinen-4-ol against clinical bacterial skin isolates and human fibroblast cells. Lett Appl Microbiol. 2008 Apr;46(4):428–33.

58. Low WL, Martin C, Hill DJ, Kenward MA. Antimicrobial efficacy of liposome-encapsulated silver ions and tea tree oil against Pseudomonas aeruginosa, Staphylococcus aureus and Candida albicans. Lett Appl Microbiol. 2013 Jul;57(1):33–9.

59. Jeon J, Kim JH, Lee CK, Oh CH, Song HJ. The Antimicrobial Activity of (-)-Epigallocatehin-3-Gallate and Green Tea Extracts against Pseudomonas aeruginosa and Escherichia coli Isolated from Skin Wounds. Ann Dermatol. 2014 Oct;26(5):564–9.

60. Serra DO, Mika F, Richter AM, Hengge R. The green tea polyphenol EGCG inhibits E. coli biofilm formation by impairing amyloid curli fibre assembly and downregulating the biofilm regulator CsgD via the σ(E) -dependent sRNA RybB. Mol Microbiol. 2016 Jul;101(1):136–51.

61. Morroni G, Alvarez-Suarez JM, Brenciani A, Simoni S, Fioriti S, Pugnaloni A, et al. Comparison of the Antimicrobial Activities of Four Honeys From Three Countries (New Zealand, Cuba, and Kenya). Front Microbiol. 2018;9:1378.

62. Tan HT, Rahman RA, Gan SH, Halim AS, Hassan SA, Sulaiman SA, et al. The antibacterial properties of Malaysian tualang honey against wound and enteric microorganisms in comparison to manuka honey. BMC Complement Altern Med. 2009 Sep 15;9:34.

63. Müller P, Alber DG, Turnbull L, Schlothauer RC, Carter DA, Whitchurch CB, et al. Synergism between Medihoney and rifampicin against methicillin-resistant Staphylococcus aureus (MRSA). PloS One. 2013;8(2):e57679.

64. Sienkiewicz M, Wasiela M, Głowacka A. [The antibacterial activity of oregano essential oil (Origanum heracleoticum L.) against clinical strains of Escherichia coli and Pseudomonas aeruginosa]. Med Dosw Mikrobiol. 2012;64(4):297–307.

65. Bitu V de CN, Fecundo HDTF, da Costa JGM, Coutinho HDM, Rodrigues FFG, de Santana NM, et al. Chemical composition of the essential oil of Lippia gracilis Schauer leaves and its potential as modulator of bacterial resistance. Nat Prod Res. 2014;28(6):399–402.

66. de Oliveira ADL, Galvao Rodrigue FF, Douglas Melo Coutinho H, da Costa JGM, de Menezes IRA. Chemical Composition, Modulatory Bacterial Resistance and Antimicrobial Activity of Essential Oil the Hyptis martiusii Benth by Direct and Gaseous Contact. Jundishapur J Nat Pharm Prod. 2014 Aug;9(3):e13521.

67. Kwiatkowski P, Mnichowska-Polanowska M, Pruss A, Masiuk H, Dzięcioł M, Giedrys-Kalemba S, et al. The effect of fennel essential oil in combination with antibiotics on Staphylococcus aureus strains isolated from carriers. Burns J Int Soc Burn Inj. 2017 Nov;43(7):1544–51.

68. Coêlho ML, Ferreira JHL, de Siqueira Júnior JP, Kaatz GW, Barreto HM, de Carvalho Melo Cavalcante AA. Inhibition of the NorA multi-drug transporter by oxygenated monoterpenes. Microb Pathog. 2016 Oct;99:173–7.

69. Kubo I, Muroi H, Himejima M. Antibacterial activity of totarol and its potentiation. J Nat Prod. 1992 Oct;55(10):1436–40.

70. Lavigne J-P, Bourg G, Combescure C, Botto H, Sotto A. In-vitro and in-vivo evidence of dose-dependent decrease of uropathogenic Escherichia coli virulence after consumption of commercial Vaccinium macrocarpon (cranberry) capsules. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2008 Apr;14(4):350–5.

71. Behera S, Khetrapal P, Punia SK, Agrawal D, Khandelwal M, Lohar J. Evaluation of Antibacterial Activity of Three Selected Fruit Juices on Clinical Endodontic Bacterial Strains. J Pharm Bioallied Sci. 2017 Nov;9(Suppl 1):S217–21.

72. Weir E, Lawlor A, Whelan A, Regan F. The use of nanoparticles in anti-microbial materials and their characterization. The Analyst. 2008 Jul;133(7):835–45.

73. Pharmacokinetics and Biodistribution of Nanoparticles | Molecular Pharmaceutics [Internet]. [cited 2021 Sep 30]. Available from: https://pubs.acs.org/doi/10.1021/mp800049w

74. Shaikh S, Nazam N, Rizvi SMD, Ahmad K, Baig MH, Lee EJ, et al. Mechanistic Insights into the Antimicrobial Actions of Metallic Nanoparticles and Their Implications for Multidrug Resistance. Int J Mol Sci. 2019 May 18;20(10):2468.

75. Li L-H, Yen M-Y, Ho C-C, Wu P, Wang C-C, Maurya PK, et al. Non-cytotoxic nanomaterials enhance antimicrobial activities of cefmetazole against multidrug-resistant Neisseria gonorrhoeae. PloS One. 2013;8(5):e64794.

76. Akram FE, El-Tayeb T, Abou-Aisha K, El-Azizi M. A combination of silver nanoparticles and visible blue light enhances the antibacterial efficacy of ineffective antibiotics against methicillin-resistant Staphylococcus aureus (MRSA). Ann Clin Microbiol Antimicrob. 2016 Aug 17;15(1):48.

77. Scandorieiro S, de Camargo LC, Lancheros CAC, Yamada-Ogatta SF, Nakamura CV, de Oliveira AG, et al. Synergistic and Additive Effect of Oregano Essential Oil and Biological Silver Nanoparticles against Multidrug-Resistant Bacterial Strains. Front Microbiol. 2016;7:760.

78. Zhang Y, Huang P, Wang D, Chen J, Liu W, Hu P, et al. Near-infrared-triggered antibacterial and antifungal photodynamic therapy based on lanthanide-doped upconversion nanoparticles. Nanoscale. 2018 Aug 23;10(33):15485–95.

79. Ullah S, Ahmad A, Subhan F, Jan A, Raza M, Khan AU, et al. Tobramycin mediated silver nanospheres/graphene oxide composite for synergistic therapy of bacterial infection. J Photochem Photobiol B. 2018 Jun;183:342–8.

80. Rajesh S, Koshi E, Philip K, Mohan A. Antimicrobial photodynamic therapy: An overview. J Indian Soc Periodontol. 2011;15(4):323–7.

81. Hu X, Huang Y-Y, Wang Y, Wang X, Hamblin MR. Antimicrobial Photodynamic Therapy to Control Clinically Relevant Biofilm Infections. Front Microbiol. 2018;9:1299.

82. Liu Y, Qin R, Zaat SAJ, Breukink E, Heger M. Antibacterial photodynamic therapy: overview of a promising approach to fight antibiotic-resistant bacterial infections. J Clin Transl Res. 2015 Dec 1;1(3):140–67.

83. García I, Ballesta S, Gilaberte Y, Rezusta A, Pascual Á. Antimicrobial photodynamic activity of hypericin against methicillin-susceptible and resistant Staphylococcus aureus biofilms. Future Microbiol. 2015;10(3):347–56.

84. Bartolomeu M, Rocha S, Cunha Â, Neves MGPMS, Faustino MAF, Almeida A. Effect of Photodynamic Therapy on the Virulence Factors of Staphylococcus aureus. Front Microbiol. 2016;7:267.

85. Fang Y, Liu T, Zou Q, Zhao Y, Wu F. Water-soluble benzylidene cyclopentanone based photosensitizers for in vitro and in vivo antimicrobial photodynamic therapy. Sci Rep. 2016 Jun 21;6:28357.

86. Choi S, Lee H, Yu J, Chae H. In vitro augmented photodynamic bactericidal activity of tetracycline and chitosan against Clostridium difficile KCTC5009 in the planktonic cultures. J Photochem Photobiol B. 2015 Dec;153:7–12.

87. Kim J, Ha JR, Oh SW, Kim HG, Lee J-M, Lee DG, et al. CW-270033, a novel pyrrolidinyl-thio carbapenem, has potent antimicrobial activity in vitro and in vivo. Biol Pharm Bull. 2007 Mar;30(3):575–9.

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Figures and Figure legends:

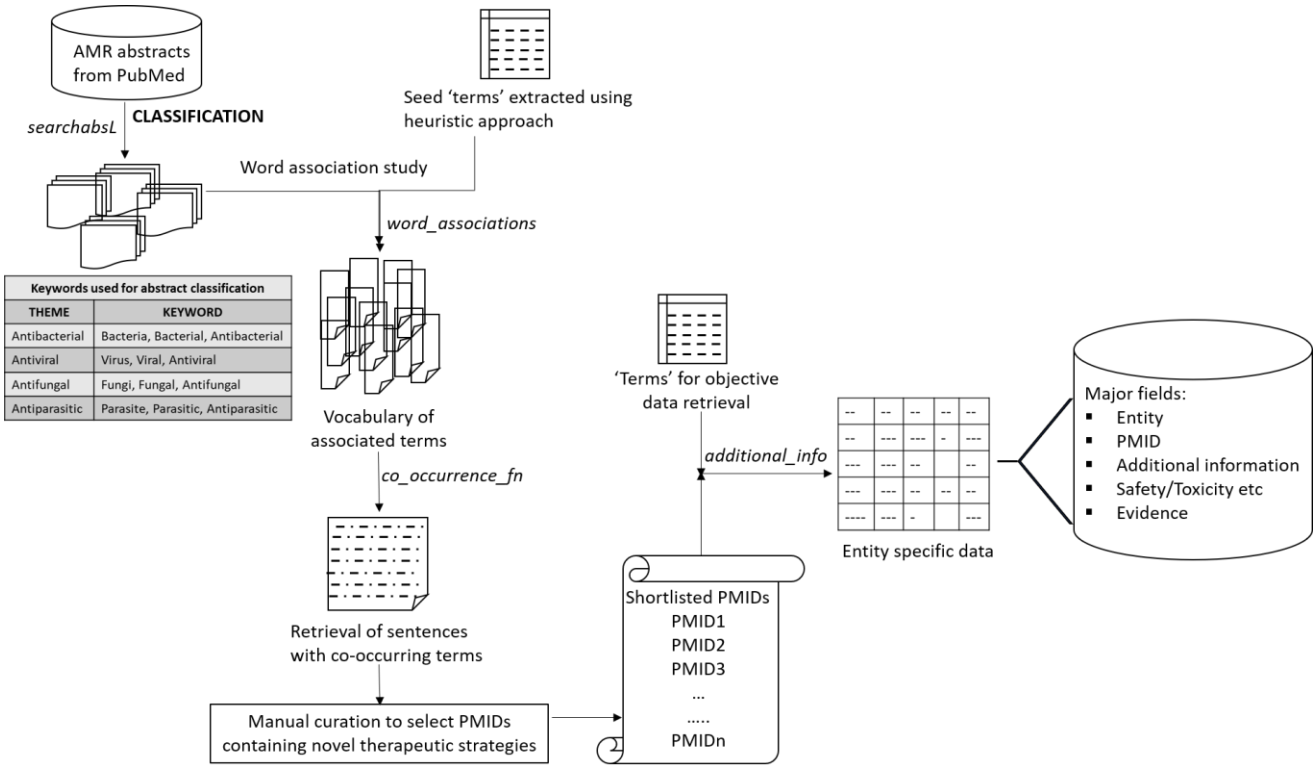

Figure 1: Infographics for data retrieval and curation

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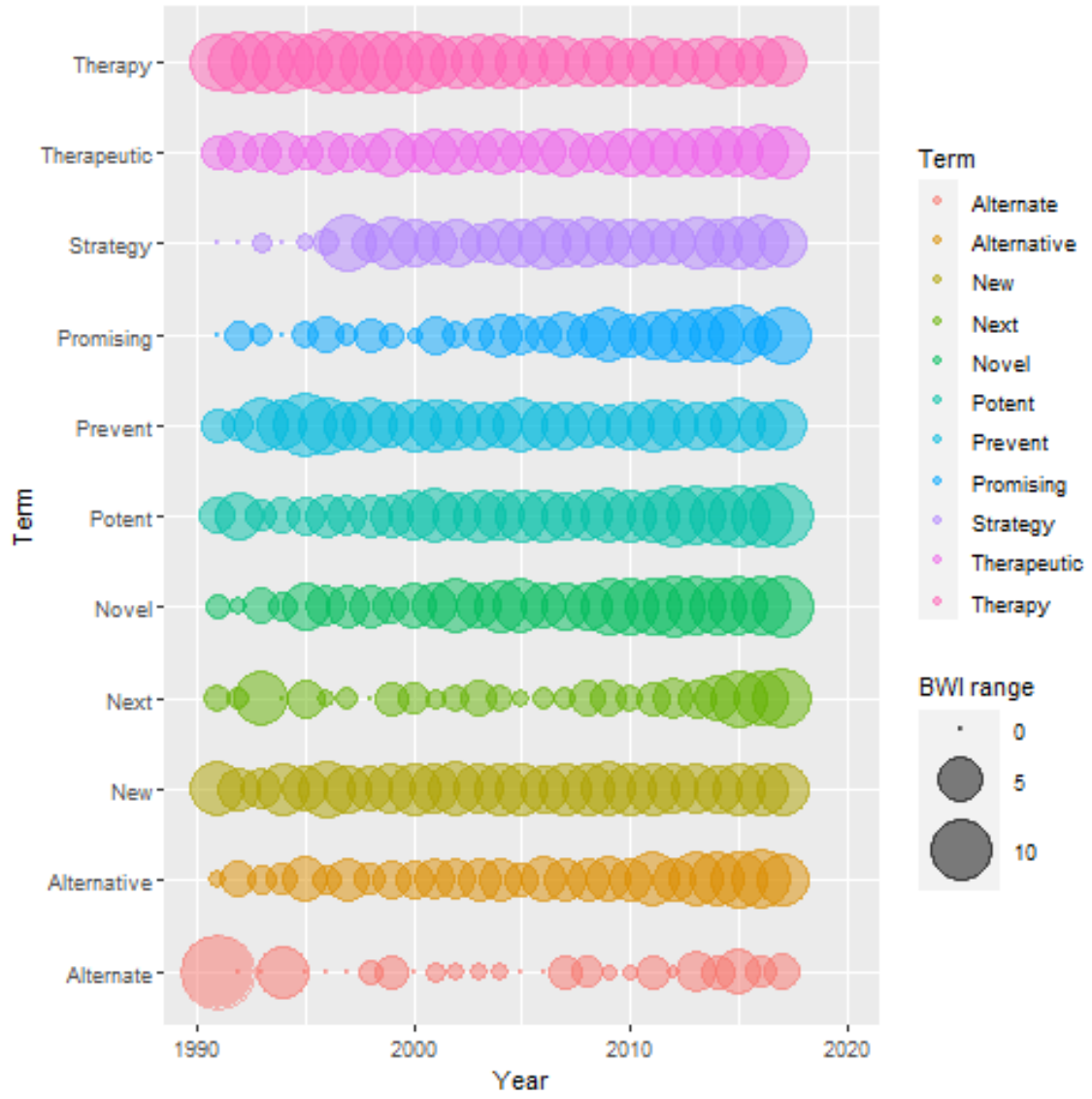

Figure 2: Bubble plot showing relative trend of anchor terms