Global Scientific JOURNALS

GSJ: Volume 9, Issue 1, January 2021, Online: ISSN 2320-9186
www.globalscientificjournal.com

SYNERGISTIC EFFICACY OF HONEY SINGLE-DOSE COMBINATION THERAPY: A SOLUTION TO SUPERBUG MENACES

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Abstracts
Honey is a sweet, viscous substance made by honey bees and related insects. It is one of the ancient long-established medicines well thought-out as a therapy for diverse microbial infections. It is an antibacterial agent that is used by many herbal practitioners as a recipe for herbal preparation. Combination therapy is described as the use of two or more pharmacologic agents in a single-dose formulation administered separately or in a fixed-dose combination of two or more active ingredients. Honey combination therapies had been documented to improve effectiveness, decrease toxicity, and decrease drug resistance growth. Laboratory researches showed that even the multidrug resistance bacterial had an excellent microbial clearance for both honey-herbal combination and honey-antibiotics combination. Honey combination therapy should be well researched and improved to stop the spread of antibiotic resistance and restore hope for health.

Key words: honey, honey-combination, therapy, multidrug resistance, single-dose and synergy

1.0 Introduction

Honey was described as a natural substance produced when nectar and sweet deposits from plants are collected, modified and stored by honeybees of the genera *Apis* and *Meliponini* in the honeycombs (Manyi-Loh *et al*., 2011). It was one of the most well-known natural antimicrobial substances used in Ayurveda as a potent multi-use drug (Ramalivhana *et al*., 2014) and successful on bacteria immune to antibiotics (Zakarias, 2015). It has also been documented that honey not only improves microorganisms' sensitivity to antibiotics, but also decreases microbial resistance (Zakarias, 2015).

As the prevalence of antimicrobial-resistant species especially the increase in multi-drug resistance (MDR), is currently alarmingly growing, the number of effective antibiotic

compounds is diminishing more rapidly than the number of new drugs being developed. Hence, the need for combination therapy to achieve the desire results (Nolan *et al.*, 2019),

Combination drug therapy is described as the use of two or more pharmacologic agents in a single-dose formulation administered separately or in a fixed-dose combination of two or more active ingredients (Rahman, 2020). Because of these benefits, combination therapies leverage the chances of improved efficacy, decreased toxicity, and decreased drug resistance development (Foucquier and Guedj, 2020). Bacterial resistance to antimicrobial agents poses a very serious threat to public health, and resistance rates are growing globally for all forms of antibiotics, including the big last resort drugs (Rahman 2020).

The mixture of honey in a single dose combination therapy has been documented by several researchers. Many herbal prescriptions have confirmed the use of honey as a herbal solvent (Kujawska *et al.*, 2012). In-vitro antimicrobial activity of honey has been documented with several medicinal plants in a single dose combination (Nwankwo *et al.*, 2015: Metwali *et al.*, 2014). Honey is usually part of the herbal mixture preparation recipe where it serves as a preservative (Ajao *et al.*, 2014).

Drug combinations can be additive; antagonist or synergist depends on the therapeutics index. Synergy between antimicrobial agents means that, when tested in vitro, the combined effect of the agents is greater than the sum of their independent activities when measured separately (Leekha *et al.*, 2011). Therefore, drug combination become a standard for the treatment of several diseases and continue to represent a promising approach in indications of unmet medical need (Foucquier and Guedj, 2020). The objective of this study was to review the synergetic efficacy of honey single-dose combination therapy against infectious agents with a view of better futuristic approach on emerging superbugs

2.0 Reasons for combination therapy

The key goal of combination therapy is to successfully prevent a medical condition if the therapeutic response to mono therapy is not effective on intended organism (Rahman1 *et al.*, 2020). Traditional and modern medicine has followed the method of drug combination, and this has always take advantage of the simultaneous use of multiple active agents to treat various diseases (Foucquier and Guedj, 2020). Because, due to the redundancy inherent in biological networks, the use of several drugs can provide more efficient responses than using a single drug.

Combination treatments are used in Morden pharmaceutical practice for the treatment of serious diseases to achieve improved therapeutic results (Che *et al.*, 2013). It has been shown that treatments consisting of mixtures of pharmacological agents have superior effects. (Vakil and Trappe, 2019).

Traditional Chinese medicine had been documented to use blends of naturally occurring herbs (Foucquier and Guedj, 2020). The modern combination therapy method is a renewal of what was advocated in Chinese medicine, which began thousands of years ago with the use of herb-herb combinations to enhance therapeutic outcomes (Che *et al.*, 2013).

Combinations of antibiotics have also been used in the treatment of drug resistant infections as they take advantage of multiple mechanisms of action. Combinations of antimicrobials that show in vitro synergy with infecting strains are more likely to contribute to successful therapeutic outcomes (Aiyegoro and Okoh, 2009).

Synergistic combinations allow dose-escalation to increase efficacy and dose-reduction to alleviate side effects (Cokol-Cakmak *et al.*, 2018). Multiple setbacks to cellular machinery can also be applied by combination therapies, thus blocking possible evolutionary escape mechanisms to resistance (Yeh *et al*., 2009).

3.0 Honey-herb combination therapy: A traditional curative medication Practice.

Honey has been recorded as a preservative and as part of the recipe for the preparation of herbal mixtures in most rural part of Nigeria (Ajao *et al.*, 2014). However, it is not unusual to find that in many herbal remedies, honey alone either acts as the prescription for the treatment of different ailments or as the main curing constituent. For example, recent literature reports in Southwest Nigeria suggested that health conditions such as constipation, duodenal ulcer, toothache (Lawal *et al.,* 2007) and other conditions such as bladder infections, arthritis, hair loss, bad breath and skin infections also have honey as one of the main components of the herbal medicine used for their treatment (Moodley *et al.*, 2008).

Kujawska *et al.* (2011) reported that pure honey and honey-based mixtures are used primarily to treat respiratory symptoms and illnesses. The most common bacteria which cause respiratory tract infection are *Pseudomonas spp., Streptococcus spp., Proteus spp., Klebsiella spp., Staphylococcus spp., Enterobacter spp., Acinetobacter spp.,* and *Haemophilus influenza* (Alemseged *et al*., 2018). It was also reported that the nonindigenous population of Misiones, Argentina used honey-based medicinal formulas and the role of honey in more than 90% of formulas is perceived as therapeutic (Kujawska *et al*., 2011).

In Kwara state, Nigeria, the following plants which includes; orange (*Citrus aurantifolia*), Garlic-*(Allium sativum),* pawpaw *(Carica papaya),* mistletoe (*Viscum album*), Lemon (*Citrus limon*), Banana (*Musa sapientum*), Onions (*Allium cepa*), Bitter kola (*Garcinia kola*), Pineapple (*Ananas comosus*), Lemon grass (*Cymbopogon Citrates)* and among others were frequently combined with honey for treatment of different ailments locally (Ajao *et al*., 2014).

In Ethiopia, honey and garlic were used extensively as a foods and traditional medicines (Alemseged et al., 2018). Different local communities use mixture of honey and garlic traditionally to treat coughing and other respiratory tract infection (Alemseged *et al.* 2018) because honey is known to contain phenol, fatty acids, lipids, amylases, ascorbic acid, peroxidases and fructose and has high osmolarity and low pH. These elements acting alone or synergistically may contribute significantly to the antimicrobial activity of honey (Al-jabri, 2005). Che *et al*. (2013) also stated that for herb to herb combination therapy, there must be reinforcement which refers to situations in which herbs possessing similar medicinal properties are used together to produce a greater efficacy

4.0 Empirical fact of honey combination therapy: An In-vitro testing report.

Honey, the most well-known antimicrobial agent used independently and dependently, had many in vitro laboratory proofs attesting to its medicinal significance (Zakarias 2015: Zeedan *et al.,* 2016:). The combination of honey plus some natural additives has superior results in its antibacterial, antifungal, and wound-healing promotion properties compared with pure bee honey and some other topical wound healing agents alone as reported by (Mboto *et al.,* 2009). Mshelia *et al.* (2018) combined Honey and lemon to test a number of infectious agents in-vitro and the results proved beyond reasonable doubt that the combination of honey with other antimicrobial herb could be effective and synergetic. Zakarias (2015) also gave an update of the synergetic activity of honey-antibiotics combination against *Pseudomonas aeuriginosa and methicillin* resistance *Staphylococcus aureus.*

The combination of the extracts of *Gacinia kola* and *Vernonia amygdalina* suspended in honey has been shown to inhibit the growth at tidy concentrations of some medically essential microorganisms *(P. aeruginosa, K. pneumoniae, S. aureus, P. mirabilis, E. coli* and *C. albicans)* (Mboto et al., 2009). A similar study was carried out on the following organisms: *Staphylococcus aureus, Streptococcus spp, Pseudomonas aeruginosa, Klebsiella pneumonia* and *Escherichia coli* isolated from Sputum of Patients Attending Federal Medical Center Umuahia, the report has it that the organisms were more susceptible to honey mixtures than when were used alone Nwankwo *et al*. (2015).

Zeedan *et al.* (2016) reported that multidrug resistance bacteria (*Staphylococcus aureus, Staphylococcus epidemdis, Escherichia coli* and *Klebsiella pneumonia*) isolated from human patient at local hospital in Riyadh region, Saudi Arabia were highly sensitive to honey mixture from Ginger, Clove and Black Cumin extracts at low concentration 0.0325 mg/ml. In a similar in-vitro study by Saad *et al*., (2012), vancomycin - sensitive *enterococci* and vancomycin - resistant *enterococci* were significantly affected by onion - honey mixture (1:1) more than onion alone and honey alone.

Alemseged et al. (2018) revealed that the inhibition capacity of mixture of garlic extract and honey against five respiratory tract infection causing bacteria such as *Pseudomonas aeruginosa, Streptococcus pneumoniae, Klebsiella pneumoniae, Haemophilus influenza* and *Staphylococcus aureus* was greater than the commercial antibiotics such as Co-trimoxazole, Cefoxitin and Erythromycin.

Betoni *et al.* (2006) showed that plants either produce antimicrobials that can function in synergy with antibiotics or have compounds that do not have intrinsic antibacterial activity but are capable of sensitizing the pathogen to a previously ineffective antibiotic

For patients with invasive infections that are difficult to treat, such as those due to multi-resistant species, combination therapy may be used to expand the antimicrobial spectrum, prevent the emergence of resistant mutants, minimize toxicity and obtain synergistic antimicrobial activity, and provide an alternative to monotherapy (Aiyegoro and Okoh 2009).The synergistic effect of

combining antibiotics with plant extracts against resistant pathogens is leading to new options for the treatment of infectious diseases (Aiyegoro and Okohh, 2009).

5.0 Conclusion

Honey combination therapy have outstanding bacterial clearance than when they are used alone both in-vivo and in-vitro. Many herbal practitioner use honey as a recipe for herbal preparation. The therapeutic efficacy of honey-combination in most cases surpassed many convectional antibiotics. The combination has no record of microbial resistance. Therefore, more research is required for honey combination therapy to effectively address the present antibiotics resistance challenge and restore hope to clinical treatment.

Conflict of interest
The authors declared that there is no conflict of interest

Acknowledgement
Many thanks to Mrs Esther Achor for creating an enabling during the review

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