Plant Phyto-constituents as Antibiotic Adjuvants: A Systematic review and Bibliometric Analysis

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Abstract:

The advent of antibiotics in the 19th century has significantly reduced the morbidity and mortality of infectious diseases. However, irrational use of antibiotics in humans as well as in animals has driven the 21st century to the rapid emergence of MultiDrug Resistance Bacteria (MRB). Moreover, the dissemination of COVID-19 pandemic has paved the way for MRB, typically due to increased use of antibiotics to avoid secondary infections.

The fast pace progression of bacterial resistance for the antibiotics and their combinations is making the management of MRB infections tough and increasing the cost of the treatment as well. However, use of Efflux Pump Inhibitors (EPI) as adjuvant for antibiotics has shown a ray of hope by retaining the susceptibility of the antibiotics and thereby reducing the burden of immediate requirement of new antibiotics for MRB. Accordingly, the present paper is aimed to scrutinize the predominant literature depicting the plant Phyto-constituents as an EPI and adjuvant for antibiotics in the management of MRB infections.

The systematic review of the present paper indicates that the plant phyto-constituents belonging to the class of alkaloids, terpenoids, flavonoids can effectively be used as EPIs for antibiotics such as Ciprofloxacin, Norfloxacin, Tetracyclines and Chloramphenicol. Bibliometric analysis indicates that the Journal of Antimicrobial Chemotherapy, Antimicrobial Agents and Chemotherapy and BMC Complementary & Alternative Medicine have published impactful articles on EPI potential of plant phyto-constituents. Further, authors Kuete, V. Dzotam, J. K.,

Falcao-silva V.D, Gibbons, S., Kuiate, J.R., Mbaveng, A.T., Tankeo, S.B. and Voukeng, I.K. are the major contributors and productive authors.

Keywords: Efflux Pump Inhibitor, MuiltiDrug Resistant Bacteria, Antibiotic Resistance, Phyto-Constituents, Antibiotic Adjuvant

Introduction:

The discovery of Antibiotic penicillin in the 19th century and subsequent development of other antibiotics such as streptomycin, sulphonamides and chloramphenicol was most important discoveries in the medicine with remarkable reduction in the morbidity and mortality rate due to infectious diseases. This was the start of the "Antibiotic era" with dramatic impact on the whole practice of medicine for common infections and as well controlling the secondary infections that occur during complicated hospital procedures such as surgery, organ transplantation, renal dialysis, cancer chemotherapies. [1]

As per the World Health Organization (WHO) report, during the year 2000 and 2015, global antibiotic consumption has increased by 65% in humans whereas use of antibiotics in animals to improve the animal products has been increased by 11.5%.[2] Moreover, antibiotics have often been perceived as 'magic bullets', and requested for every febrile episode. Unfortunately, these inappropriate perceptions about antibiotic and antibiotic overuse, irresponsible agricultural practices of using farm antibiotics to avoid plant diseases, using antibiotics to treat or prevent diseases in animals, further contributes to the emergence of MultiDrug Resistance Bacteria (MRB).

As per Global Antimicrobial Resistance Surveillance System (GLASS), report 2021, 16% bloodstream infections associated with Acinetobacter spp, Escherichia coli, Klebsiella pneumoniae, Salmonella typhi, Staphylococcus aureus and Streptococcus pneumoniae, 83 % of Urinary tract infections associated with Escherichia coli, Klebsiella Pneumoniae are due to MultiDrug Resistant Bacteria (MRB).[3]

Based on aforementioned details, it is evident that the infections due to MRB are one of the biggest threats to public health with an annual mortality rate of 700000 worldwide. To make matters worse, COVID-19 pandemic is paving the way for MRB, typically due to increased prescriptions and dispensing of antibiotics, though COVID-19 is caused by SARS-CoV-2 virus and not by bacteria.

As per the Resistance map developed by the Center for Disease Dynamics Economics and Policy (CDDEP), above mentioned bacteria shows average resistance of 50 to 80% to penicillin's like ampicillin, amoxicillin, third-generation cephalosporins and fluoroquinolone and even to combinations antibiotics such as amoxicillin-clavulanic acid.[5]

In contrast to the urgent need of antibiotics to manage the MDR bacterial infections, the rate at which new antibiotics were discovered steadily declined. Between 2003 and 2007, only five antibiotic agents were approved by the US Food and Drug Administration, the lowest number in 10 years. PAW report, shows that 41 antibiotics are in development out of which 15 were in Phase 1 clinical trials, 12 in Phase 2, 13 in Phase 3, 1 has had a new drug application submitted, 4 have been approved till December 2019. [6]

To manage MRB, various strategies were developed by governments of different countries such as providing funding for the development of new antibiotic molecules as well as for studying the resistance mechanism in bacteria. However, development of new antibiotics is time consuming and furthermore, even for new antibiotics bacteria may develop a resistance. In contrast, studies on bacterial resistance mechanisms paved the way for quick and effective solutions to manage MRB. The studies show that efflux pumps present on cell walls of the resistant bacteria are responsible for extrusion of the antibiotic out of the bacterial cell and thereby reducing its effectiveness. Accordingly, use of Efflux Pump Inhibitors (EPI) as antibiotic adjuvants is recommended in the management of the MRB. Moreover, use of EPI as adjuvant for antibiotic retains the effectiveness of the available antibiotics and thereby reduces the burden of immediate requirement of new antibiotic for MRB. [7,8]

Various studies in search of EPIs showed that phyto constituents such as piperine, curcumin, reserpine, gingerol, shagol, quercetin, rutin has potential to block the efflux pump in MRB and thereby maintaining the effectiveness of the antibiotics against MRB. The successful launch of Resorine by Cadila Pharmaceutical as anti-tuberculosis drug comprising combination of antibiotics (Rifampicin-200 mg, Isoniazid-300 mg) and EPI (Piperine-10mg), which has further created boost in the scientific world to analyze potential of various phyto-constituents of medicinal plants. [9]

However, till today, other than Resorine, not a single antibiotic adjuvant combination is available in the market. Accordingly, the present paper is focused on providing a systematic review of the literature covering aspects such as mostly studied phyto-constituents as EPI or antibiotic adjuvant, MDR bacteria and the like. Further there is unmet need to conduct a bibliometric analysis to understand the impactful author, journal, in the area of antibiotic phytoconstituent combination

Objective:

The fundamental purpose of the study is to analyze the predominant literature depicting the plant phyto-constituents as a bacterial EPI and adjuvant for antibiotics in the management of resistant bacterial infections.

Apparently, following objectives decoding the scope of the study are devised.

1. Systematic review through content analysis of the literature particularizing the phyto-compounds as an EPI and antibiotic adjuvant.
2. Publication trends in plant based antibiotic adjuvants covering antibiotics, bacteria and phyto-compounds
3. Bibliometric analysis of the literature to understand the most productive Journal and the Authors

RESEARCH METHODOLOGY

The literature search was conducted in the month of March 2021 and literature from the period 1996–2021 were selected for the systematic review and bibliometric analysis. Literature pertinent to keywords such as EPIs, overexpression of efflux proteins or pumps, phyto-constituents, plant based antibiotic adjuvants and antibiotic resistance was retrieved from the Web of Science (WOS) core collection platform and SCOPUS database. Total 168 WOS and 225 SCOPUS literature was retrieved encompassing paid as well as non-paid articles of various categories such as research, review, short communications, and conference papers.

Refining of Retrieved Literature:

The present study was aimed to focus on research articles published during the period of 1996–2021. The review articles, short communications, and conference papers were excluded to avoid the research bias. Duplication in the retrieved literature was removed using conditional formatting of MS-Excel.

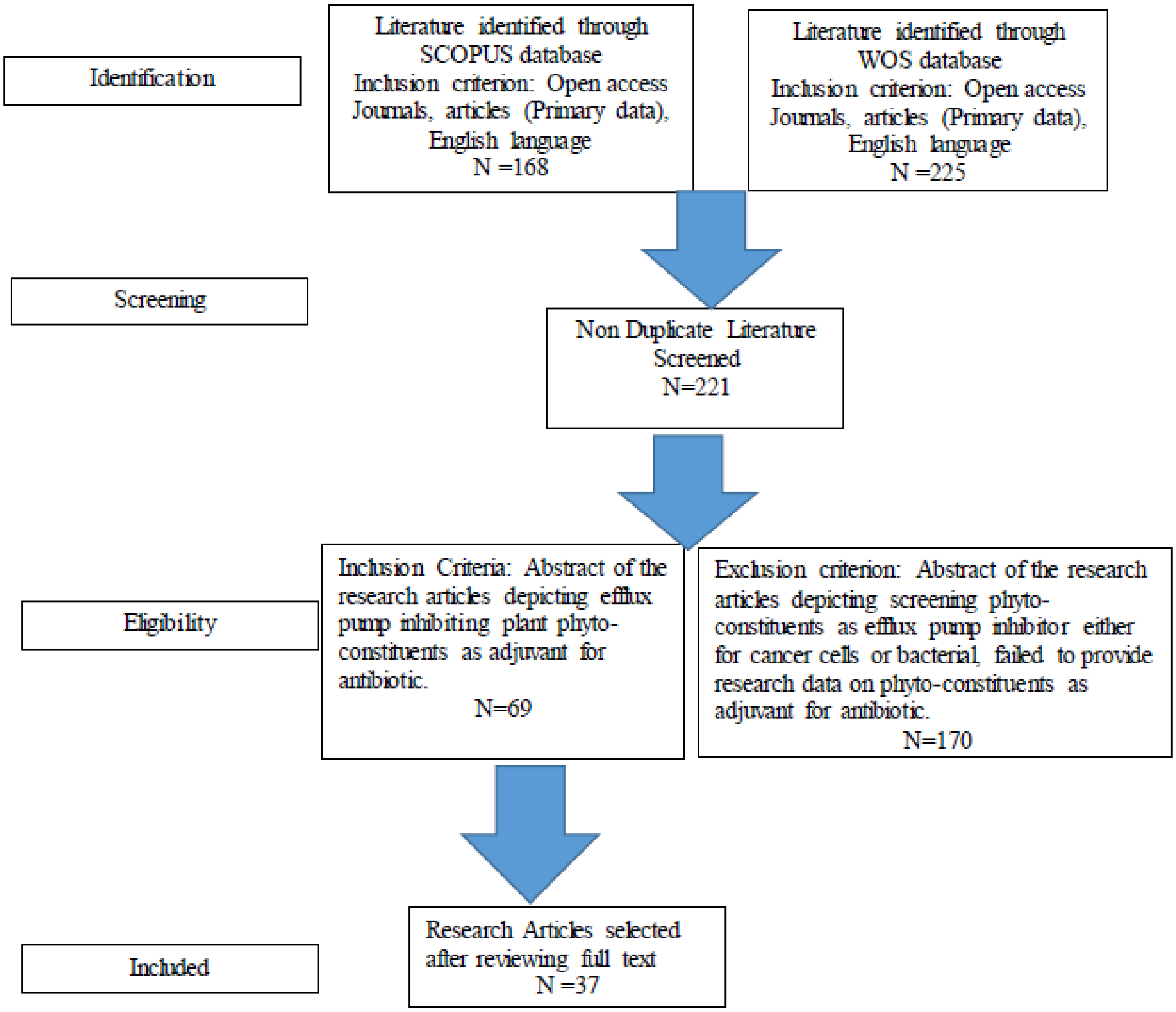
Analysis Protocol:

The literature 221 obtained after removing the duplication was reviewed and 37 research articles depicting efflux pump inhibiting plant phyto-constituents as adjuvant for antibiotics were shortlisted for the present study. The research articles screening phyto-constituents as EPIs but not explicitly elaborating on its combination with antibiotics are rejected.

The content analysis of the shortlisted 37 research articles was conducted to cluster the articles into knowledge structures such as type of bacteria, combination of antibiotics and plant phyto-constituents as adjuvant, classification of the antibiotics as per their mechanism of action and chemical classification of plant phyto-constituents.

A comprehensive bibliometric analysis of the shortlisted 37 articles was conducted to obtain the publication trend, prolific authors and their affiliated institute and countries. Author and index keyword analysis was conducted to explore the prevalent keyword in the management of antibiotic resistance using plant phyto-constituents as antibiotic adjuvant. A Prisma chart elaborating on Protocol for systematic review is portrayed in Fig 1.

Fig 1 Prisma Chart



Analysis Softwares used:

Pivot table tool of Microsoft Excel is used to evaluate the outcomes of the content analysis of the 37 shortlisted articles. Softwares like Raw Graphs and R-tool- Bibliometrix, Biblioshiny is used to comprehensively map the prolific authors and journal and the relatedness for Citation.

Content Analysis:

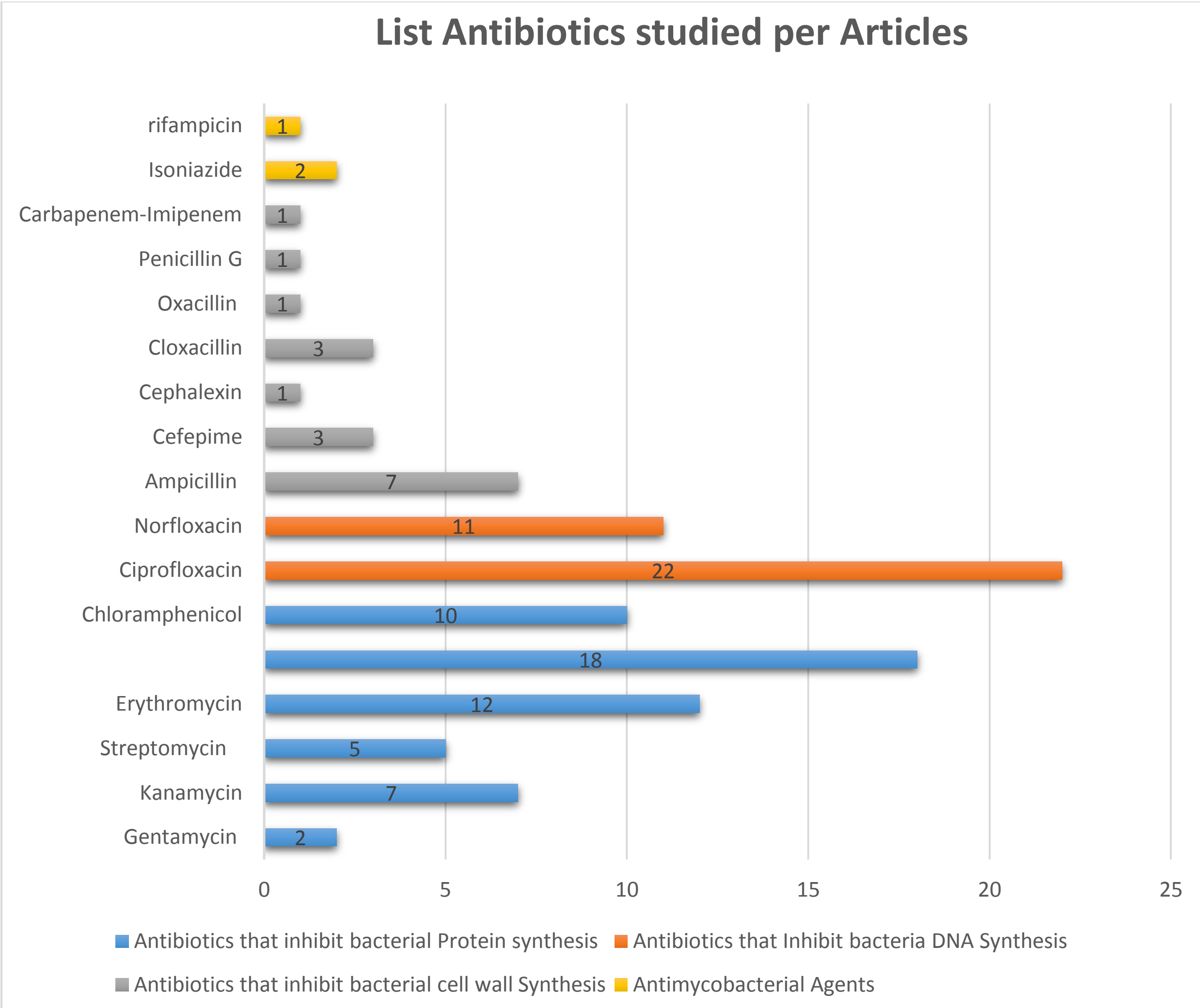
Total 37 research articles, illustrating the combination of plant phyto-constituents with antibiotics in the management of bacterial infections by way of efflux pump inhibition were selected for the content analysis. The focal point of the analysis was to understand the relationship between the type of the antibiotic and plant phyto-constituents as adjuvant, frequently studied bacteria for the antibiotic adjuvant combination, structural similarity between the phyto-constituents used as antibiotic adjuvants.

Cluster 1: Antibiotics

As per the Resistance map developed by the Center for Disease Dynamics Economics and Policy (CDDEP), the drug-resistant pathogens especially, *Escherichia coli*, *Staphylococcus aureus* , *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Enterococcus faecium and Enterococcus faecalis* shows average resistance of 50 to 80% to beta-lactum, third-generation cephalosporins and fluoroquinolone and even to combinations antibiotics such as amoxicillin-clavulanic acid. [5]

Content analysis of the 37 articles as per in Fig. 2 also indicated similar trend wherein Beta-lactam antibiotics, Fluoroquinolones, Norfloxacin,Tetracyclines and Chloramphenicol are the classes of antibiotics mostly evaluated for their combination with plant phyto-constituents as compared to carbapenem class. Amongst these antibiotic classes, antibiotics such as ciprofloxacin, erythromycin, norfloxacin, chloramphenicol, and tetracycline are studied frequently against Gram positive and Gram-negative bacteria as compared to other antibiotics such as streptomycin, kanamycin, cloxacillin and cefepine. Antibiotics such as oxacillin, penicillin G, cephalexin, rifampicin and imipenem are least studied antibiotics. Further, segmentation of the results shown in Fig 2 indicates that antibiotics that inhibit the Protein synthesis are mostly studied as compared to other classes as Antibiotics that inhibit bacterial DNA Synthesis, cell wall and antimycobacterial agents. [10,11,12,13,14,15,16,17,18]

Fig. 2: Analysis of the Antibiotics studied per Shortlisted articles



Cluster 2: Frequently studied bacteria for the antibiotic adjuvant combination

Content analysis of the 37 research articles indicates that 95% research articles are focused on WHO listed high priority ESCAPE pathogens namely, *Pseudomonas aeruginosa, Escherichia coli*, *Enterobacter aerogenes, Klebsiella pneumoniae* and *Staphylococcus aureus*. In addition, the 64 % research articles are focused Gram-Negative bacteria while only 36% on Gram positive bacteria.

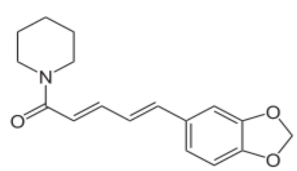
The prior studies on bacterial resistance indicates that Gram negative bacteria like Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia and Pseudomonas aeruginosa develops resistance by limiting uptake of antibiotics in to the cell, inactivation or modification of antibiotics and efflux pump activation. In contrast, Gram positive bacteria like Enterococcus faecium, Enterococcus faecalis and Staphylococcus aureus develops resistance by inactivation or modification of the antibiotics and less likely through activation of efflux pump and limiting uptake of antibiotics. The similar outcome is depicted by the content analysis of this paper as 90% of papers have selected the Gram-negative bacteria such as Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia and Pseudomonas aeruginosa for evaluating bacteriocidal potential of antibiotic-adjuvant combination whereas only 10% selected Gram positive (Staphylococcus aureus) for the similar study.[2,10–41]

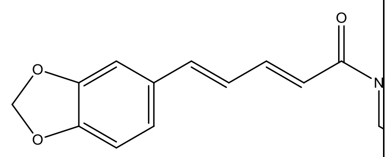
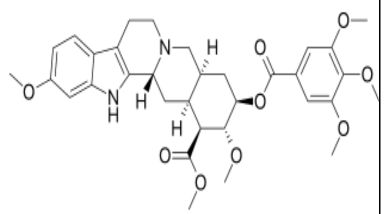
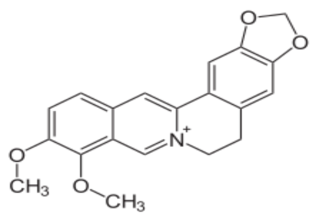
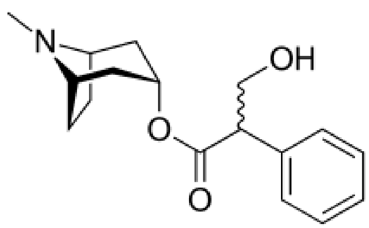
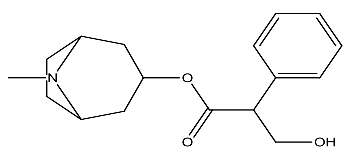
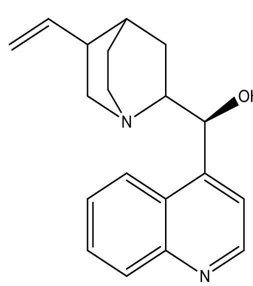
Cluster 3: Phyto constituents as Antibiotic Adjuvants

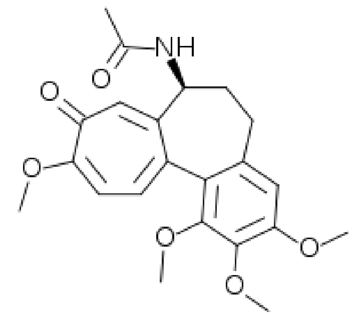
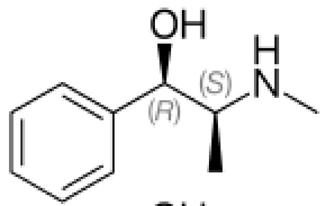
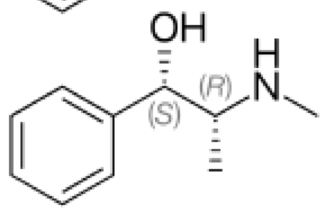
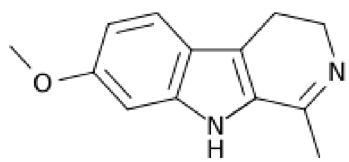
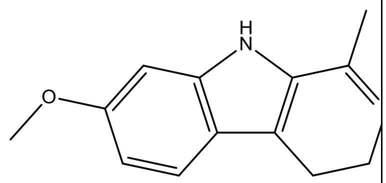
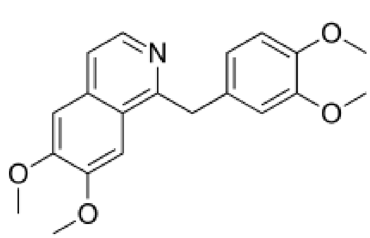
Plant produces various phyto-constitutes having widespread pharmacological potential from being antibiotic adjuvant to anticancer drugs. The Phyto-constituents analysed as the antibiotic adjuvants in the shortlisted 37 papers includes piperine, reserpine, styryllactone, altholactone, 2,6-dimethoxyisonicotinaldehyde, stearic acid, stigmasterol, β-sitosterol, palmatin homomangiferin, mangiferin, β-amyrin, 3-O-β-D-glucopyranosylstigmasterol, 3-O-methyl-D-chiro-inositol, epicatechin,quercetin-3-O-glucoside, berberine, morin, rutin, quercetin, hesperidin, catechin, kaempferol rhamnoside, atropine; berberine; cinchonine; colchicine; ephedrine; harmaline; papaverine; quinine; scopolamine; strychnine, resveratrol and stilbene.

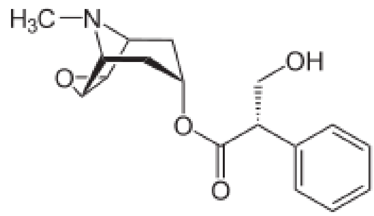
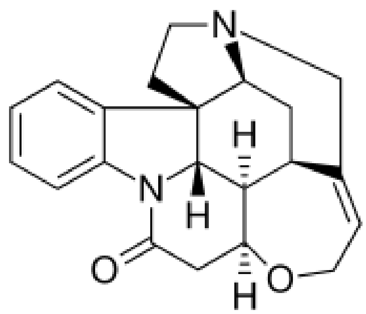
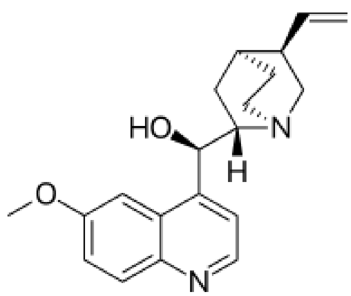
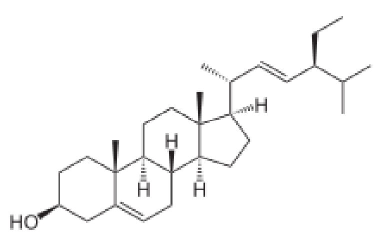
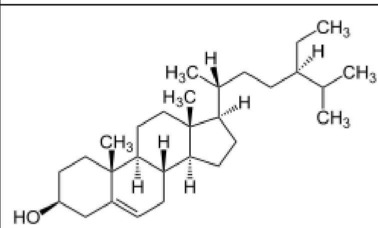
The structural elucidation of these Phyto-constituents as per table 1 shows that the presence of either Two co-planar aromatic rings, a positively charged Nitrogen Group, or a Carbonyl group and are belonging to class of alkaloids, anthocyanins, anthraquinones, flavonoids, phenols, saponins, tannins, sterols and triterpenes are frequently studied as antibiotic adjuvants. [2,10–41, 42,43]

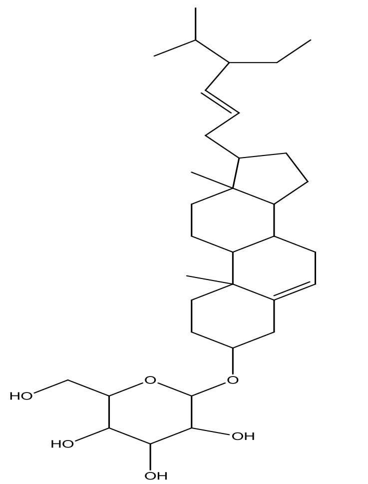
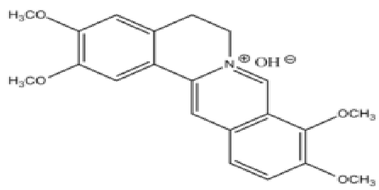
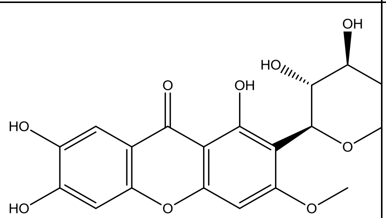
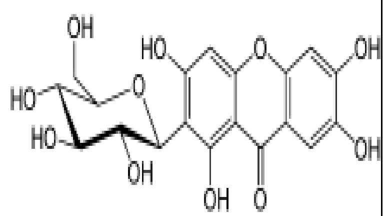
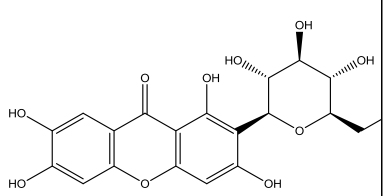
Table 1: Plant phyto-constituents as EPIs

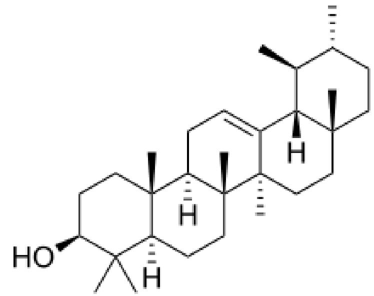
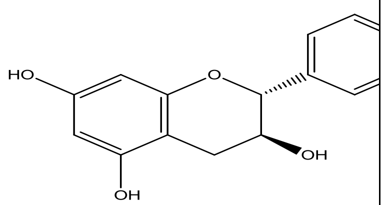
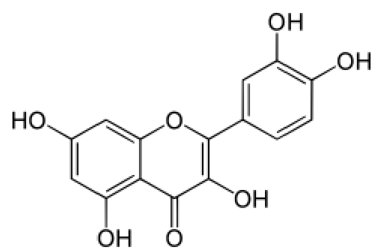
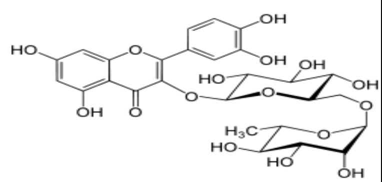
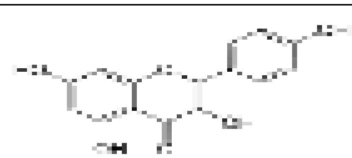
Sr. No.	Name of Phyto-Constituent	Class of the Phyto-Constituent	Structure	Structural Elucidation
	Piperine	Alkaloid		(2E,4E)-5-(2H-1,3-Benzodioxol-5-yl)-1-(piperidin-1-yl)penta-2,4-dien-1-one

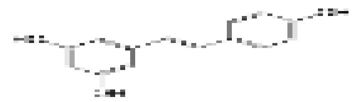
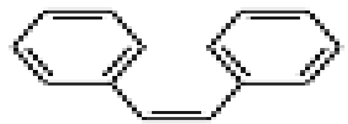
				
	Reserpine	Alkaloid		methyl (3β,16β,17α,18β,20α)-11,17-dimethoxy-18-[(3,4,5-trimethoxybenzoyl)oxy]yohimban-16-carboxylate
	Berberine	Alkaloid		9,10-Dimethoxy-5,6-dihydro-2H-7λ5-[1,3]dioxolo[4,5-g]isoquinolino[3,2-a]isoquinolin-7-ylium
	Atropine	Alkaloid	 	(RS)-(8-Methyl-8-azabicyclo[3.2.1]oct-3-yl) 3-hydroxy-2-phenylpropanoate
	Cinchonine	Alkaloid		(9S)-cinchonan-9-ol

	Colchicine;	Alkaloid		N-[(7S)-1,2,3,10-Tetramethoxy-9-oxo-5,6,7,9-tetrahydrobenzo[a]heptalen-7-yl]acetamide
	Ephedrine	Alkaloid	 	rel-(R,S)-2-(methylamino)-1-phenylpropan-1-ol
	Harmaline	Alkaloid	 	7-methoxy-1-methyl-4,9-dihydro-3H-pyrido[3,4-b]indole
	Papaverine	Alkaloid		1-(3,4-Dimethoxybenzyl)-7,8-dimethoxyisoquinoline

	Scopolamine	Alkaloid		(–)-(S)-3-Hydroxy-2-phenylpropionic acid (1R,2R,4S,5S,7α,9S)-9-methyl-3-oxa-9-azatricyclo[3.3.1.02,4]non-7-yl ester
	Strychnine	Alkaloid		Strychnidin-10-one
	Quinine	Alkaloid		(R)-(6-Methoxyquinolin-4-yl)[(1S,2S,4S,5R)-5-vinylquinuclidin-2-yl]methanol
	Stearic acid	Fatty acid		Octadecanoic acid
	Stigmasterol	Sterol		Stigmasta-5,22-dien-3β-ol
	β-sitosterol	Sterol		Stigmast-5-en-3β-ol

	stigmasterol	Sterol		3-O-β-D-glucopyranosylstigmasterol
	Palmatin	Alkaloid		2,3,9,10-tetramethoxy-5,6-dihydroisoquinolino[2,1-b]isoquinolin-7-ium
	Homomangiferin			1,6,7-trihydroxy-3-methoxy-2-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]xanthen-9-one
	Mangiferin	xanthonoid	 	1,3,6,7-Tetrahydroxy-2-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]-9H-xanthen-9-one

	β-amyrin	triterpene		α: (3β)-Urs-12-en-3-ol β: (3β)-Olean-12-en-3-ol δ: (3β)-Olean-13(18)-en-3-ol
	Epicatechin	Catechin		(2R,3S)-2-(3,4-Dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol
	Quercetin-	Flavonol		3,3′,4′,5,7-Pentahydroxyflavone
	Rutin	Flavonoid glycoside		3′,4′,5,7-Tetrahydroxy-3-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyloxy]flavone
	Hesperidin	Flavanone glycoside		(2S)-3′,5-Dihydroxy-4′-methoxy-7-[α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranosyloxy]flavan-4-one
	Kaempferol	Flavonoid		3,4′,5,7-Tetrahydroxyflavone

	Resveratrol	Phytoalexin		5-[(E)-2-(4-Hydroxyphenyl)ethen-1-yl]benzene-1,3-diol
	Stilbene			1,2-Diphenylethylene

The analysis of the 37 shortlisted papers, also indicates that the 95% of papers evaluated the potential of the plant total extract whereas only 5 % papers are elaborating the potential of isolated phyto-constituents as antibiotic adjuvants. The plant extracts are preferred owing to its synergistic effect typically due to the presence of mixture of phyto-constituents belonging to classes such as alkaloids, anthocyanins, anthraquinones, flavonoids, phenols, saponins, tannins, sterols and triterpenes, as compared to the isolated phyto-constituent belonging to only one of the classes.

The content analysis of the shortlisted articles 33 plants are studied for its EPI. Further, segregation of these plants based on the families indicates that Rutaceae, Lauraceae, Anacardiaceae, and Annonaceae are mostly studied families.

Bibliometric Analysis:

Publication Trend:

Figure 3 illustrates the progression of articles published in the Scopus and WOS data on Plant phyto-constituents as antibiotic adjuvants in the period 1991 to 2020. There has been steady growth in the article publication from 1996 till 2010 (16 Articles) with upsurge during 2011 to 2015 (23 Articles), whereas comparatively, less number of articles published in the time period between 2016-2020, indicating possible impact of COVID 19 typically, in the year 2019. [2,10–41]

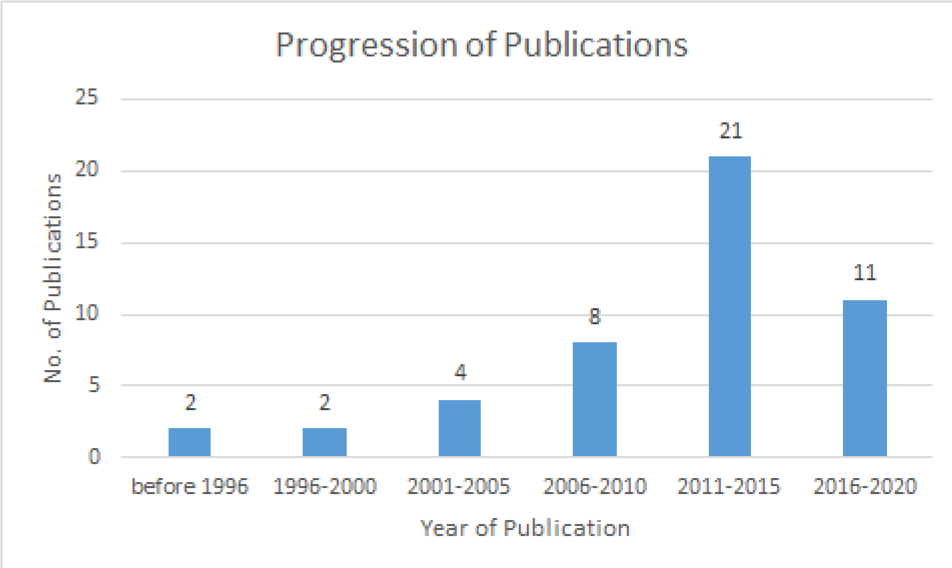


Fig 3: Year Wise publication trend

The 37 publications analyzed are dispersed across 24 journals and 6 subject areas. Fig 4 depicts that 26 are published in the journals covered under the subject area Medicine followed by Immunology and microbiology (16), Biochemistry, Genetics and Molecular Biology (10), Pharmacology, Toxicology and Pharmaceutics (08). Further, the total citation score indicates that articles and journals covered under the Medicine subject area are creating a greater impact on the scientific community than other subject areas. [2,10–41]

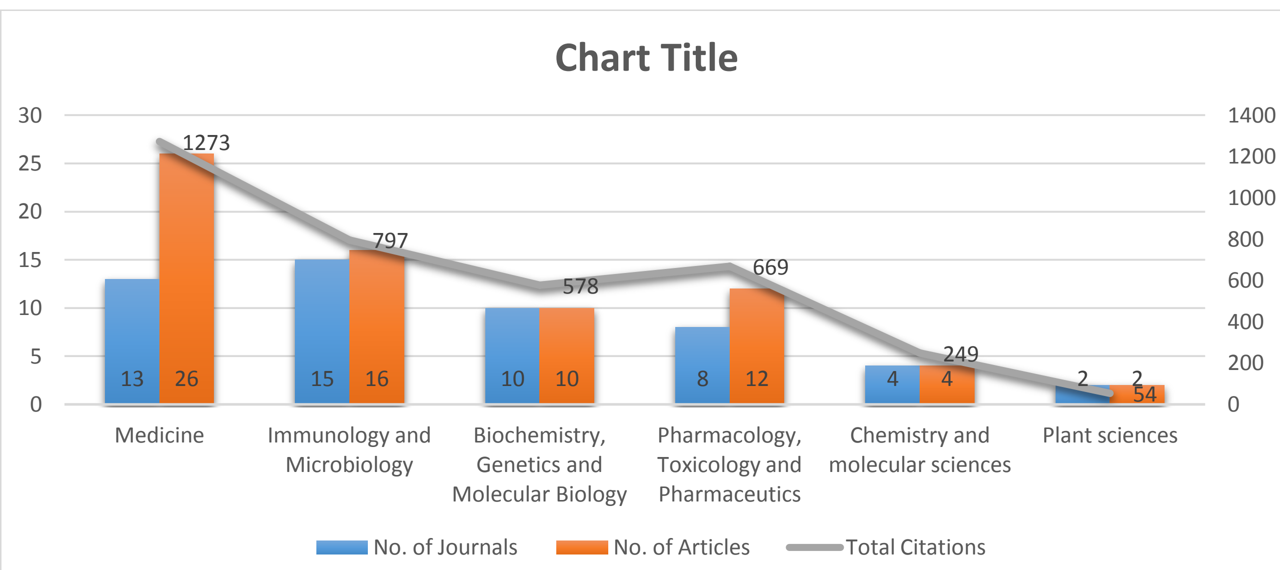


Fig 4: Subject area wise Impact analysis of the Articles and Journals

After analyzing the impact of each subject area on the scientific community, the analysis of the citation score of the individual journal as shown in Fig 5 indicates that, BMC Complementary and Alternative Medicine has published maximum 8 articles, followed by the Journal of Antimicrobial Chemotherapy, Antimicrobial Agents and Chemotherapy, Evidence Based Complementary and Alternative Medicine, International Journal Of Antimicrobial Agents. [10,11,14,21,27,33,38]

However, comparison between the no. of papers published and the citation score as per Fig 4 indicates that though the journals like Journal of Antimicrobial Chemotherapy[44] and Antimicrobial Agents and Chemotherapy[45], has published only 4 and 2 articles respectively, but the citation score is higher than BMC Complementary and Alternative Medicine, directing that for the subject area Medicine, Antimicrobial Chemotherapy and Antimicrobial Agents and Chemotherapy has greater impact on scientific community.

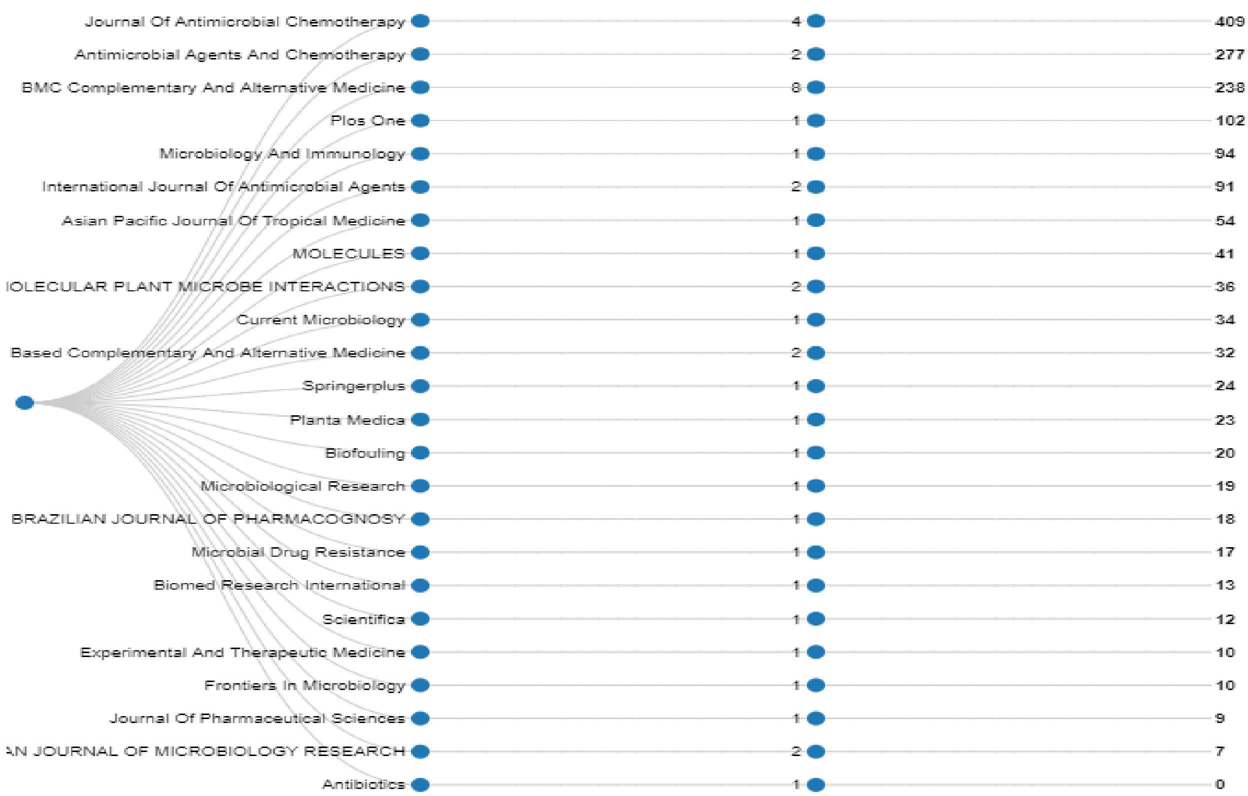


Fig 5 Most Productive Journals based on no. of Articles and the Citation Score

Top contributors based on their number of publications and Citation Score

As per Fig 6, Kuete, V. is the major contributor with 11 publications during the period of 2011 to 2019 and he is also most prolific author with highest citations as 284. Dzotam, j.k., falcao-silva vd, Gibbons, S., Kuiate, J.R., Mbaveng, A.T.,Tankeo, S.B., Voukeng, I.K., have also contributed 3 articles each and Abreu, A.C., BARBOSA JM, Beng, V.P., DE ARAUJO JX, Dzoyem, J.P., Hofmann, B., Khan, I.A., Lall, N., Mendonça-Junior, F.J.B., Pages, J.M., Saavedra, M.J., Scotti, L., Simões, M.,Tane, P. with 2 articles. [8,10,11,13,14,19,27]

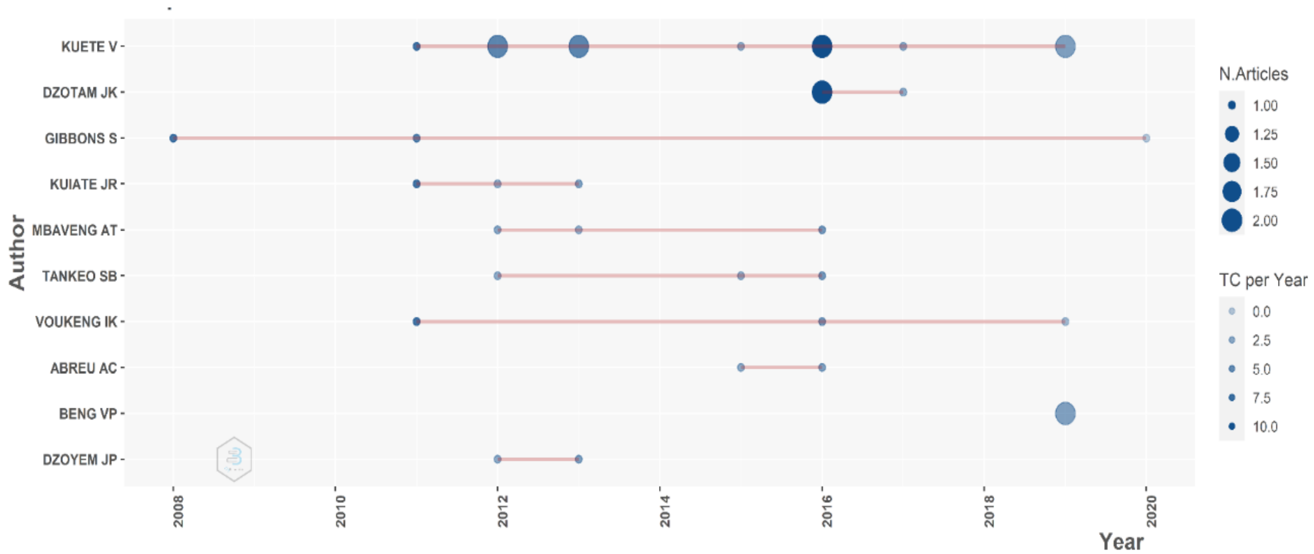


Fig 6 Prolific authors over the Time

- The line indicate the period
- Bubble Size is equivalent to the number of articles published by the author in the particular year.
- Color intensity of the bubble indicates total number of citations per year.

Result and Discussion:

The systematic review of the literature indicates that 221 papers were providing the potential of the plant phyto-constituents as EPIs; however, only 37 papers evaluated the synergistic effect of the EPI for a specific type of antibiotics. Further, 90% of papers are elaborating the potential of alkaloids, anthocyanins, anthraquinones, flavonoids, phenols, saponins, tannins, sterols and triterpenes on Gram negative bacteria such as Acinetobacter baumannii, Escherichia coli, Klebsiella pneumonia and Pseudomonas aeruginosa whereas only 10% selected Gram positive (Staphylococcus aureus) for the similar study. Further, majority of the research papers were focused on evaluating the potentials of EPI along with the Fluoroquinolone antibiotics, specifically, ciprofloxacin. Moreover, majority of the articles evaluated antibiotic adjuvant combinations for the antibiotics which inhibit the protein synthesis like tetracycline, erythromycin and Chloramphenicol.

With respect to citation score of the shortlisted papers, Kuete, V is the most prolific author and the Journal of Antimicrobial Chemotherapy, Antimicrobial Agents and Chemotherapy BMC Complementary and Alternative Medicine are the most productive journal. The subject area wise segregation of shortlisted article shows that authors are preferring subject area Medicine to publish the papers. Moreover, the journals published under the subject area Medicine showed higher impact on the scientific community as correlative to its higher citation score.

Conclusion:

For more than 80 years, antibiotics have saved millions of lives and significantly transformed the health care. However, irrational use of the antibiotics and frightening spread of multidrug resistant bacteria is leading the 21 century to a silent pandemic with “No antibiotic era”. Moreover, use of antibiotics for patients with COVID 19 infection to reduce the chances of secondary bacterial infections have accelerated the antimicrobial resistance (AMR), all over the world.

To tackle the issue of No antibiotic era and the multi drug resistant bacterial infections various strategies such as responsible prescribing of the antibiotics, development of new antibiotic molecules as well as perusing the resistance mechanism in bacteria are adopted by the government and the research scientist. Amongst these strategies, studies on bacterial resistance mechanisms may paved the way for quick and effective solutions to manage MRB.

Accordingly, present paper provided systematic review and the bibliometric analysis on plant phyto-constituents as Antibiotic Adjuvants. The systematic review and the content analysis of three cluster indicates that the Antibiotics such as Ciprofloxacin, Norfloxacin, Tetracyclines and Chloramphenicol can appropriately be combined with plant phyto-constituents such alkaloids, terpenoids, flavonoids to inhibit the efflux pump of Gram negative bacteria, and Gram Positive

Bibliometric analysis of the journals and the authors covering 37 shortlisted articles of the present paper directs that Kuete, V. is the major contributor and productive author with 11 publicationsand 284 while Journal of Antimicrobial Chemotherapy and Antimicrobial Agents and Chemotherapy, BMC Complementary and Alternative Medicine are the most product journals. Other productive authors, includes Dzotam, J. K., Falcao-silva V.D, Gibbons, S., Kuiate, J.R., Mbaveng, A.T., Tankeo, S.B. and Voukeng, I.K. [8,10,11,13,14,19,27]

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