Review of: "[Review] The antibacterial activity of Allium sativum, Thymus vulgaris, Origanum vulgare, Curcuma longa, Rosmarinus officinalis, and Cinnamomum species against various antibiotic-resistant strains of bacteria: A Literature Review"

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Potential competing interests: No potential competing interests to declare.

The antibacterial activity of Allium sativum, Thymus vulgaris, Origanum vulgare, Curcuma longa, Rosmarinus officinalis, and Cinnamomum species against various antibiotic-resistant strains of bacteria: A Literature Review

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Reviewer

Overall: This is an extensive study with a lot of work done on what has been published of the above-named botanicals on (multi-drug) resistant bacteria between 2007 and 2018 on the subject. It is very important in the age of increasing antibiotic resistance to study what is available on this subject. The conclusion that certain botanicals may be used as monotherapy is too strong (Abstract). Also, I would love to see toxicity data for the use of extracts and oils. Moreover, suggestions for practical use would be welcome. Several studies are cited but what kind of extract is used is not clear in all studies cited, please specify.

Specific paragraphs:

1.1 This paragraph needs a bridge between penicillin and methicillin after ….*antibiotic-resistant strains (Ventola, 2015).*' E.g.: Methicillin was developed in the 1950s to overcome the penicillinase-producing ability of staphylococci.

1.2 '*Overpopulation provides additional growth mediums for bacteria'* Kindly rephrase this sentence using risk factors and explanations like overcrowding and poor sanitary situations.

1.3 In general: it is common practice in microbiology to write a dot after the S. of Staphylococcus, P. of Pseudomonas.

For *E. coli* deaths statistics: it is impossible that only 60 deaths occur due to all infections with*E. coli*, as it is a very common cause of urinary tract infections and urosepsis in the US and the rest of the world. Are the authors only relating to Shiga-toxin related diarrheal diseases or HUS? Please specify.

5.

The mechanisms of action of these antibacterial agents include interfering with the production of the cell wall or membrane, reducing folate synthesis, disrupting DNA or RNA replications, or impeding the generation of proteins (Kapoor et al., 2017).This is an unspecific and incomplete description of the workings of various antibiotics, please elucidate. Eg. Group antibiotics according to the mechanism of action: Beta-lactam antibiotics like penicillins, cephalosporins, cephamycins and carbapenems interfere with cell wall synthesis, trimethoprim and sulfonamides interfere with folate synthesis. Etc.

Quinolones = fluoroquinolones.

6.1 *Staphylococcus aureus*

'*and in the community as it can become MRSA*.' MRSA is found both in communities, live-stock and health-care settings. Please change.

'colonized on' = colonizing

Add postoperative wound infections to the infections caused by *S. aureus*.

MRSA: The main mechanism for beta-lactam antibiotic resistance in MRSA is an altered penicillin-binding protein. Please use another citation e.g. by Larsen in Nature 2022: Methicillin resistance in S. aureus is mediated by the mecA and mecC genes, which encode the enzymes penicillin-binding protein 2a (PBP2a) and PBP2c, respectively. mecA and mecCconfer resistance to almost all β-lactam antibiotics, including penicillinase-labile penicillins (such as penicillin G), penicillinase-stable penicillins (such as methicillin) and cephalosporins (such as cefoxitin).

6.2 *S. pneumoniae*

Resistant strains cannot have been detected in 1912. Kim describes reduced susceptibility to penicillin in 1967.

S pneumoniae has been found to be resistant to penicillin, erythromycin, and trimethoprim-sulfamethoxazole (Kim, 2016). Penicillin targets peptidoglycan in the cell wall in gram-positive bacteria binding to the active site of transpeptidase, which prevents the cross-linking of the cell wall, interfering with synthesis (Kim, 2016). Research indicates that mutations in the gene encoding transpeptidase reduce the binding affinity of penicillin, resulting in antibiotic resistance (Kim, 2016). Why explain the working of penicillin (a betalactam antibiotic) here and not earlier?

Other antibiotics that have been administered are different forms of penicillin, ampicillin, cephalosporin, clindamycin, cefdinir, or cefuroxime (Kim, 2016). Cefdinir and cefuroxime are types of cephalosporines (betalactam antibiotics). Please rephrase.

6.3 *Pseudomonas aeruginosa*

P aeruginosa is associated with the development of hospital- acquired infections in the US and is termed MDR as it is often resistant to at least three or more antibiotics (Shortridge, 2019). AS or WHEN?

Hospital-acquired infections can become septic or cause pneumonia (Moradali, 2017) HAI can lead to pneumonia or sepsis.

P.aeruginosa also infects those with structural lung disease, e.g. COPD and cystic fibrosis.

or in patients requiring the use of a catheter (CDC, 2019c). Urinary tract and/or intravenous catheter?

Please add biofilm formation as a virulence factor.

MDR P aeruginosa is treated with piperacillin, piperacillin with tazobactam, cephalosporins, carbapenems, ciprofloxacin, gentamicin, tobramycin, and polymyxin (Yayan, 2015). If you describe the aminoglycosides gentamicin and tobramycin, please add amikacin which is usually the only AG still susceptible in MDR *Pseudomonas*.

6.4 *Escherichia coli*

E coli are a group of gram-negative, anaerobic, pathogenic bacilli E coli grows both in aerobic and anaerobic environments. Please change.

E. coli is the most frequent cause of UTI and urosepsis. (This is also what we see in clinical care.) Please add.

If you elaborate on ESBL, then please add carbapenemase activity which is even more worrying nowadays.

Antibiotic-resistant strains of E coli are treated with nitrofurantoin drugs, which have been shown to have a resistance rate of 7.3% (Olorunmola, 2013). Of course, nitrofurantoin can only be used for cystitis, limiting its use.

Other antibiotics that E coli may be susceptible to are fluoroquinolones, ciprofloxacin, and norfloxacin (Olorunmola, 2013). Fluroquinolones like ciprofloxacin and norfloxacin.

Ceftazidime and cefotaxime administered in conjunction with clavulanic acid were effective against EsβL-producing E coli Rasheed, 2014). However, in clinical situations carbapenems are often used.

Please group Oregano studies and Curcuma studies in different paragraphs.

6.5 *Campylobacter jejuni*

It is estimated thatC jejuni is implicated as the pathological agent in 90% of illnesses that affect humans and is the most common cause of GI illnesses around the world (CDC, 2022a; Johnson, 2017). This cannot be correct. Please rephrase (e.g. bacterial food-borne gastro-enteritis).

A possible mechanism associated with antibiotic resistance ofC jejuni is a substitution mutation of amino acids affecting DNA-gyrase and topoisomerase IV (Lluque, 2017). This first describes fluoroquinolone resistance mechanisms without full describing known % of FQ resistance in the US. Please elaborate.

Alterations of genes may also occur through the direct transfer of genetic material with other bacteria, increasing the probability of resistance (Johnson, 2017; Lluque, 2017). Modifications in the uptake of certain antibiotics have occurred as

a result of resistance as well (Lluque, 2017). This is a general description of a few resistance mechanisms and does not add good information to the text.

Azithromycin, ciprofloxacin, and a combination of amoxicillin and clavulanic acid have been utilized to treat antibiotic-resistant strains of the bacteria (Schiaffino, 2019). Actually, azithromycin and ciprofloxacin is normally used if antibiotic treatment is needed (in the young, the old, the immunocompromised) but increasingly tested resistant. When resistance arises, the lab tests e.g. amoxiclav, tetracyclins, carbapenems, clindamycin. Please elaborate.

6.6 *Salmonella typhimurium*

Salmonella is not only anaerobic but facultatively anaerobic when cultured. Moreover, they are facultatively intracellular pathogens which adds to pathogenicity.

*MDR species of S typhimurium were first identified in the early 1980s (Crump, 2015).*Please note that MDR is a characteristic and not a Salmonella species. Rephrase.

Serotypes of this bacterium may be immune to fluoroquinolone, ampicillin, streptomycin, sulfonamides, cephalosporins, ceftriaxone, chloramphenicol, trimethoprim-sulfamethoxazole and tetracycline (Crump, 2015). Cephalosporins like ceftriaxone.

An alteration of the genes that encode the folic acid pathway can increase its resistance to certain antibiotics (Crump, 2015). Folic acid pathway inhibitors are sulfonamides and trimethoprim, please rephrase.

*Modification of DNA gyrase and topoisomerase IV reduces the susceptibility of S typhimurium to quinolone antibiotics (Crump, 2015).*Fluoroquinolone antibiotics.

Ciprofloxacin has been utilized as a monotherapy or in conjunction with levofloxacin, ofloxacin, and norfloxacin for the treatment of S typhimurium-resistant strains (Wang, 2019). All antibiotics named here are fluoroquinolone antibiotics and will never be used in conjunction with another FQ due to toxicity! Please rephrase.

8.2

Another study showed that garlic (A sativum) enhanced the activity of cefoxitin, oxacillin, and piperacillin against MRSA and cefoxitin, levofloxacin, ceftriaxone, cefazolin, and ampicillin against P aeruginosa (Li, 2015). Normally Pseudomonas is not susceptible to cefoxitin, cefazolin, ceftriaxone, nor to ampicillin: is this really correct?

*Thyme (T vulgaris) amplified the effects of tetracycline, ampicillin, and cloranfenicol against MDR P. aeruginosa (Nascimento, 2000).*Chloramfenicol?

Lastly, synergism has been demonstrated between thyme (T vulgaris) and ciprofloxacin, amphotericin B, ethambutol, isoniazid, and cefotaxime against various strains of bacteria (Rahgozar, 2018; van Vuuren, 2009; Benameur, 2018). Amphoterin B has antifungal activity, but is not used against bacteria. Please rephrase.

9.*The pro-inflammatory effects generated by this bacterium can increase the risk of morbidity and mortality from an*

*infection (Berdasco, 2019).*This sentence is out of context and needs to be specific.