

Review

Medicinal Value of *Croton macrostachyus* and *Solanum incanum* against Causative Agent of Foodborne Diseases

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ABSTRACT

Foodborne diseases are a public health threat which causes a large economic impact across the worldwide. *Escherichia coli* (*E. coli*), *Listeria monocytogenes* (*L. monocytogenes*), *Salmonella species* (*S. species*), *Staphylococcus aureus* (*S. aureus*) and many more other organisms are the leading causes of foodborne illness and death in the world. Increment of antibiotic resistance exhibited by the actions of microbial infectious agents has led to screening of several medicinal plants for their potential antimicrobial activity. Therefore, the aim of this paper is to review on the medicinal value of *Croton macrostachyus* (*C. macrostachyus*) and *Solanum incanum* (*S. incanum*) against causative agents of foodborne disease. Antimicrobial compounds of medicinal plants differ from antibiotics as they have fewer side effects, better patient tolerance, relatively less expensive, acceptance due to a long history of use and being renewable in nature. There are so many medicinal plants used to treat foodborne diseases which associated with gastroenteritis in humans and animals, among plants *S. incanum* and *C. macrostachyus* are the common for treatment of foodborne diseases associated with diarrhea. *S. incanum* has different bioactive substances which have medicinal importance against skin diseases, abdominal pains, fever, stomachaches and indigestion, treatment of dandruff, wounds, sore throat, angina, ear inflammation, liver disorders, wart and ringworm and treatment of cow driosis, dermatophilosis, foot rot, pasteurellosis, black leg, fasciolosis and snake bite. Bioactive compounds which present in *S. incanum* are including alkaloids, steroids, saponins, tannins, glycosides, flavonoid and terpenoids. *C. macrostachyus* is medicinal plant which have bioactive compounds including terpenoids, alkaloids, flavonoids, lignoids, proanthocyanidins, sesquiterpenoids and lupeol, saponins, resins, crotepeoxide. *C. macrostachyus* have medicinal value in treatment of malaria, rabies, gonorrhea, wound, diarrhea, hepatitis, jaundice, abdominal pain, cancer, toothache, pneumonia, typhoid and gastrointestinal disorder. Which is also used as abortifacient and uterotonic to expel retained placenta. Therefore, *S. incanum* and *C. macrostachyus* have different medicinal value against foodborne disease and drug-resistance infectious agents. However, an advanced study have not been conducted on the extract of pure bioactive compounds and toxicity analysis. Therefore, further studies should have to be conducted to extract pure compounds from these medicinal plants for pharmaceuticals industry.

Keywords

Bioactive substance; Drug resistance; Food borne disease; Infectious agent; Medicinal plants.

INTRODUCTION

Foodborne diseases are a public health threat which causes a large economic impact across the worldwide. It can be caused by pathogens including bacteria, viruses and parasitic organisms.¹ Foodborne pathogens including *Escherichia coli* (*E. coli*), *Listeria monocytogenes* (*L. monocytogenes*), *S. species*, *Staphylococcus aureus* (*S. aureus*) and many more other organisms are the leading causes of foodborne illness and death in the world.² Foodborne zoonotic diseases often occur due to the consumption of contaminated food-stuffs

especially from animal products such as meat and milk.^{3,4}

Diarrheagenic *Escherichia coli* (DEC) strains is one of the causative agent of foodborne diseases which leading causes of diarrheal illnesses throughout the world both in humans and animals.^{5,6} Gastroenteritis due to foodborne disease is one of the most common illnesses in Ethiopia, and it is a leading cause of death among people of all ages in the country.⁷ The occurrence of *E. coli* in foods of animal origin in Ethiopia is arguably high due to many reasons like illegal slaughtering of animals in open fields, un-

hygienic slaughter practices in the abattoirs, and the risk of disease is high because of a widespread tradition of raw meat consumption.^{8,9} DEC contamination is usually associated with contaminated water and food, their presence reflects fecal contamination of both human and animal's origin.¹⁰

S. aureus is an opportunistic foodborne gram positive pathogen which causes many human and animal diseases.¹¹ *S. aureus* causes an infection in animals and humans which including inflammations of bone, meningitis, septicemia and rashes, mastitis (inflammation of mammary gland in bovine) and inflammation of lower part of the foot in poultry.^{12,13} *S. aureus* is an important pathogen both in community acquired and healthcare associated infections due to its fast growing resistance to antibiotics. In particular, methicillin resistant *S. aureus* presents major infection control problems and threats globally.¹⁴

Antimicrobial resistance in bacterial pathogens is a worldwide challenge associated with high morbidity and mortality. Multidrug-resistant patterns in gram-positive and negative bacteria have resulted in difficult to treat with conventional antimicrobials. Broad spectrum antibiotics are liberally and mostly unnecessarily used and result in emergence of resistance bacteria.¹⁵ The emergence of resistant infections caused by most bacteria has led to mortality and morbidity and there is an urgent need to find solutions to combat bacterial resistance.¹⁶ The effectiveness of currently available antibiotics is decreasing due to the increasing number of resistant strains causing infections; this is due to excessive use of antimicrobial, incorrect antimicrobial dosage and unregulated access to drugs.¹⁷ The reservoir of resistant bacteria in food animals implies a potential risk for transfer of resistant bacteria, or resistance genes, from food animals to humans.^{18,19}

The increasing antibiotic resistance exhibited by pathogenic microbial infectious agents has led to the screening of several medicinal plants for their potential antimicrobial activity.²⁰ Medicinal plant has great role in care of primary health of humans and animals due to its biological and medicinal activities, high safety margins and ability to overcome drug resistance action of pathogens.^{21,22} Medicinal plants are an important source of traditional drugs, modern medicines, folk medicines, nutraceuticals, pharmaceutical intermediates and entities for synthetic drugs since plant extracts contain many medicinal metabolites such as alkaloids, glycosides, terpenoids, flavonoids and lignins.²³ Antimicrobial compounds of medicinal plants differ from antibiotics as they have fewer side effects, better patient tolerance, relatively less expensive, acceptance due to long history of use and being renewable in nature.²⁴ Ethnoveterinary practice to animal health care is as old as the domestication of various livestock species.²⁵ There are so many medicinal plants used to treat foodborne diseases which associated with gastroenteritis in humans and animals, among plants *Solanum incanum* (*S. incanum*) and *Croton macrostachyus* (*C. macrostachyus*) are the common for treatment of foodborne diseases associated with diarrhea.²⁶

C. macrostachyus have different phytochemical which act as antidiarrheal, antimicrobial, anticonvulsant and sedative, anthel-

mintic, antidiabetic, anti-inflammatory, antileishmanial, antioxidant, antiparasitic, larvicidal and antifungal activity. The secondary bioactive compounds which have pharmaceutical activities are including alkaloids, amino acids, anthraquinones, carbohydrates, cardiac glycosides, coumarins, essential oil, fatty acids, flavonoids, phenolic compounds, phlobatannins, polyphenols, phytosteroids, saponins, sterols, tannins, terpenoids, unsaturated sterol, vitamin C, and withanoides.²⁷⁻²⁹ The bioactive compound tannin is found in *S. incanum* have antiseptic and vasoconstrictor affects, and also have the ability to decrease diarrhea *via* forming protective layers of the mucous membranes. But, not only tannin, and also astringent phenolic compounds, triterpenoids and saponins also have an antidiarrheal effect.³⁰

Fruit extracts of *S. incanum* exhibited potent antibacterial effect while leaf extracts showed antimicrobial activity against the *E. coli*, *S. pyogenes*, *S. aureus*, and *P. aeruginosa*. Therefore, the main objective of this paper is to review on the medicinal value of *C. macrostachyus* and *S. incanum* against causative agents of foodborne diseases.

MEDICINAL PLANTS AND PATHOGENIC BACTERIA

Study of Medicinal Plant

Medicinal plants are the sources of bioactive compounds which used mainly for medicinal purposes to tackling different diseases of animals and humans especially in developing countries.³¹ The clinical efficacy of many existing antibiotics is being threatened by the emergence of multidrug-resistant pathogen.^{32,33} Medicinal plants have been widely used all over the world and formed the integral part of basic health care in many countries including Ethiopia. Modern veterinary medicine are not well-developed in most of the countries and it is estimated that the traditional remedies are sometimes the only source of therapeutics for human population and animal.³⁴

Ethiopia is well-known with having tremendous medicinal plants which has been used for treatment of livestock and human ailments, but medicinal values of plant is not well-documented which impedes widespread use, evaluation and validation. In recent time, many young people are lack of indigenous knowledge of medicinal plant, this raised from limitation of transferring indigenous knowledge of this medicinal plants.^{35,36} Application practices of medicinal plant range from administration of the roots, barks, stems, leaves and seeds to the use of extracts, infusions, powders and decoction from the plant.^{37,38} The innovational approach between plants and healthy is launching new generation of multi-component of botanic drugs, dietary supplements and plant produced recombinant proteins.^{31,39}

Ethnoveterinary medicine is the scientific term for traditional animal health care, encompasses the knowledge, skills, methods, practices, and beliefs about animal health care found among the members of a community. The knowledge base differs not only from region to region but also among and within communities. It has been developed through trial and error and deliberate

experimentation.⁴⁰

The plant-based human and livestock health care persists and remains as the main alternative treatment for different ailments in Ethiopia, largely due to shortage of pharmaceutical products, prohibitive distance of the health service stations, unaffordable prices by small holder farmers and pastoralists for conventional drugs, emergence and re-emergence of certain diseases and appearance of drug resistant microbes and/or helminthes.⁴¹ Studying of medicinal plant have great role in innovating the novel drug or alternative antimicrobial components from different plant parts. World Health Organization (WHO) estimates show that about 80% of African people rely on folklore herbal medicine for their primary health care due to scarcity or exorbitant prices of modern medicines. It is believed that herbal medicines exhibit less toxic and cost effective than the synthetic counterpart modern one.⁴² Research investigation of *S. incanum* and *C. macrostachyus* have been showed the medicinal value of these plants which including in treatment of gastrointestinal infections, toothaches, dermatitis, wound, malaria and dandruff.⁴³

Solanum incanum: *S. incanum* have different names in different languages such as; Hiddii loonii (Afan Oromo), Embouy (Amharic) and Sodom/bitter apple (English) as indicated in Figure 1(B). The name *S. incanum* is derived from Latin words, 'Solamen' meaning "relief" indicating the narcotic effects of the plant and 'incanum' meaning "white".⁴⁴ It is a native African shrub which belongs to Solanaceae family and also grows in many regions of Africa, Middle East and Far East Asia.⁴⁵⁻⁴⁷ *S. incanum* is a delicate perennial plant often cultivated as an annual crop. It grows 1-3 m high with simple leaves, ovate, elliptic, 2.5-12 cm long and 2.5-8 cm wide. The fruit is fleshy, less than 3 cm in diameter on wild plants but much larger in cultivated forms. Botanically the fruit is classified as a berry and contains numerous small, soft seeds which are edible, but are bitter because they contain an insignificant amount of nicotinoid alkaloids. Flowers are in clusters along the branches corolla pale to deep blue, purple, occasionally white. Fruit is spherical, green, often striped or mottled with white, turning yellow to orange brown when ripe. *S. incanum* is the bushy herbal plant, native to north and north eastern Africa including Ethiopia. It found at forest edges and in bush land, grass land from sea level-up to 2500 m altitude.⁴⁸

Figure 1. Medicinal Plant, A: *Croton Macrostachyus* and B: *Solanum Incanum* (Taken by: Dr. Tagesu Abdisa)



Phytochemical constituent of *S. incanum*: The bioactive substances which exist in fruit of *S. incanum* includes: alkaloids, steroids, cardiac glycosides, saponins, flavonoids, tannins, oxalates and cyanogenic glycosides, but anthraquinones is absent.⁴⁹ The leaves of *S. incanum* contains alkaloid, steroid, glycosides, flavonoid, saponin, tannins, triterpenes and cardiac glycosides. Root of *S. incanum* consist of spirostanol saponin, four known saponins, indioside D, dioscin, protodioscin, methylprotodioscin and steroid glycoalkaloid solamargine. Aerial part (the part above soil) consists of two steroidal glycosidal alkaloids, solasonine and solamarginine and non-steroidal components like three phenylalkanoic acids, benzyl-O-b-d-xylopyranosyl-b-D-glucopyranoside, flavonoids, chlorogenic acid, adenosine and new compound kaempferol.⁵⁰⁻⁵²

The medicinal value of *S. incanum*: *S. incanum* is a medicinal plant widely employed around the world as antifungal, antiulcerogenic, antinociceptive, antipyretic, anti-spasmodic, orexigenic, hypoglycemic, antimicrobial, antischistosomal, laxative, antimicrobial, hemorrhoids and snake bites.^{48,53} *S. incanum* have various medicinal importance, it was employed in eastern and southern Africa for the treatment of skin diseases, general infections, abdominal pains, fever, stomachaches and indigestion, treatment of dandruff (fruit), wounds, sore throat, angina, ear inflammation, liver disorders, wart, ringworm.^{54,55} In Oromia region the fruit of *S. incanum* is the main medicinal plant used for the treatment of cowdriosis, dermatophilosis skin lesion, foot rot and pasteurellosis and also the root decoction of *S. incanum* is used to treat black legs, fasciolosis and snake bite.⁵⁶

As one research reported⁵⁷ that *S. incanum* have the antimicrobial activities against gram positive and gram negative bacteria such as: *S. aureus*, *Bacillus subtilis*, *P. aeruginosa*, *E. coli*, *Salmonella paratyphi* and *Vibrio cholera*. Fruit of *S. incanum* is used for control of tick infestation in Ethiopia.⁵⁸ *S. incanum* also used in pain relieve in toothache and cure poison of snake bites as well as used in curdling milk or making cheese, leather tanning and soap making due to its alkaloid constituent.^{59,60}

The extraction of *S. incanum* have great role in treatment of cancer, which containing the active ingredient solamargine, can induce apoptosis via up regulation of tumor necrosis factor expression and activation of the mitochondrial apoptosis pathway, and also have therapeutic effect in treatment of patient with actinic keratosis.^{61,62} The alkaloid also rapidly induced membrane blebbing which could not be prevented by chelating either the intracellular or extracellular calcium ions though it was inhibited by some polyethylene glycols. It also disrupted the cytoplasmic actin and microtubules.⁶³

The *S. incanum* have antitypanosomal compound which is steroidal alkaloids derivatives such as cistol-A, solasonine, solamargine and chaconine; this compounds act as antitypanosomal activity against *Typanosoma cruzi* and *Typanosoma brucei* and also have anti-leishmaniasis, *S. incanum* antiprotozoal effect has been reported for the first time against *P. falciparum*, *L. infantum*, *T. brucei* and *T. cruzi*.^{64,65}

C. macrostachyus: *C. macrostachyus* is commonly known as; rush foil (English), Bakkaniisa (Afan Oromo) and Bisana (Amharic) as indicated in Figure 1(A). It belongs to the Euphorbiaceae with 300 genera and 8,000- 10,000 species and most abundant plant in the tropics.^{66,67} It is native to Ethiopia, Eritrea, Kenya, Tanzania, Uganda and Nigeria which is a medium-sized deciduous tree of East Africa particularly wide spread between 200-2500. In mountainous forests and savannah of the tropical regions and ever green bush land areas that receive between 700-701, 200 mm rainfall annually.⁶⁸⁻⁷⁰ The name of Croton comes from a Greek word 'Kroton' which means ticks, because of the seeds' resemblance to ticks, the specific name "macrostachyus" is a contraction of two words, the Greek word "macro" meaning large and "stachyus" relating to the spike, hence, a species characterized by large spikes.⁷¹ *C. macrostachyus* is regarded as a multipurpose tree by subsistence farmers in Ethiopia, Kenya, and Tanzania and the species has potential in playing an important role in the primary healthcare. The bark, fruits, leaves, roots, and seeds of *C. macrostachyus* are reported to possess diverse medicinal properties and *C. macrostachyus* is used as herbal medicine for at least 61 human and 20 animal diseases and ailments. In the distribution area there is a high degree of medicinal use consensus for bleeding, blood clotting, cancer, constipation, diarrhea, epilepsy, malaria, pneumonia, purgative, ringworm, skin diseases or infections, stomach ache, typhoid, worm expulsion, and wounds.^{29,72}

Phytochemical constituent of C. macrostachyus: The genus Croton is rich in terpenoids (diterpenoids and triterpenoids), alkaloids, flavonoids, lignoids, proanthocyanidins and volatile oils containing monoterpenoids, sesquiterpenoids and some shikimate-derived compounds. Previous studies showed the existence of crotin (a chalcone), lupeol (a triperpene), crotepoxide (a cyclohexane diepoxide), proteins, fatty acids, saponins, resins and alkaloids.^{29,73} The activity of *C. macrostachyus* stem bark extracts is comparable to studies where antiplasmodial activity has been related to a range of several classes of secondary plant metabolites including alkaloids and sesquiterpenes, triterpenes, flavonoids, inonoids, and quassinoids.⁷³

Medicinal value of C. macrostachyus: Traditionally *C. macrostachyus* used for treatment of malaria, rabies, gonorrhea, wound, diarrhea, hepatitis, jaundice, scabies, toothache, abdominal pain, cancer, typhoid, pneumonia and gastrointestinal disorders and as ethnoveterinary medicine.⁷⁴⁻⁷⁶ Pharmacological studies on *C. macrostachyus* indicate that it has a wide range of pharmacological activities such as anthelmintic, antibacterial, antimycobacterial, antidiarrheal, antifungal, anticonvulsant and sedative, antidiabetic, anti-inflammatory, antileishmanial, antioxidant, antiplasmodial, and larvicidal effects.²⁹ The leaves and shoots of *C. macrostachyus* are used to treat fever and oedema and also mashed leaves used for treatment of hemorrhoids. Moreover, the maceration of *C. macrostachyus* stem bark is used as abortifacient and uterotonic to expel retained placenta.⁷⁷

C. macrostachyus have the activities of against diarrhea; traditional healers in Ethiopia use a wide range of medicinal plants with antidiarrheal properties.²⁸ The chemical constituent in the *C. macrostachyus*, Terpenoids such as abietic acid and steroids like phytosterols have been showed to inhibit production of prostaglandin

E2 which have a crucial role in stimulation of intestinal secretion, therefore it has antidiarrheal activities.^{78,79}

Study of Pathogenic Bacteria

Escherichia coli and its infection: *Escherichia coli* a gram negative non-spore forming facultative anaerobic rod. Genus *E. coli* belongs to the bacterial group formally called "coliforms" which are member of the "enterics" known as Enterobacteriaceae family.⁸⁰ The strain of *E. coli* are motile because they have flagella arranged in peritrichous, but those lack of flagella are non-motile.⁸¹ *E. coli* is a catalase positive, oxidase negative, lactose fermenter, coccobacillus gram negative non spore forming rod shaped bacteria.⁸² *E. coli* requires the ability to adapt to variations or extreme changes in temperature, pH, and osmolality conditions commonly encountered in nature. For example, the exopolysaccharide (EPS) production of *E. coli* is associated with heat and acid tolerance, and the alteration of lipid composition in membranes is induced by heat stress.⁸³ *E. coli* can survive for a long time in water, especially at cold temperatures. Water trough sediments contaminated with bovine feces can serve as a long-term (>8-months) reservoir of *E. coli*, and the surviving bacteria in contaminated troughs is a source of infection.⁸⁴

E. coli are one of the major etiological agents of calf diarrhea with severe lethal outcome and major damage to the livestock industry worldwide, consequently highly mortality rate in calves under three weeks old and up to 3-months-old has been reported.^{85,86} Diarrhea in animals especially in young cattle is one of the frequently encountered clinical syndromes, it causes economic losses from mortality and morbidity, treatment costs and time spent on care as well as chronic ill-thrift nature of calf diarrhea.⁸⁷

DEC can be divided into six pathogens includes; Enterotoxigenic *E. coli* (ETEC), Enteropathogenic *E. coli* (EPEC), Enterohemorrhagic *E. coli* (EHEC), Enteroinvasive *E. coli* (EIEC), Diffusely adherent *E. coli* (DAEC) and Vero or shiga like toxin producing *E. coli*.^{88,89} The food types most commonly associated with outbreaks of food poisoning due to *E. coli* are mostly of bovine origin, in particular, beef and beef burgers and unpasteurized milk.^{90,91} However, it has been increasingly recognized that fresh vegetables and fruits other than beef or beef-product can be the sources of Shiga toxin-producing *E. coli* (STEC) infection.⁹²⁻⁹⁴

DEC is the most common pathogenic to human which cause bloody diarrhea and HUS or TTP but, it has no any clinical disease except diarrhea in cattle and other animals.^{95,96} The human can be infected with *E. coli* through consumption of contaminated food of bovine origins, fecal contaminated of food products and direct contact with infected animals.⁹⁷ *E. coli* are part of the intestinal microflora of health animals and humans which can carry genes that allow them to produce toxins known as Vero toxins or Shiga-like toxins. Verotoxigenic *E. coli* (VTEC) are not pathogenic to ruminants, but they cause serious diseases in humans worldwide, including diarrhea, hemorrhagic colitis, hemolytic-uremic syndrome, and sometimes death.⁹⁸ Shiga toxin producing *E. coli* is

ubiquitous food and water borne pathogens inhabiting different animals, wildlife and humans.⁹⁹⁻¹⁰¹

Shiga toxin producing *E. coli* are associated with dysentery in calves. As it was reported that, *E. coli* O157:H7 was isolated from fecal samples of calves.¹⁰² The pathogenic *E. coli* is carried in the intestinal tract and excreted in the feces, and also present on the skin which can be transferred to carcass during evisceration. The contaminate during slaughter may cause the spread of *E. coli* to carcass and the human can be infected after consumption.¹⁰³

After ingestion of *E. coli*, the bacteria bind to intestinal mucosa and begin releasing Shiga toxin. The produced toxins disrupt protein synthesis in the epithelial cells lining intestinal mucosa, small vessels of the intestine, kidney and brain resulting in thrombotic microangiopathy. *E. coli* attaches to the microvilli of intestinal epithelial cells and initiates colonization and establishes intimate attachment which is responsible for the translocation of a variety of effectors which alter the structure and function of host cells.¹⁰⁴ Vero toxin producing *E. coli* are widespread in animals but ruminants thought to be the natural reservoir. *E. coli* colonizes the terminal colon of cattle and can be shed in very large numbers by herd mates known as "super shedders". Feces containing these organisms act as a source of contamination for a variety of foods and the environment.¹⁰⁵

Staphylococcus aureus and its infection: *S. aureus* is a facultative anaerobic which belongs to the family of Staphylococcaceae. It is gram positive coagulase and catalase positive and non-spore forming non-motile which have paired cocci in grape like bunch structural shape.¹⁰⁶ *S. aureus* causes mastitis in milking herds, and occasionally purulent dermatitis in their milkers.¹⁰⁷ *S. aureus* is the most commonly affected part of the body due to infection is the skin. The skin infections are including small benign boils, folliculate, impetigo, cellulitis and invasive soft tissue infections.¹⁰⁸

S. aureus is an important cause of hospital and community acquires infections which frequently resistance to many different classes of antimicrobial drugs. It was first described as hospital acquired methicillin-resistant *S. aureus* (MRSA) in 1961 as nosocomial infections. Later on the pathogen was observed in healthy humans without hospitalization and it terms community acquired MRSA.^{109,110} Livestock-associated MRSA was first associated with human disease in 2003, when a MRSA clone associated with a reservoir in pigs and cattle was isolated from a human.¹¹¹ MRSA has been found in horse and livestock. MRSA can be transmitted from livestock to care takers, during milking and treating of animals.¹¹²⁻¹¹⁴ *S. aureus* is unique in its ability to clot plasma during coagulase test which distinguish Staphylococcus epidermidis and *S. hyicus* (coagulase negative). *S. aureus* are tolerant to high concentration of salt and show resistance to heat. *S. aureus* is grown on mannitol salt agar with golden orange to yellowish colonies which distinguish it from *S. epidermidis* and *S. hyicus*.^{115,116}

Antimicrobial Resistance

Antimicrobial resistance is one of the most common disastrous

factor to global public health. Bacterial resistance to antibiotics has increased rapidly within recent years which have led to the increase in the incidence of infectious diseases caused by those multi-drug resistant bacteria. Infections caused by multi-drug resistant bacteria involve higher morbidity, mortality, and a burden to health care systems. The common cause for antimicrobial resistance effect of bacteria is drug residue, due to contamination of meat products with antibiotic residues when the human consume meat with drug residue, then the appearance of resistant bacteria may occur.¹¹⁷⁻¹¹⁹ The main mechanisms of microorganism for antimicrobial resistance are antibiotic inactivation, target modification, changes in permeability and altering metabolic pathway, decreased antibiotic penetration, β lactamase production and efflux pumps.¹²⁰

The antimicrobial drug resistance can be caused by intrinsic and acquired methods. Intrinsic mechanisms are those specified by naturally occurring genes found on the bacterial chromosome. Intrinsic mechanism is due to the presence of outer cell membrane in gram negative bacteria and expression of efflux pumps. The acquired resistance mechanism is due to chromosomal mutation and horizontal transfer of mobile genetic elements from other bacteria in the environment *via* carrying the resistance gene including plasmids, transposon and integrons. The genetic element can be transferred from one bacterium to other through conjugation (cell-to-cell contact between elements), transduction (bacteriophage facilitated transfer of genetic information) and transformation (uptake of free deoxyribonucleic acid (DNA) from the environment.^{71,121-123} Gram negative bacteria possesses high permeability barrier for numerous antibiotic molecules. Their periplasmic space contains enzymes which are capable of breaking down foreign molecules, so gram negatives are less susceptible to plant extraction than gram positive bacteria.¹²⁴

Drug Extraction and Phytochemical Bioactive Compounds

Crude extraction of medicinal plant: The plant extract drugs are new interest as antiseptics and antimicrobial agents in medicine which have safer biologically active compounds with acceptable therapeutic index for development of novel drugs.^{125,126} Plant extracts have more active target sites against drug resistant pathogens.¹²⁷ Plant extraction is the procedure of the separation of medicinal active portions of plant from inactive component part of plants, which undergoes by using solvents diffuse into the solid plant material and solubilize compounds with similar polarity.¹²⁸ Plant extraction can be carried out in different steps including collection of plant parts, drying, size reduction (grinding into pieces), extraction by mixing with solvents, filtration, concentration by rota vapor, drying and reconstitution. The quality and quantity of crude extraction may be influenced by several factors including plant part, solvent, procedure and ration of solvent to plant.^{129,130}

The concept of solubility 'like dissolve like' which mean polar solvent (water, ethanol, methanol) extracts out polar substances and non-polar solvents extracts out non-polar solvents (petroleum ether, acetone and chloroform), this mechanism is depending of functional groups of solvents.¹³¹ There are so many methods for crude extraction from plant including, maceration,

soxhlet apparatus, infusion. Maceration is one of the extraction techniques which have been used in wine making and medicinal plant research investigation. It involves soaking plant materials in a container with solvent and allowed to stand at room temperature for 3-7-days with frequent agitation.¹²⁹

Phytochemical secondary bioactive compounds: Plant produces many secondary metabolites which constitute an important source of antimicrobial, pesticides and pharmaceutical drugs and also medicinal plants are best source to obtain novel drugs.^{132,133} Phytochemicals can be classified as primary and secondary compounds. Chlorophyll, proteins and common sugars are included in primary constituents and secondary compounds have terpenoid, alkaloids and phenolic compounds.¹³⁴ Terpenoids exhibit various important pharmacological activities i.e., anti-inflammatory, anti-cancer, anti-malarial, inhibition of cholesterol synthesis, anti-viral and anti-bacterial activities. Terpenoids are very important in attracting useful mites and consume the herbivorous insects. Alkaloids are used as anaesthetic agents and are found in medicinal plants.¹³⁵

Glycosides moieties including saponins, cardiac glycosides and flavonoids are used to inhibit tumor growth, serve to protect against gastrointestinal infection which caused by pathogens those that cause enteric infection.^{136,137} Secondary metabolites of medicinal plants have different mechanism of actions against bacteria agents. The mechanism can be through inhibition of bacterial enzymes, affecting cell division, bacterial membrane disruption and affecting virulence genes. The mode action of alkaloid is through inhibition of FtsZ (Flamenting temperature sensitive mutant Z) assembly and its GTPase activities which causes cell elongation without cell division. Protein FtsZ have greater role in bacterial cell division which have homolog of the eukaryotic tubulin, then this protein has the affinity to bind with alkaloid which inhibit cell division.¹³⁸

The hydrophobic nature of essential oils (non-polar bio active compounds) disrupted metabolic activities and energy production line of the bacterial cells. It affected on the plasma membrane which makes bacterial cells more permeable to other bioactive compounds.¹³⁹ The mechanism of phytochemical secondary metabolites act with forming complexes with bacterial cell and inhibit cell activities. Flavonoids can for complexes with bacterial cell proteins and interfere with cell activities in the process of bacterial adhesion. Tannin and flavonoids have an antibacterial effect which can bind with proteins and inhibiting cell protein synthesis.¹⁴⁰

CONCLUSION AND RECOMMENDATIONS

Foodborne diseases and drug resistance infectious agents are the most common disaster against the health of animals and humans throughout the world. Bacterial resistance to antibiotics has increased rapidly which have led to increase in the incidence of infectious diseases caused by those multi-drug resistant bacteria. Infections caused by multi-drug resistant bacteria involve higher morbidity, mortality, and a burden to health care systems. Moreover, foodborne disease which caused by *E.coli* and *S. aureus* is the most common in developing countries especially in young animals

and children. However, medicinal plants are the natural resources which have so many bioactive secondary metabolites against pathogenic organisms. Bioactive compounds have different mechanisms against infectious agents through affecting cell division, enzyme inhibition of bacteria, bacterial membrane disruption, affecting virulence genes and disruption of protein synthesis of bacteria. Therefore, *S. incanum* and *C. macrostachyus* have different medicinal value against foodborne disease and drug resistance infectious agents. These medicinal plants have various novel bioactive compounds, although further research studies have not been conducted on the extract of pure bioactive compounds and toxicity analysis. Therefore, the further study should have to be conducted to extract pure compounds rather than crude extract from these medicinal plants for pharmaceuticals industry.

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