Review Article

A review on phytoconstituents: The potent synergistic approach in antimicrobial formulations

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ABSTRACT

Since the past few decades, microbial infections are the main threat to human life and cause a serious series of events. Antibiotics are the main weapon to fight these microbial infections and health of human life has been benefited. However, from past few decades antibiotics are becoming less and less effective in certain infections due to increasing resistance in microbes. This resistance is not specific to antibiotic used, also extended to other classes of antibiotics. Many of antibiotics produce toxic effects due to the emergence of multidrug resistance (MDR) bacteria and cause serious illness to human life. A common approach to treat diseases is to use antibiotics or plant extracts individually and/or an alternative approach is the use of antibiotics and plant extracts combinations or synergistic therapy. The latter therapy, i.e., combination synergistic approach; against multidrug-resistant bacteria may provide an alternative path to treat infectious diseases and provide a useful area for further investigations in the future. Combination approach provides safe and alternative treatment for patients with severe infections caused by bacteria and fungi. The present review explains in detail, the noticed synergistic effects between natural plant extracts and common antibiotics therapy fighting common fungal and bacterial infections. The mechanism of action of the individual drug is significantly different from the combination therapy; therefore, selecting suitable combination is essential and crucial which entails understanding the mechanism of infection between antimicrobial agents and plant extracts.

KEY WORDS: Antimicrobials, Natural antimicrobials, Natural extracts, Synergistic therapy

INTRODUCTION

According to a study performed by the World Health Organization, more than 80% of the population depends on conventional remedy for their key healthcare needs. The old medicinal methods, mainly the use of medicinal herbs, still play a vigorous part to shelter the basic health desires in the developing countries.[1] The medicinal value of these plants depends on the chemical active constituent that produces a known functional action on the metabolism of human body. Within the recent years, ever-increasing therapeutic problems are the increased level of infections and antibiotics resistance.[2] The use of plant and its products have been used from many long time, that began with traditional medicine and over the years has been combined into allopathic medicine. Since the distant past, many plants classes testified having pharmacological effects as they are known to have various 2° metabolites such as glycosides, saponins, flavonoids, steroids, tannins, alkaloids, and terpenes which are, therefore, should be employed to encounter the microbes.[3] With the improvement in Science and Technology, extraordinary advancement has been made in the area of medicine with the findings of many natural and synthetic medicines. Antibiotics are unquestionably one of the greatest significant therapeutic discoveries of the 20th century that had usefulness against serious bacterial infections. However, these synthetic products are only able to treat one-third of the infectious diseases. This is due to the development of resistant microbes that is beyond doubt the consequence of years of extensive use. A broad information of how to use the plants counter to different diseases may be expected to have added in areas where the usage of herbs is still of excessive significance. Plants yield a various chemical constituents to defend themselves contrary to a variety of pathogens.[4] The medicinal value of plants is found in some chemical compounds that produce a certain physiological action on the human body metabolism. The most significant of these bioactive compounds of plants are alkaloids, flavonoids, tannins, and phenolic compounds. It is revealed that plant extracts viewing target sites other

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than which are used by antibiotics will be active against a drug-resistant microorganism.[5] Medicinal plants have been used as conventional treatments for many human illnesses in many parts of the world from many years. Use of herbal medicines in Asia shows a long history of human connections with nature.[6] Herbs used in conventional medicine contain a wide range of chemical constituents that can be used to treat and control continuing as well as infectious diseases. Natural products obtained from higher plants may have a new foundation of antimicrobial medication with the possibly innovative mode of action.[7] They are useful in the treatment of infectious diseases while at the same time reducing many of the side effects that are often associated with chemically produced antimicrobials.[8] Therefore, it is of great attention to carry out a study of these herbs to quantify their use in popular medicine and to disclose the mechanism of action by segregation and description of their constituents.

HERBS AS ANTIMICROBIAL

Herbs have been used from ancient times as food and outdated remedy in contradiction of many infectious agents. The most frequently used herbs that have antimicrobial properties are garlic, black cumin, cloves, cinnamon, thyme, mustard, neem, curcumin, Tamarindus, tea, etc.

Garlic as Antimicrobial Agent

Garlic (*Allium sativum* L.) is a common spice that has been traditionally popular with strong folkloric awareness. It is used by the old-style remedy physicians in the handling of bacterial related diseases such as pile, cough, and rheumatism; it is mainly the edible bulb of the lily family Liliaceae which is extensively used as a flavor in diet. Garlic contains at least 33 sulfur compounds such as aliin, vinyldithiin, S-allylmercaptocysteine, allicin, ajoene, allyl propyl, diallyl, trisulfide, s-allylcysteine, and others. In addition, sulfur compounds, garlic contains 17 amino acids and their glycosides, arginine, and others. Minerals such as selenium and enzymes such as allinase, peroxidases, myrosinase, and others.[9] Other than any *Allium* species garlic comprises a complex concentration of sulfur compound. Allicin (diallyl thiosulfinate) (Figure 1) is the key component to which the antimicrobial and antifungal activity of garlic is attributed; and a volatile molecule that gives it its characteristic odor.[10] It is not found in the intact plant, it is produced by the action of enzyme alliin alkyl-sulfenate-lyase on the nonprotein amino acid S-allylcysteine S-oxide (alliin). Amino acid and enzymes are deposited in different cellular sections.

Bioactive compounds in the plants which provide protection on them against bacteria, fungi, and viruses have been associated with the antimicrobial effects of the extracts of these plants.

Neem as Antimicrobial Agent

Azadirachta indica from the family Meliaceae, commonly known as neem. Neem is feasibly the most used outdated medicinal plant. Every possible part of the tree has been used as beneficial medicine as a domestic remedy against many human diseases. The tree is now known as "village dispensary" in India. Most of the parts of the plant such as fruits, leaves, bark seeds, and roots contain chemically active components with known antiulcer, anti-inflammatory, antiseptic, antiviral, antipyretic, and antifungal properties.[11] Leaf and seed extracts of neem were tested for antidermatophytic activity and have proven effect against some microorganism such as *Trichophyton violaceaum, Trichophyton rubrum, Epidermophyton floccosum* and *Microsporum nanum*. The chief ingredients of leaves contain minerals, protein (7.1%), Vitamin C, calcium, phosphorus, carotene, carbohydrates (22.9%), etc., they also contain aspartic acid, glutamic acid, praline, tyrosine, alanine, and glutamine such as amino acids and some fatty acids (dodecanoic, elcosanic, tetradecanoic, etc.). Sesquiterpene derivatives are present in essential oils; the flowers comprise flavonoids such as kaempferol and melicitrin other than nimbosterol. Flowers also yield a material which is waxy in nature comprises several fatty acids such as oleic (6.5%), stearic (8.2%), behenic (0.7%), arachidic (0.7%), palmitic (13.6%), and linoleic (8.0%).[12] The pollen presents in neem mainly have various amino acids such as methionion, aminocaprylic acid glutamic acid, tyrosine, histidine, arginine, phenylalanine, and isoleucine. Nimbin (Figure 2) is triterpenoid in nature, which is a main chemical constituent of neem oil

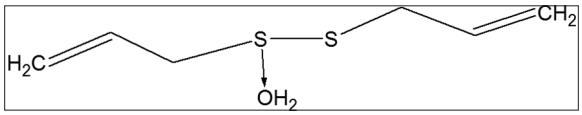

Figure 1: Structure of allicin

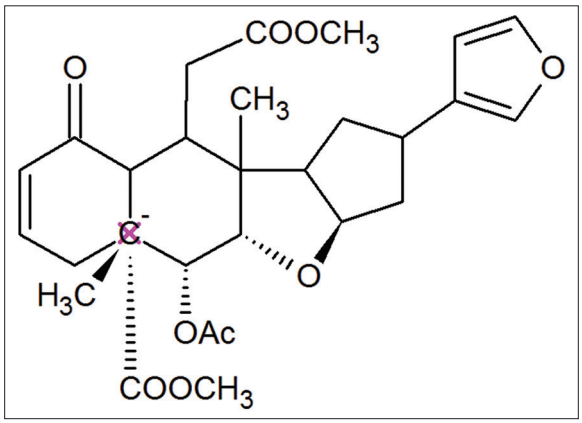

Figure 2: Structure of nimbin

Different parts of neem such as leaf, bark, and seed oil have been shown to have wide pharmacological actions including; antioxidant, antimutagenic, anticarcinogenic, anti-inflammatory, antihyperglycemic, antiulcer, and antidiabetic properties.[13]

Curcuma longa as Antimicrobial Agent

C. longa L. belongs to Zingiberaceae family and its polyphenolic compound curcumin has been used for the determination of various antimicrobial study due to broad traditional uses and some side effects. Curcumin or diferuloylmethane and other curcuminoids constitute the main phytochemicals of *C. longa* L. Antimicrobial activities done by curcumin and extract of *C. longa* against various fungi, bacteria, viruses, and parasites have been checked and reported.[14]

With the help of synergism *C. longa* shows a good antimicrobial activity with synergistic antimicrobial agents indeed, antimicrobial activity has been improved with the help of various experiments. Water solubility and cell permeability have been increased by reacting with various chemical derivatives[15] A mixture of curcumin with various antimicrobial drugs (fluconazole) is used for the manufacturing of antimicrobial skin gels and emulsions with enhanced skin protection and wound healing properties. Curcumin (Figure 3) reported to has significant inhibitory effect against *Candida albicans* due to its membrane-lytic properties as well as the capacity to prevent the adhesion on host epithelial cell popular antifungal are belongs to azoles category mainly works based on the mechanism of target blood protein.[16]

Tamarindus indica L. as Antimicrobial Agent

T. indica, commonly known as tamarind, belonging to the Caesalpiniaceae family, is a medium-sized tree. From many centuries tamarind has been used as a medicinal herb; its fruit is the most valuable portion which has repeatedly been found as curative in various pharmacopeias. Tamarindus is a tropical evergreen plant. The leaves, seeds, pulp, and bark have been used as ayurvedic medicine and food purposes.[17] Due to the presence of an antimicrobial, antiseptic, and antifungal effects, tamarind leaves have an extensive use in many parts of Latin America. Benzyl benzoate and limonene are the major compounds out of total 13 essential oils; other are pentadecanol and hexadecanol. Essential oils are main secondary metabolites having antimicrobial and antifungal activities, one of the best examples is thyme oil.[18] It is widely used in making drinks and main components for many decoctions as health remedies, cultivated as acidic ornamental tree. Tamarind contains various classes of compounds such as carvacrol (Figure 5), epicatechin, cinnamaldehyde (Figure 4), lupeol, and tartaric acid. All of these compounds show antibacterial, antifungal, antiviral, antioxidant, and other properties like a laxative.[19]

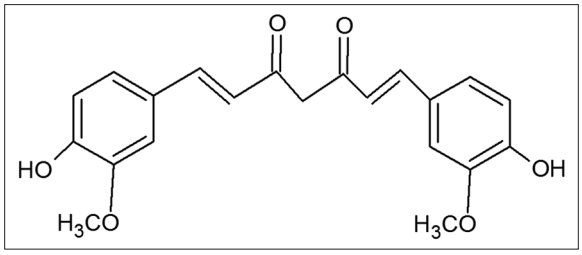

Figure 3: Structure of curcumin

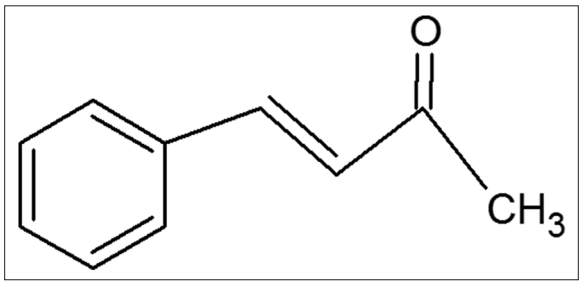

Figure 4: Structure of cinnamaldehyde

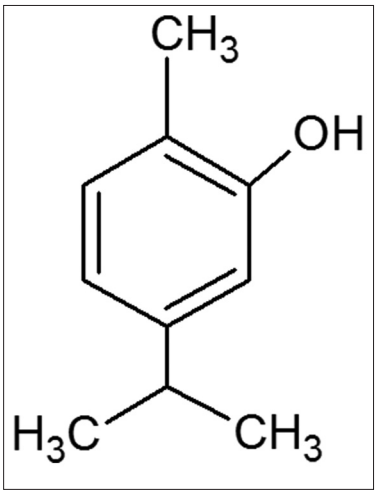

Figure 5: Structure of carvacrol

Pulp has been proven for the restoration in the case of paralysis. Dried or boiled leaves and flowers are proven for the treatment of swollen joints, sprain, and boils. Various lotions and creams have been used for the treating dysentery, jaundice, hemorrhoids, and various other ailments related to the microorganism. The bark contains astringent and febrifuge properties. Fried remedy with salt and milled to ash is given for the treatment of indigestion, also lotions made from the bark are used to treat open sores and rashes causes by the caterpillar. Alone or as a mixture with lime juice, milk, and honey camphor, the pulp has been shown effective as digestive, remedy for bile disorders, and the scorbutic disease.

Other uses of tamarind are in case of sunstroke, digitalis poisoning, and alcoholic intoxication. Leaves of the plant contain good levels of protein, fat, and fiber, protein, fat, some

vitamins (thiamine, riboflavin, ascorbic acid, and niacin), etc., Antimicrobial activity of flavonoid, polyphenols, and other metabolites have been studied obtained from Tamarindus leaves.[20]

Tea Tree as Antimicrobial Agent

Many antimicrobial studies have been conducted on various essential oil; one of them is *Melaleuca alternifolia* (tea tree oil) belongs to family Myrtaceae has known for its antiseptic and antimicrobial properties. Promising effects against methicillin-resistant bacteria *staphylococcus aureus* have been reported, other than antiviral activities, as well as anti-inflammatory effects also been founded in various studies. The chemical composition of green tea is not completely defined.[20] Flavonoids such as catechin (Figure 6) and Epicatechin (Figure 7) are polyphenols in nature present in green tea

The fresh leaves of green tea comprise caffeine proportion (after boiling founded to be approximately 3.5% of the total dry weight, or about 50 mg/cup), in addition to the amino acid theanine, methylxanthines, theophylline, theobromine, lignin, and organic acids chlorophyll, and free amino acids are found in lower amount.[21] The antimicrobial activity of green tea has been started after 1980s, founded for many years by unscientific evidence, was first founded 100 years ago in the laboratory. McNaught (1906), showed that black tea killed *Salmonella typhi* and *Brucella melitensis* and other harmful pathogens and endorsed that the water bottles of troops should be filled with tea for the prevention in the conditions of infections due to various microorganism.[22] Studies have revealed that green tea can inhibit and kill a widespread variety of pathogenic bacteria at a typical concentration level in fermented tea. The effectiveness of tea tree oil as anti inflammatory agent has been reported. The cream prepared to contain sorbelone was added in 10% tea tree oil was compared with commercially available tolnaftate. It is not easy to conduct the precise antibacterial activity spectrum of green tea, and there are many contradictory reports of circumstantial antimicrobial effects. By differentiating the definition of "resistant" and "susceptible," and by the numerous approaches of testing that have been conducted.[23] Aside these observations, there is consent that unfractionated extracts of both green tea have moderate antimicrobial activity.

Musa acuminate as Antimicrobial Agents

Banana is a tropical fruit which belong to family Musaceae, can be found in many countries. *Musa* sp. Banana is possibly known as the world's oldest cultivated plant. After wheat, rice, and maize it is fourth most usable food all around the world.[24] High fiber content has been reported in banana, thus it can lower cholesterol and

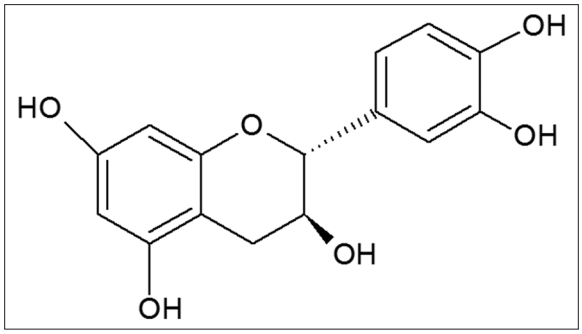

Figure 6: Structure of catechin

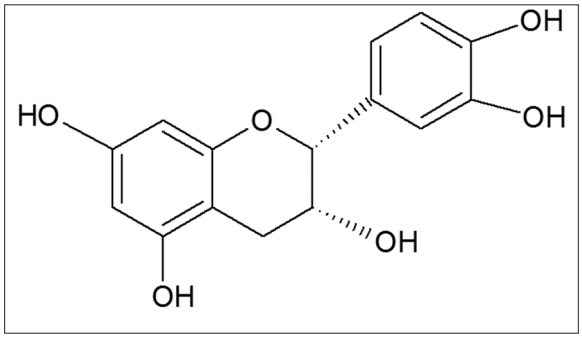

Figure 7: Structure of epicatechin

helps to treat symptoms of indigestion like constipation and also used in the cure cancer of colon. Other than this, it contains very high potassium content which is reported to be useful in the inhibition and cure of hypertension and muscle pain, on the other hand, it has been reported that gastric mucosa damaged by aspirin can be treated by unripe banana.[25] Due to the presence of high fluoride and potassium content banana is used for the treatment of tooth decay and cavities. Fluorides and its derivatives are mainly used to strength the enamel.[26]

Activities such as antioxidant and antibacterial and other such as antidiarrheal, anti-tumoral, antiulcerogenic, and anthelminthic have been found by many researchers. The phytoconstituents such as saponins, glycosides, steroids, and dopamine present in Banana also found to have various pharmacological effects. Various amino acids such phenylalanine, leucine, threonine, and valine are present in significant quantities in banana peels. Carbohydrates are present in the maximum amount. In the treatment of nervous diseases such as hysteria and epilepsy and other digestive problems such as dialarhea and dysentery, stem juice can be used. Various oligosaccharides including galactose, mannose, glucose, xylose, and fructose occur naturally in banana making it an exceptional prebiotic for the selective growth of valuable microbial florae in the human intestine. It reliefs in diarrhea and dysentery and helps the healing of intestinal lesions in ulcerative colitis. Roots can be used as anthelmintic, flowers as astringent and fruits are used as mild laxative.[25]

Calotropis procera (Aak) as Antimicrobial Agent

C. procera (Sodom apple) belongs to the plant family Asclepiadaceae, it is usually acknowledged as Apple of Sodom. The English name is milkweed. In the Western part of Nigeria, it is called *Bomubomu* by the Yorubas, the Hausas call it *tumfafa*, and in Sudan, it is called *Oshar*. It is called *calotrops* in Italian, *pomme de sodome* in French, and *kisher* in Arabic.[27] In India, the juice obtained from the root bark is usually used for the skin infection treatments, abdominal viscera enlargement, and Senegal intestinal worms. Cutaneous diseases (leprosy, ringworm, and syphilitic sores) can be treated by the latex milk of *C. procera*.

Many studies have been done for the determination of chemical constituent activities; mainly cardenolides show antibacterial activity in *C. procera*. The recent cardenolide is 7B, 14B-dihydroxy-5-card-20[22] enolide (proceragenin) have shown antimicrobial activity against *Pseudomonas pseudomallei*, a causative agent of melioodosis. Other chemical constituents are benzoylinesolone, calotropin, calotropenyl acetate, multiflavenol, czarigenin, and terpinol. Further chemical investigation has shown the presence of triterpenoids, calotropursenyl ester, calotropoleanyl, etc.[28]

It has been reported that the excretions from the root bark of *C. procera* are used conventionally in India for the treatment of skin diseases and intestinal worms. In Nigeria, it has been used traditionally to treat diseases such as fever, eczema, diarrhea, leprosy, ringworm, cough, asthma, and convulsion.[29]

Acacia mellifera as Antimicrobial Agent

Acacia, the second largest genus in the family Leguminosae, it comprises more than 1200 sps. *A. mellifera* is a valuable herb, frequently used in Kenyans folk medicine. Various parts such as stem bark and leaves are used in syphilis, and *Pneumonia* agent. Cytotoxic and antibacterial activities have been shown by the triterpenoids obtained from the plant.[30] Infectious diseases such as respiratory and gastrointestinal are serious problems worldwide, mainly among third world children. On the other hand, currently, is used result in serious adverse side effects. The main chemical constituents which show the antimicrobial effects are the lupine btained from the stem bark of acacia mellifera. In some research works performed on the laupanes mainly lupenol (Figure 9) showed the maximum chemical stability as antimicrobial agents.[31]

On various microorganisms such as *Escherichia coli, S. aureus, Streptococcus pneumonia, Pseudomonas aeruginosa,* and fungal strains such as *C. albicans*, *Microsporum gypseum,* and *Trichophyton* mentagrophytes observation of antimicrobial activities have been reported.[31]

Ocimum gratissimum as Antimicrobial Agent

O. gratissimum belongs to spices plants group, belongs to family Labiatae, founded in tropical Africa and India. In South Asia, it found as a home garden crop, but in Vietnam, it cultivated for commercial values.[32] In traditional medicine leaves of *Ocimum* mainly used for treating diarrhea and as a general tonic agent, and conjunctivitis treatment inserting directly into eyes. Due to nature of its antagonism with various antibiotics, it is a great area of discussion for the using with antibiotics as synergistic effects.[30] Chemical constituents mainly Eugenol (Figure 10), rosmarinic acid (Figure 11), and β-selinene show the antimicrobial and antioxidant properties. *O. gratissimum* has shown the synergistic effects with various antibiotics such as ciprofloxacin, septrin, streptomycin, ampicillin, ketoconazole, and nystatin *O. gratisssimum*.[33]

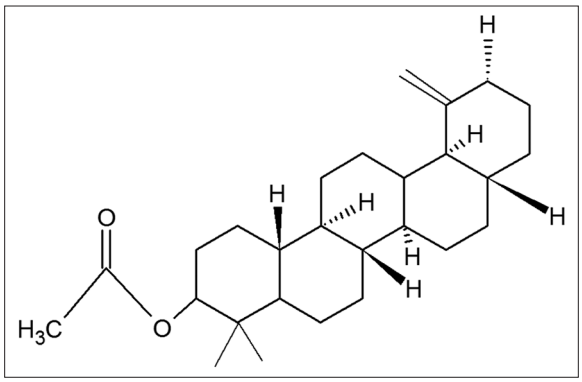

Figure 8: Structure of calotropenyl acetate

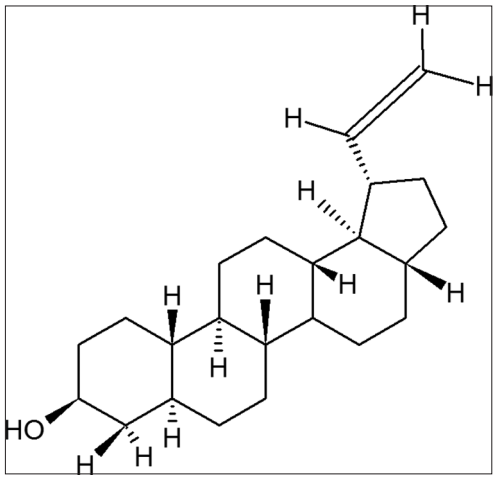

Figure 9: Structure of lupeol[2]

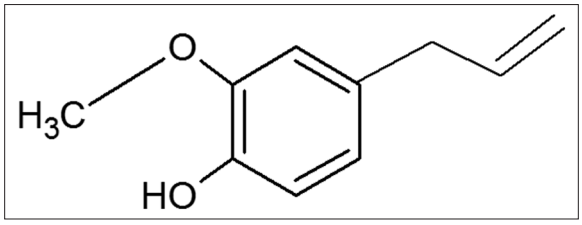

Figure 10: Structure of eugenol

SYNERGISTIC EFFECTS OF HERBAL EXTRACTS WITH VARIOUS ANTIMICROBIAL AGENTS

Once considered as miracle drugs, antibiotics are now at the stage of ending. Nowadays hardly any antibiotics available to treat MDR, total drug resistance, and extended drug-resistant microbes to cure. Other challenges include the absence of an alternative to antibiotics, no regulations for the usage of antimicrobial agents mostly in the developing countries; increase the number of drug-resistant strains all over the environment, ignoring of antimicrobials effects while recommendation the therapy and no bothered for side effects of the therapy. Synergistic combinations help in reducing resistant mutants, exhibit more antimicrobial action, toxicity and show further effectiveness contrary to various infections. With increasing incidence of antimicrobial resistance and day by day appearance of new infectious diseases many natural products been investigated for their antimicrobial effects and resistance modifying ability. Plant-derived antimicrobial agents provided much-needed therapeutics. In phytomedicine research, synergy assessment between commonly used antibiotics and effective antimicrobial agents has become an interesting key of research because many agents possess complex pathophysiology and multicausal agents require drug treatment with well-chosen drug combination with a single drug therapy. There are important advantages linked with herbal and antimicrobial synergistic interactions in phytotherapy. The main advantages associated are (1) enhanced efficiency, (2) undesirable effects reduction, (3) bioavailability and stability enhancement, and (4) an adequate therapeutic index with low dosage as compare with single drug antimicrobial therapy.

A synergistic effect is scientifically proven used of two therapeutic agents having either same or different mode of action and chemical composition. Herbs can be used together to improve effectiveness and synergistic actions and also to reduce toxicity. Use of herbal antimicrobial agents with synthetic antimicrobial agents has been recently increasing. Secondary metabolites such as tannins, terpenoids, flavonoids, glycosides, and phenolic compounds have shown proven antimicrobial effects. Various dosage forms such as creams, gel, ointments, soap, and mouthwash been manufactured on the bases of synergistic effect concept. Various herbs possess antimicrobial properties, mainly extract obtained from plant's root, leaves, bark, berries, and flowers have these properties. Various studies have been performed using alone or in a combination of plant extract on various microorganisms (Table 1). The

Table 1: List of some herbal extracts showing synergistic effects with antibiotics against infection-causing microorganism

Plant name	Extract	Antibiotics	Microorganism	Reference
F. exasperata vahl	Ethanol	Gentamycin, tetracycline, erythromycin, samitrin, chloramphenicol	*S. albus*	[30]
M. indica L.	Ethanol	Norfloxacin, tetracyclin, erythromycin	*S. aureus*	[39]
E. hirta L.	Methanol	erythromycin	*S. aureus*	[40]
R. coriaria L.	Ethanol	Oxytetracycline, HCl, penicillin, cefalexin, enrofloxacin	*P. aeruginosa*	[41]
R. officinalis	Ethanol	Nystatin, gentamycin, cefalotin, ceftriaxone	*E. faecalis* ATCC, *B. megaterium* NRS, *B. brevis* FMC3, *M. luteus* LA 2971	[42]
S. persica wall.	Ethanol	Tetracycline, penicillin	*S. aureus*	[43]
S. officinalis	Aqueous	Sodium benzoate, sodium nitrite, potassium sorbate	*B. subtitles* PMF-kg-B2, *B. mycoides* PMFKg-B, *Staphylococcus* PMFKg-B30, *A. tumefaciens* PMFKg-B11	[44]
T. grandis L.	Methanol	Tetracycline	*S. typhimurium*, *K. pneumonia* MTCC432, *Pseudomonas, P. mirabalis* MTCC 425, *E. coli* MTCC 729, *Aeruginosa* MTCC 1688	[43]
T. populnea L.	Ethanol	Oxytetracycline	*S. sonnei* ATCC 29930, *Rhodococcus terrae* NCIM *5126, M. flavum* NCIN 2984, *E. coli* ATCC 11229, *F. devorans* NCIN 258, *S. boydii ATCC 8700*	[45]

F. exasperate: Ficus exasperate, M. indica: Magnifera indica, E. hirta: Euphorbia hirta, R. coriaria: Rhus coriaria, R. officinalis: Rosmaronus officinalis, S. persica: Salvadora persica, S. officinalis: Salvia officinalis, T. grandis: Tectora grandis, T. populnea: Thespesia populnea, S. albus: Staphylococcus albus, S. aureus: Staphylococcus aureus, P. aeruginosa: Pseudomonas aeruginosa, E. faecalis: Enterococcus faecalis, B. megaterium: Bacillus megaterium, B. brevis: Bacillus brevis, M. luteus: Micrococcus luteus, B. subtitles: Bacillus subtitles, B. mycoides: Bacillus mycoides, A. tumefaciens: Agrobacterium tumefaciens, S. typhimurium: Salmonella typhimurium, K. pneumonia: Klebsiella pneumonia, P. mirabalis: Proteus mirabalis, E. coli: Escherichia coli, S. sonnei: Shigella sonnei, M. flavum: Micrococcus flavum, F. devorans: Flavobacterium devorans, S. boydii: Shigella boydii

resistance of pathogens to the antimicrobial agents is still an untreated threat to the health of public around the globe. It is rapidly increasing problem resulting need of novel antimicrobial agents. Microorganisms have adapted the mechanism of action of antimicrobial agents, resulting in resistance to the drugs. Herbal antimicrobial agents either in combination or alone may reduce the risk of resistance, bacteria such as *E. coli* and *Enterococcus* species have been reported as a resistant species. Preparation of formulations containing herbal antimicrobial extracts in combination with synthetic therapeutic agents may effect the resistance capabilities of bacteria. A major strategy has been incorporated in the case of emerging infectious disease, which has a combination of plant extracts with first-line antimicrobial drugs.

Acne vulgaris is most common skin disease mainly characterized by symptoms such as comedones (blackheads and whiteheads), nodules (large papules), pimples, seborrhea (scaly red skin), and possibly scarring. It is difficult to predict the duration of acne vulgaris. Therapy is cumbersome process require several months to years for complete treatment of infection. Various dosage forms such as creams, gels, and ointment require proper penetration for the complete removal of acne vulgaris. An anti-acne gel containing hydro alcoholic garlic extract had been prepared and been succeed to treat various human skin infections. Other plants which have been used for the treatment of skin disease *Glyceyrrhiza glabra* root extract, Piper betle leaves extract, and *A. indica* leaves extract has been tested in the cream formulation in the form of combination and alone.

Various naturally obtained antimicrobial agents such as eugenol (Figure 13), thymol (Figure 12), carvacarol, cinnamaldehyde, and allyl isothiocyanate reported having synergistic antimicrobial activity with an antibiotic such as tetracycline, ampicillin, erythromycin, novobiocin, and bacitracin.[34]

Using both the fractional inhibitory concentration index (FICI) and minimum inhibitory concentration (MIC) one can determine the synergism of two different therapeutic agents either natural or synthetic.[35]

FICI (drug combination) = FIC of drug-1 + FIC of drug-2.[35]

Where,

1. FIC of drug-1 = MIC (drug combination)\MIC of drug-1.
2. FIC of drug-2 = MIC (drug combination)\MIC of drug-2.
3. FICI values = 0.5, represent synergistic interaction.

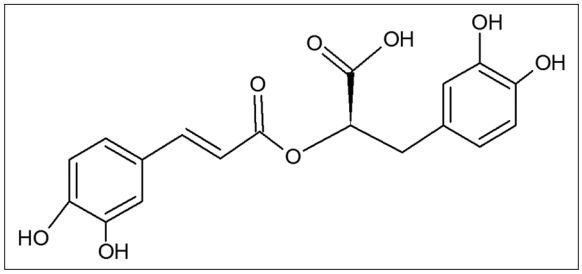

Figure 11: Structure of rosmarinic acid

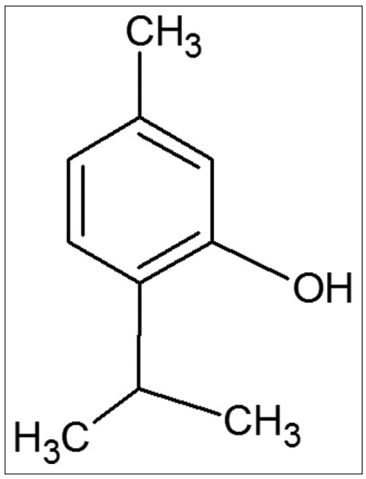

Figure 12: Structure of thymol

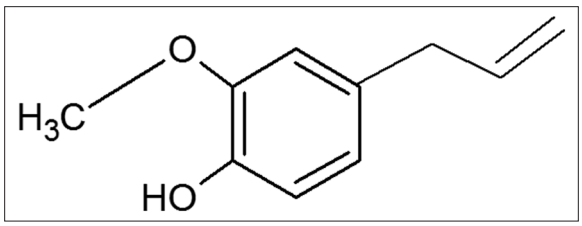

Figure 13: Structure of eugenol

- 4.0, represents antagonist effects.
- Value between both values represents no interactions.

Creams are topical dosage form, prepared for the better penetration of medicament in the skin. Creams can be used either for the beautifying action or for the therapeutic purpose. Creams contain an oily base for the better incorporation of medicament at the site of action. An herbal cream containing extract of neem leaves has been shown the antimicrobial effects against various Gram-positive and Gram-negative bacteria and against various fungal strains.

Candidiasis is a fungal infection mainly caused by a yeast *Candida*. More than 20 species of *Candida* can cause candidiasis in humans. *Candida* yeast mainly resides in the intestinal tract and can be found on mucous membrane without causing an infection; mainly overgrowth is responsible for the infection. Symptoms such as fatigue, weight gain, joint pain,

and gas can cause uncomfortable behavior in patients. *Candida* can exist mainly in two forms, the yeast can survive in acidic conditions, although the fungal form flourishes in a neutral or alkaline ph. Therefore, it is difficult to treat with a single therapy.[36] A two-fold effect of curcumin and fluconazole combination may improve the therapeutic efficacy against *C. albicans* infection. In wound dressing, curcumin composition with hydrogel nanoparticle can improve the antimicrobial effect.

Melissa officinalis is a potent antimicrobial agent and showed the synergistic effects with streptomycin, chloramphenicol, tetracycline, amoxicillin, rifamycin against *E. coli, P. aeruginossa,* and *Proteus mirabilis*.[37] Due to its lemon like the taste it referred as lemon balm. It also can be taken in case of digestive problems. Lemon tea was conventionally needed in Europe as a minor tranquilizing and to treat migraine, insomnia and nervous tension, and in treating fever and cold. Cream formulation of lemon balm extract is prepared for the treatment of herpes mouth, which effects by decreasing healing time of herpes mouth sores. In past years, there were many studies performed to find out the advantageous part of lemon balm plant extract to increase the *in vitro* efficacy of antibiotics.[37]

A plant of genus Acacia, *Acacia mearnsii* is also a potent plant and showed the synergistic antimicrobial effects with various antibiotics such as amoxicillin, erythromycin, kanamycin, nalidixic acid, tetracycline, metronidazole, and ciprofloxacin.[38] *A. mearnsii* belongs to family Fabaceae, considered as a wild plant due to its ability to as effective as an indigenous plant. Combination of *A. mearnsii* extract with these antibiotics can improve the effects of these antimicrobial drugs and reduces the chance of infection caused by MDR microorganisms. Synergistic effect of *A. mearnsii* with antibiotics represents that many infections may be cured efficiently through medicinal combination with herbal extracts rather than single drug antibiotic therapy.[38]

CONCLUSION

From the review of this investigation indicates that the plant herbal extract and antibiotics combination approach provide significant therapy for the development of potential treatment for microbial infections. As discussed in this review, many herbal extracts are showing mechanism as antimicrobial agents and providing synergistic antimicrobial effects with various common synthetic antimicrobial agents. This finding is may be due to the action mechanism understanding of drugs contrary to these microorganisms and appropriate collection of ordinary chemicals obtained from plant extracts. There is an essential need for conducting more researches about synergistic interaction molecular basis, to find the mechanism of action of synergistic action for the development of pharmacological drugs to treat microbial infections by using herbal plants extracts. Hence, more studies should be conducted for the identification of more herbs which show synergistic action with synthetic agents.

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