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Antimicrobial Activity of Medicinal Plant Extracts and Their Synergistic Effect on Some Selected Pathogens

Desalegn Amenu*

College of Natural and Computational Science, Biology Department, Wollega University, P. O. Box, 395, Ethiopia

ABSTRACT

Antibiotics provide the main basis for the therapy of microbial (*bacterial and fungal*) infections. Since the discovery of these antibiotics and their uses as chemotherapeutic agents there was a belief in the medical fraternity that this would lead to the eventual eradication of infectious diseases. There is a continuous and urgent need to discover new antimicrobial compounds with diverse chemical structures and novel mechanisms of action because there has been an alarming increase in the incidence of new and re-emerging infectious diseases. Another big concern is the development of resistance to the antibiotics in current clinical use. In recent years, drug resistance to human pathogenic bacteria has been commonly reported from all over the world. In the present scenario of emergence of multiple drug resistance to human pathogenic organisms, this has necessitated a search for new antimicrobial substances from other sources including plants. Higher plants produce hundreds to thousands of diverse chemical compounds with different biological activities. The antimicrobial compounds produced by plants are active against plant and human pathogenic microorganisms. It is expected that plant extracts showing target sites other than those used by antibiotics will be active against drug-resistant microbial pathogens.

Keywords- Herbal extracts, Antimicrobial agent, Multi-drug resistant.

INTRODUCTION

The development of bacterial resistance to presently available antibiotics has necessitated the need to search for new antibacterial agents. Gram positive bacteria such as *Staphylococcus aureus* are mainly responsible for post-operative wound infections, toxic shock syndrome, endocarditis, osteomyelitis and food poisoning[5]. Gram negative bacterium such as *Escherichia coli* is present in human intestine and causes lower urinary tract infection, coleocystis or septicaemia[6]. Multiple drug resistance in human pathogenic microorganisms has been

developed due to indiscriminate use of commercial antimicrobial drugs commonly used in the treatment of infectious diseases. The development of antibiotic resistance is multi factorial, including the specific nature of the relationship of bacteria to antibiotics, the usage of antibacterial agent, host characteristics and environmental factors. This situation has forced scientists to search for new antimicrobial substances from various sources as novel antimicrobial chemotherapeutic agents, but the cost production of synthetic drugs is high and they produce adverse effects compared to plant derived drugs[2].

These antimicrobial substances are of natural origin, and it is thought that their influences on the environment are few and can be used as biological control agents. However, some medicinal herbs for some reasons have not found wider application and sometimes are referred as 'forgotten plants'. Even though pharmacological industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased. In general, bacteria have the genetic ability to transmit and acquire resistance to drugs, which are utilized as therapeutic agents[10].

From these microbes resistant to antibiotics, Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of nosocomial infections. MRSA infections are very difficult to cure because MRSA strains are resistance against almost all clinically available antibiotics. For most MRSA strains, glycopeptide-type drugs such as vancomycin are the only effective antimicrobial agents. However, vancomycin-resistant *S. aureus* (VRSA) has been reporte[3]. *Pseudomonas aeruginosa* also causes nosocomial infections as a result of its ubiquitous nature, ability to survive in moist environments and resistance to many antibiotics and antiseptics. A main problem is the emergence of multidrug-resistant *P. aeruginosa* strains resistant to different antimicrobial agent classes. Perhaps, this high degree of multidrug resistance related to the presence of antibiotic efflux systems which provide resistance to multiple antimicrobial agents[3].

Multidrug-resistant Enterobacteriaceae, mostly *Escherichia coli*, produces extended-spectrum β lactamases-M (ESBLs) enzymes. These enzymes suchwere as the named for their greater activity against cefotaxime as other oxyimino-beta-lactam substrates such as ceftazidime, ceftriaxone, or cefepime have emerged within the community setting as an important cause of urinary tract infections (UTIs). Recent reports have also described ESBL-producing *E. coli* as a cause of bloodstream infections associated with these community-onsets of UTI[12]. Some Palestinian plants exhibit significant potency against human bacterial pathogens. However, at present, plant extracts are rarely used as antimicrobials or as a systemic antibiotics and this may be due to their low level of activity, especially against gram-negative bacteria[3].

Wadi Gaza is an essential part of natural life in Palestine and has a rich biodiversity in terms of fauna and flora. As many as 70 plant species belonging to 32 families and 24 orders were identified in Wadi Gaza. The aster or daisy family (Compositae) is the largest found family which composed of 14 plant species (20%) of the recorded species. The natural flora of Wadi Gaza was commonly used in different ways as a source of food, herbal medicine, fodder for grazing animals, timber and fuel production[1].

Objective

To assess the antimicrobial and synergistic effect of some medicinal plant extracts with antibiotic and non-antibiotic drugs against isolates *E. coli*, *S. aureus* and *P. aeruginosa*.

LITERATURE REVIEW

Medicinal plants

Plants as a source of medicinal compounds have continued to play a dominant role in the maintenance of human health since ancient times. According to the World Health Organization plant extracts or their active constituents are used as folk medicine in traditional therapies of 80% of the world drugs are of natural product origin[22].

The specific function of many phytochemicals is still unclear; however, a considerable number of studies have shown that they are involved in the interaction of plants/pests/diseases. Antimicrobial screening of plant extracts and phyto-chemicals, then, represents a starting point for antimicrobial drug discovery. Phyto-chemical studies have attracted the attention of plant scientists due to the development of new and sophisticated techniques. These techniques played a significant role in the search for additional resources of raw material for pharmaceutical industry[33].

Medicinal plants possess immunomodulatory and antioxidant properties, leading to antibacterial activities. They are known to have versatile immunomodulatory activity by stimulating both non-specific and specific immunity[32].The use of plant extracts and phytochemicals, both with known antimicrobial properties, can be of great significance in therapeutic treatments. In the last few years, a number of studies have been conducted in different countries to prove such efficiency. Many plants have been used because of their antimicrobial traits, which are due to compounds synthesized in the secondary metabolism of the plant[29].

In Palestine, there are numerous medicinal plants described for treatment of many diseases. Herbal medicine is considered an integral part of the Palestinian culture and plays a pivotal and indispensable role in the current public healthcare. The hills and mountains of Palestine are covered with more than 2600 plant species of which more than 700 are noted for their uses as medicinal herbs or as botanical pesticides[19].

The following are some of the medicinal plants that have been studying its effect against some clinically isolated bacteria.

Nerium oleander

In history this plant has been used in medicine. It is popularly used as an ornamental plant, for its evergreen nature. Although it's toxic to human and animals, but it is also proved to contain medicinal value like antibacterial activity and Anti-inflammatory activity, and with these considerations, this plant is now being studied for its uses medicine with caution [22]. All parts of the plant are poisonous, from roots to stems, from leaves to flowers and seeds, including the smoke if we try to burn them. Many experiments have been made in time, and there is now common knowledge that chewing or simply biting the leaves a couple of times can lead to severe intoxication (in extreme cases followed by death), that even dry leaves are toxic, that cattle, horses and sheep being experimentally poisoned have died, etc. Humans have even died after eating meat[42].

The leaves and the flowers are cardiotonic, diaphoretic (is excessive sweating commonly associated with shock and other medical emergency conditions), diuretic, anticancer, antibacterial, antifungal and expectorant. And also the flowers, leaves, leaf juice, bark and roots have been used against corns, warts, cancerous ulcers, carcinoma, ulcerating or hard tumors [41]. The root is better; aphrodisiac, tonic good for chronic pain in the abdomen and pain in the joints, very poisonous, but an antidote to snake-venom. The juice of the young leaves

is poured into eyes in ophthalmia with copious lachrymation[16].

Essential oils and their components are widely used in medicine as constituents of different medical products, in the food industry as flavouring additives and also in cosmetics as fragrances and pharmaceutical industries and also are generally used in the cosmetic, medical and food industries. The essential oil of *Nerium oleander* has been the object of several studies antifungal, antibacterial, molluscicidal, antioxidant, anti hyperglycemic, antifungal, cytotoxial and insecticidal activity[14].

Artemisia herba-alba

The genus *Artemisia* L. (family Asteraceae, tribe Anthemideae), comprises a variable number of species from 200 to over 400, (depending on the authors) found throughout the northern half of the world. The genus may be divided into sections Artemisia and Dracunculus[26].

The genus *Artemisia* is known to contain many bioactive compounds; artemisinin exerts not only antimalarial activity but also profound cytotoxicity against tumor cells and arglabin is employed for treating certain types of cancer[22]. *Artemisia* is used for the treatment of diabetes mellitus in Iraq, and for hypertension and diabetes in oriental Morocco. Many Artemisia species have a high economic value in several fields, as food plants and as antihelminthic and antimalaria in medicine. This species of sagebrush is widely used in folk and traditional medicine for its antiseptic, vermifuge and antispasmodic properties. Artemisia herba-alba was reported as a traditional remedy of enteritis, and various intestinal disturbances, among the Bedouins in the Negev desert. In fact, essential oil showed antibacterial activity, as well as, antispasmodic activity on rabbits[39].

Withania somnifera

Withania somnifera belongs to Solanaceae family commonly known as Ashwagandha/Indian ginseng/winter cherry[8].

The main active constituents of *Withania somnifera* are steroidal lactones, alkaloids, flavonoids, tannin etc. The major chemical constituents of these plants, with anolides, are mainly localized in leaves[21]. Numerous studies indicated that ashwagandha possesses antioxidant, antitumor, antistress, anti-inflammatory, immunomodulatory, hematopoetic, anti-ageing, anxiolytic and also influences various neurotransmitter receptors in the central nervous system. In recent studies done on human breast, lung and colon cancer cell lines, plant extracts inhibited the growth of these cell lines[35]. Its roots, leaves and seeds are used in Ayurvedic and Unani medicines, to combat diseases ranging from tuberculosis to arthritis. The pharma-cological activity of the plant is attributed to the presence of several alkaloids and withaniols. Roots are prescribed in medicines for hiccup, several female disorders, bronchitis, rheumatism, dropsy, stomach and lung inflammations and skin diseases. Its roots and paste of green leaves are used to relieve joint pains and inflammation. It is also an ingredient of medicaments prescribed for curing disability and sexual weakness in male. Leaves are used in eye diseases. Seeds are diuretic. It is a constituent *Lactare*' which of is the galactagogue[20]. Also have several medicinal properties such as sedative, hypotensive, aphrodisiac, bradycardiac, respiration stimulatory, antiperoxidative, cardiotonic, radiosensitizing and thyro-regulatory effects[9].

Beside its use as general tonic. And several recent reports have demonstrated immunomodulator (also known as an immunotherapy is a substance (e. g. a drug) which has an effect on the immune system)

and antitumor effect of ashwagandha as well[31].

Ficus sycomorus

The Sycamore Belongs to family Moraceae is one of the old and historic plant species in the Palestine coastal valley and the study area as well. The trees have some medicinal values as the sap extracted from the trunk can cure some skin diseases 1 The active principles of many drugs found in plants are secondary metabolites. These secondary metabolites which constitute an important source of the pharmaceutical drugs have been isolated from different parts of plants. Some of these compounds have been reported to be present in the *Ficus species* such as tannins, saponins, flavonoids, steroids, anthraquinone glycosides and reducing sugars. *Ficus sycomorus* have been suspected to possess anti-diarrhoeal activities and sedative and anticonvulsant (are a diverse group of pharmaceuticals used in the treatment of epileptic seizures) properties of this plant have also been reported[30]. Reported different solvent extracts of some plants to have different pharmacological properties. Reported organic stem extracts of *F. sycomorus* with higher antifungal activity than aqueous extracts[17]. The fruit extracts of *Ficus sycomorus* L exhibited antitumor activity in the potato disc bioassay. it had significant antibacterial activity, but no antifungal activity[28].

Allium sativum

Allium sativum; commonly known as garlic, is a species of the onion family Alliaceae. *Allium sativum* is a natural plant being used as a food as well as folk medicine for centuries in all over the world, in 1996, Reuter *et al.* described garlic a plant with various biological properties like antimicrobial, anti-cancer, antioxidant. As well as different properties such as antiviral, antifungal, expectorant, anti-septic, anti-histamine[16.]

And has a long folklore history as a treatment for cold, cough and asthma and is reported to strengthen the immune system. It has many medicinal effects such as lowering of blood cholesterol level, antiplatelet aggregation, anti-inflammatory activity and inhibition of cholesterol synthesis[37].

Different garlic extracts demonstrated activity against Gram negative and Gram-positive bacteria including species of Escherichia, Salmonella, Staphylococcus, Streptococcus, Klebsiella, Proteus, Bacillus, clostridium, *Helicobacter pylori* and even acid-fast bacilli (AFB) such as *Mycobacterium tuberculosis*. Allicin is thiosulfinate compound of garlic reported for its antibacterial activity. Allicin is proved to be anti-bacterial as it inhibits RNA synthesis[16].

Eucalyptus camaldulensis

Eucalyptus camaldulensis is an important ethnomedicinal plant belonging to the family Myrtaceae. There are more than 700 species that comprise this genus, most are native of Australia, though they are also widely cultivated throughout the tropics, especially in Asia and Central America as well as Africa[6]. Are used in China folk medicine for a variety of medical conditions. For examples, hot water extracts of dried leaves used as analgesic, anti-inflammatory and antipyretic remedies for the symptoms of respiratory infections, such as cold, flu, and sinus congestion. and also known to contain bioactive products that display antibacterial, antifungal , analgesic and anti-inflammatory effects and anti oxidative activities[10]. Some studies have demonstrated that the oil and leaf extracts of Eucalyptus spp. have antifungal and repellent activity. Crude methanolic extract of *E. Camaldulensis* has been reported to inhibit the growth of Candida albicans. Also, it has been shown that ethanolic leaf extract of

Eucalyptus camaldulensis had marked fungicidal effect against clinical dermatophytic fungal isolates; Microsporium gypseum and Trichophyton mentagrophytes[15].

The bacteria

Clinical isolated bacteria used in the study are *Escherichia coli, Pseudomonas aeruginosa and Staphylococcus aureus.*

Escherichia coli

Classification

Escherichia coli is the most commonly encountered member of the family Enterobacteriaceae in the normal colonic flora and the most common cause of opportunistic infections. All members of the family Enterobacteriaceae are facultative, all ferment glucose and reduce nitrates to nitrites and all are oxidase negative[36].

Morphology and identification

Escherichia coli is gram-negative, non-sporing bacilli with most strains being motile and generally possessing both sex pili and adhesive fimbriae[24]. Because most strains rapidly ferment lactose, colonies grown on MacConkey media are smooth, glossy, and translucent and are rose-pink in colour. Some strains grown on blood agar result in colonies being surrounded by zones of haemolysis. Colonies are smooth, circular, 1 –1, 5 mm in diameter and yellow opaque if lactose fermenting (blue, if non-lactose fermenting) when grown on cystine-lactose-electrolyte deficient (CLED) medium[25].

Epidemiology

Strains of *Escherichia coli* predominate among the aerobic commensal bacteria present in the healthy gut[25].

Escherichia coli Infections

Escherichia coli was initially considered a non-harmful member of the colon flora, but is now associated with a wide range of diseases and infections including meningeal, gastrointestinal, urinary tract, wound and bacteremia infections in all age groups[24]. Other infections caused by *Escherichia coli* include peritonitis, cholecystitis, septic wounds and bedsores. They may also infect the lower respiratory passages or cause bacteraemia and endotoxic shock especially in surgical or debilitated patients[25].

Antimicrobial Susceptibility

Within the community, *Escherichia coli* strains are commonly susceptible to all agents active against the Enterobacteriaceae. However, because of the frequent occurrence of R plasmids, strains acquired in hospitals may be resistant to any combination of potentially effective antimicrobics and therapy must therefore be guided by susceptibility testing[36].

Staphylococcus aureus

Classification

Members of the genus Staphylococcus (staphylococci) are Gram-positive cocci that tend to be arranged in grape-like clusters[33].

Morphology and identification

Staphylococci are spherical cells about 1 m in diameter arranged in irregular clusters. Single cocci, pairs, tetrads, and chains are also seen in liquid cultures. Young cocci stain strongly gram-positive; on aging, many cells become gram-negative. Staphylococci are non-motile and do not form spores[7]. *Staphylococcus aureus* is a facultative anaerobe that grows at an optimum temperature of 37ºC and an optimum pH of 7, 5. *S. aureus* produces white colonies that tend to turn a buff-

golden color with time, which is the basis of the species epithet aureus (golden). Most, but not all, strains show a rim of hemolysis clear surrounding β the colony (Ryan and Ray, 2004). On nutrient agar, following aerobic incubation for 24 hours at 37ºC, colonies are 1 – 3mm in diameter, have a smooth glistening surface, an entire edge and an opaque pigmented appearance. In most strains, pigmentation is golden with orange, yellow and cream varieties. On Mac Conkey agar, colonies are small to medium in size and pink or pink-orange in colour[25].

Epidemiology

Staphylococci are highly successful colonizers of humans and animals. They reside mainly on the skin, particularly in moist areas such as the anterior nares (nose), axilla and groin. Between one-third and three-quarters of individuals carry these organisms at any one time. Staphylococcal infections occur worldwide and newly emerging hyper virulent or multi resistant strains spread rapidly over wide geographical areas. The bacteria survive in the air, on objects or in dust for days, therefore they can contaminate environments (such as hospitals) and continue to be transmitted over long periods of time. Some individuals may shed the organism more heavily than others. Staphylococcal infections are acquired from either self (endogenous) or external (exogenous) sources[18].

Infections

S. aureus causes serious infections of the skin, soft tissues, bone, lung, heart, brain or blood[18]. Include pneumonia, bacteremia leading to secondary pneumonia and endocarditis, osteomyelitis secondary to bacteremia and septic arthritis, seen in children and in patients with a history of rheumatoid arthritis. Diseases caused by Staphylococcal toxins include scalded skin syndrome and toxic shock syndrome[36].

Antimicrobial Susceptibility

Resistance to penicillin G can be predicted by a positive test for β-lactamase; approximately 90% of S aureus produce β-lactamase. Resistance to nafcillin (and oxacillin and methicillin) occurs in about 35% of *S. aureus* and approximately 75% of *S. epidermidis* isolates[7]. Alternative antibiotics for resistant organisms (e.g. MRSA) include vancomycin, erythromycin and gentamicin. Some strains become resistant to multiple antibiotics[18].

Pseudomonas aeruginosa

Classification

Pseudomonas aeruginosa is a classic opportunist pathogen belonging to the genus Pseudomonas[25].

Morphology and Identification

Is obligate aerobe, motile, rod-shaped, and measuring about 0.6 x 2 µm. It is gram-negative and occurs as single bacteria, in pairs, and occasionally in short chains. Sometimes producing a sweet or grape like or corn taco-like odor (Brooks *et al*., 2007). Its production of blue, yellow, or rust-colored pigments differentiates it from most other Gram-negative bacteria. The blue pigment, pyocyanin, is produced only by *P. aeruginosa*. Fluorescin, a yellow pigment that fluoresces under ultraviolet light is by *P. aeruginosa* and other free-living less pathogenic *Pseudomonas* species. Pyocyanin produced and fluorescin combined produce a bright green color that diffuses throughout the medium (Ryan and Ray, 2004). *P aeruginosa* grows well at 37–42 °C; its growth at 42 °C helps differentiate it from other *Pseudomonas* species. It does not ferment carbohydrates, but many strains oxidize glucose[7].

Epidemiology

P. aeruginosa normally inhabit soil, water, and vegetation and can be isolated

from the skin, throat, and stool of healthy persons. They often colonize hospital food, sinks, taps, mops, and respiratory equipment. Spread is from patient to patient via contact with fomites or by ingestion of contaminated food and water[4]

Infections

Pseudomonas aeruginosa causes infections in healthy individuals and those who are hospitalized or have a compromised immune system as a result of other diseases. A variety of human infections are commonly associated with this bacterium: Urinary tract infections, Ventilator-associated pneumonia, Surgical site infection, Respiratory infections, Ocular infections, Ear infections (external otitis, malignant external otitis), Skin and soft tissue infections, including hot tub folliculitis, and osteomyelitis and Burn sepsis Individuals with compromising conditions, such as HIV/AIDS, cystic fibrosis, chemotherapy-related neutropenia, and diabetes have an increased risk of acquiring an infection and developing complications[38].

Antimicrobial Susceptibility

Pseudomonas aeruginosa is frequently resistant to many commonly used antibiotics. Although many strains are susceptible to gentamicin, tobramycin, colistin, and amikacin, resistant forms have developed, making susceptibility testing essential[4].

Antibiotic resistance

The discovery of antibiotics in the mid-twentieth century revolutionized the management and treatment of infectious disease caused by bacteria. Infections that would normally have been fatal were now curable. Since then, antimicrobial agents (antibiotics and related medicinal drugs acting on bacteria, viruses, fungi and parasites) have saved the lives and eased the suffering of millions of people. Today, antibiotics are crucial not only for the treatment of bacterial infections, but also for prophylactic coverage of high risk patients e.g. those in intensive care, organ transplants, cancer chemotherapy and prenatal care. However, these gains are now seriously jeopardised by the rapid emergence and spread of microbes that are resistant to antimicrobials (www.earto.eu).

The mass production of penicillin in 1943 dramatically reduced illness and death from infectious diseases caused by bacteria. However, within four years, bacteria began appearing that could resist the action of penicillin. Pharmaceutical companies fought back by developing other types of antibiotics. After more than 50 years of widespread use of these “miracle drugs”, as effective as they anti-biotics once was. Virtually all important bacterial infections in throughout the world are becoming resistant[20]. And even though pharmacological industries have produced a number of new antibiotics in the last three decades, resistance to these drugs by microorganisms has increased. In general, bacteria have the genetic ability to transmit and acquire resistance to *drugs*, which are utilized as therapeutic agents[29].

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of nosocomial infections. MRSA infections are very difficult to cure because MRSA strains are resistance against almost all clinically available antibiotics[1]. MRSA infections that are acquired by persons who have not been recently hospitalized or had a medical procedure (such as dialysis, surgery and catheters) are known as Healthcare associated MRSA (HA MRSA) first appeared in the 1960s and has typically been linked to persons with health care associated risk factors such as hospitalization or nursing home care, chronic dialysis,

antibiotic treatment, or exposure to invasive devices or procedures. HA MRSA is a highly resistant and important nosocomial pathogen in both acute care and long term care settings and causes infections associated with increased morbidity, mortality, and cost when compared to infections due to susceptible strains of *S. aureus*[11]. Beginning in the 1990s community associated MRSA (CA MRSA) infections emerged in persons having none of the risk factors associated with MRSA in the past. CA MRSA is currently defined as an infection with MRSA in a person who does not have any prior history of a health care exposure such as hospitalization, surgery, permanent intravenous lines or other indwelling devices, or hemodialysis[13].

Multi drug resistant *Pseudomonas aeruginosa*

Pseudomonas aeruginosa also causes nosocomial infections as a result of its ubiquitous nature, ability to survive in moist environments and resistance to many antibiotics and antiseptics. A main problem is the emergence of multidrug-resistant *P. aeruginosa* strains resistant to different antimicrobial agent classes. Perhaps, this high degree of multidrug resistance related to the presence of antibiotic efflux systems which provide resistance to multiple antimicrobial agents[1].

Multi drug resistant Enterobacteriaceae

Multidrug-resistant Entero-bacteriaceae, mostly *Escherichia coli*, produces extended-spectrum β lactamases-M (ESBLs) enzymes. These enzymessuch were as th named for their greater activity against cefotaxime than other oxyimino-beta-lactam substrates such as ceftazidime, ceftriaxone, or cefepime have emerged within the community setting as an important cause of urinary tract infections (UTIs). Recent reports have also described ESBL-producing *E. coli* as a cause of bloodstream infections associated with these community-onsets of UTI[12].

CONCLUSION

On the basis of the antibacterial assay of this study *S. aureus* was found the more (susceptible to the employed plant extracts) than *E. coli* and *P. aeruginosa*.

All plant extracts were evaluted for their MIC against *E. coli*, *S. aureus* and *P. areuginosa*, The MIC value for each of methanolic extract of *E. camaldulensis* against *E. coli* was 3.125 mg/ml. And the methanol and aquatic extract of *F. sycomorus* (leaves) against *S. aureus* was from 6.25-3.125 mg/ml. And the ethanol extract of *E. camaldulensis* against *P. areuginosa* was 6.25 mg/ml. Suggesting that very small amount of the extracts are required to inhibit the growth of the bacteria thus *E. camaldulensis* (methanol extract), leaf extract of *F. sycomorus* (methanol and aquatic extract) and *E. camaldulensis* (ethanol extract) had very potent activity against *E. coli*, *S. aureus* and *P. areuginosa*, respectively.

Ethanolic plant extracts were showed antimicrobial and synergistic activity with antibiotics better than methanolic and aquatic extracts. The strongest effect agaist *E. coli* was recorded when *F. sycomorus* (leaves and bark) were mixed with Ofloxacin. And the strongest effect on *S. aureus* was observed when *A. sativum* was combined with Ofloxacin and Tetracyclin. The strongest effect against *P. areuginosa* was observed when Ceftazidime was combined with most plant extracts, especially with *F. sycomorus* (leaves and bark); when the extracts of *N. oleander*, *A. herba-alba* and *W. somnifera* were combined with Amikacin and also when the extract of *W. somnifera* and *L. camara* were mixed with Neomycin.

Vitamin C alone did not show any antibacterial activity against all tested

bacteria. It is likely that used distilled water as solvent has reduced the effectiveness it. Paracetamol showed antibacterial activity against *S. aureus* and *P. aeruginosa*, especially at a concentration of 10 µM (inhibited zone=11mm). Loperamide Hcl was showed antibacterial activity against *S. aureus*, *P. aeruginosa* and *E.coli*, at a concentration of 100 µM, 10 µM and 10 µM, respectively (inhibited zone= 12, 13 and 12, respectively). The synergistic activity of plant extracts and Non-antibiotic drugs was the best among the aqueous extracts of *L. camara* and each of Paracetamol, loperamid Hcl and vitamin C against *E. coli*. As well, the best synergistic activity among the aqueous extracts of *A. herba-alba* and each of Paracetamol and loperamid Hcl was against *S. aureus*. And the best synergistic activity was observed between *N. oleander* and Paracetamol (at a concentration of 50 and 10µM) against *P. aeruginosa*.

Regards the synergistic activity between the antibiotics and non-antibiotic drugs, the best synergistic activity was recorded between Ampicillin and each of paracetamol and loperamide HCL against *S. aureus*, and among Nalidixic acid and each of paracetamol and loperamide Hcl. In addition synergistic activity was observed with Co-trimoxazole and each of paracetamol and loperamide Hcl against *E. coli*; Amikacin and paracetamol and loperamide Hcl against *P. aeruginosa*.

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