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Review

Potential Role of Plant Extracts and Phytochemicals Against Foodborne Pathogens

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Abstract: Foodborne diseases are one of the major causes of morbidity and mortality, especially in low-income countries with poor sanitation and inadequate healthcare facilities. The foremost bacterial pathogens responsible for global outbreaks include *Salmonella* species, *Campylobacter jejuni*, *Escherichia coli*, *Shigella* sp., *Vibrio*, *Listeria monocytogenes* and *Clostridium botulinum*. Among the viral and parasitic pathogens, norovirus, hepatitis A virus, *Giardia lamblia*, *Trichinella spiralis*, *Toxoplasma* and *Entamoeba histolytica* are commonly associated with foodborne diseases. The toxins produced by *Staphylococcus aureus*, *Bacillus cereus* and *Clostridium perfringens* also cause these infections. The currently available therapies for these infections are associated with various limited efficacy, high cost and side-effects. There is an urgent need for effective alternative therapies for the prevention and treatment of foodborne diseases. Several plant extracts and phytochemicals were found to be highly effective to control the growth of these pathogens causing foodborne infections in in vitro systems. The present review attempts to provide comprehensive scientific information on major foodborne pathogens and the potential role of phytochemicals in the prevention and treatment of these infections. Further detailed studies are necessary to evaluate the activities of these extracts and phytochemicals along with their mechanism of action using in vivo models.

Keywords: foodborne diseases; giardiasis; herbal drugs; ethnobotany; toxoplasmosis

1. Introduction

Foodborne diseases are caused by consumption of microbial contaminated foods, herbs and beverages as well as hazardous chemicals including heavy metals, mycotoxins, bacterial toxins as well as fermentation byproducts like biogenic amines and ethyl carbamate [1–3]. Most these foodborne diseases are caused by pathogenic bacteria, viruses and parasites and are of global public health concern [4]. Each year about 600 million people are affected by foodborne diseases worldwide and

about 420,000 people die due to these illnesses [5–8]. The most common symptoms associated with pathogens-induced foodborne diseases are vomiting, abdominal pain, diarrhea, fever and chills that may progress to severe complications such as life-threatening dehydration and hemolytic uremic syndrome (HUS) [9]. The bacterial-induced foodborne diseases are caused by infections with *Salmonella*, *Campylobacter* spp., *Escherichia coli*, *Shigella*, *Vibrio*, *Listeria monocytogenes* and *Clostridium botulinum* and *Clostridium perfringens* [4]. The commonly reported viruses are Norovirus and Hepatitis A, while the parasites involved are *Cryptosporidium* spp, *Giardia lamblia, Trichinella spiralis*, *Cyclospora* spp, *Toxoplasma canis* and *Entamoeba histolytica* [10,11] The toxins produced by *Staphylococcus aureus*, *Bacillus cereus* and *Clostridium perfringens* also prompt this debilitating disease [12]. Recently, there is a dramatic increase in the outbreak of foodborne disease, part of which is due to the emergence of pathogens resistance against current therapies and decontamination strategies [13]. Theses pathogens use food stuff as carrier to get transferred from one host to another one [14]. The diseases caused by these pathogens are a major public health concern and globally produce a social and economic impact.

The proper handling, use of cold chain and addition of chemical preservatives are currently the mainstay to ensure the preservation and safety of food materials. However, the use of synthetic preservatives is associated with a high occurrence of side-effects, thereby raising the demand for the use of natural preservatives [15,16]. The main treatment options for foodborne diseases are systematic treatments like antidiarrheal and antiemetic medications, use of oral rehydration salts and the use of antibiotics [17]. However, the emergence of multi drug-resistant (MDR pathogens) is another global issue that requires the discovery of alternative antimicrobial agents [18–20].

Medicinal plants play a vital role in the treatment and prevention of various diseases and their promotion and there is growing interest in the search for new drugs from natural resources [21–26]. People living in many developing countries in Asia and Africa are mostly dependent on traditional medicines for healing purposes due to their limited access to modern medical facilities. They also have more cases of foodborne diseases because of their poor hygiene and exposure to contaminated drinking water and food materials [27,28]. Various studies have regularly reported the antimicrobial activities of traditional medicines from this part of the world. Medicinal plants offer a substantial opportunity as they contain various bioactive chemical constituents (phytochemicals) that can act as antimicrobial agents. Natural products are also reported to act as synergists along with many modern drugs to combat MDR pathogens [29]. Thus, the exploration of these natural antimicrobials is a hope to curtail foodborne diseases. Traditional medicines have long been used for treating diseases caused by foodborne pathogens and various studies have shown their efficacy in the management of foodborne diseases [30]. Recently, there is a greater interest in the naturally occurring preservatives due to the side-effects associated with the use of artificial preservatives in foodstuffs. Crude plant materials including extracts, essential oils and isolated components have been extensively evaluated to prevent the invasion of pathogens responsible for food spoilage and therefore may limit the spread of foodborne infections [31].

Plants/plant-derived products inhibit/modify the growth of bacteria by several mechanisms. These may include, inhibiting the adherence of the pathogen to host cells [32], causing loss of osmoregulation of microbe and loss of transmembrane electrochemical gradient, increasing NO production thus causing lethal action [33], inhibition of synthesis of the cell wall, proteins and nucleic acids of the pathogen [34]. This review summarizes the therapeutic effectiveness of medicinal plants and isolated natural compounds against pathogens implicated in foodborne infections.

2. Materials and Methods

Published literature related to the role of phytochemicals in foodborne infections was collected using different search engines like PubMed, Google Scholar, SciFinder, Scopus, Web of Science, EBSCO, PROTA and JSTOR. Only in-depth, well designed (having control groups) studies reporting mechanistic results and published in journals of good quality were included in the manuscript.

3. Plant Extracts and Phytochemicals against Bacteria Causing Foodborne Diseases

3.1. Campylobacter Species

Campylobacter jejuni is a Gram-negative, non-spore-forming and non-fermenting bacteria. It is one of the most common causes of foodborne diseases in the US and Europe. Humans are usually infected by the ingestion of contaminated food, milk, water or interaction with animals [35]. Globally, about 9.6 million people are infected by *C. jejuni* annually [36]. For the treatment of *C. jejuni* infection, tetracyclines and fluoroquinolones are the drugs of choice; however, these days they are associated with a high degree of antibiotic-resistance [37,38]. Alternatively, phytochemicals can be utilized as they have the potential to combat foodborne diseases caused by *C. jejuni*. Dholvitayakhun et al. reported the inhibitory activity of extracts of *Adenanthera pavonina* L., *Moringa oleifera* Lam. and *Annona squamosa* L. against *C. jejuni* [39]. In these plants, among the flavonoids, kaempferol, quercetin and rutin are present which possess strong antimicrobial properties [40]. *Mammea africana* Sabine is used traditionally for the treatment of infections, stomach pain and skin ailments in Africa [41]. A coumarin, mammea A/AA was isolated by Canning et al. from *Mammea africana* and evaluated its activity against *C. jejuni*. It was found to be very potent with a minimum inhibitory concentration (MIC) value of 0.25 µg/mL [42]. Castillo et al. evaluated 28 plants against *C. jejuni*, out of which 21 were active. Of these 21 active plants, 4 plants including *Artemisia ludoviciana* Nutt., *Acacia farnesiana* (L.) Willd. *Opuntia ficus-indica* (L.) Mill. and *Cynara scolymus* L. were most potent having minimal bactericidal concentration (MBC) values of 0.5, 0.3, 0.4 and 2 mg/mL, respectively. They also tested the anti-adherence activity of these 4 plants against *C. jejuni,* as adherence of the microbe to mucosal cells is important for its virulence. The results proved that extracts were able to inhibit the attachment of *C. jejuni* [32]. Another mechanism of *C. jejuni* pathogenicity is cell lysis, entry into the host cell and production of a virulent cytotoxin, cytolethal distending toxin (CDT) [43]. Extracts of *A. ludoviciana* and *A. farnesiana* were shown to prevent the production of CDT along with a decrease in cytoplasmic pH and cellular ATP concentration and damages the bacterial cell membrane [44]. Moreover, motility also contributes to the virulence of *C. jejuni*. The subinhibitory concentrations of natural compounds, i.e., carvacrol (0.002%), *trans*-cinnamaldehyde (0.01%) and eugenol 0.01%) prominently decrease the motility of *C. jejuni*. Furthermore, these natural compounds also reduce other virulence potentials of this pathogen [45].

Several researchers have reported the potential antibacterial activity of essential oils (EO) of various plants against *C. jejuni* that are commonly used in the traditional system of medicine. These plants include *Syzygium aromaticum* (L.) Merr. & L.M.Perry [46,47], *Citrus limon* (L.) Osbeck and *Citrus bergamia* Risso [48], tea tree oil, Leptospermum oil [49], coriander (*Coriandrum sativum* L.) [50], *Daucus carota* L. [51], *Cuminum cyminum* L. [52], garlic (*Allium sativum* L.) [53], clove (*Syzygium aromaticum*), thyme (*Thymus vulgaris* L.) [54], eucalyptus (*Eucalyptus globulus* Labill.), sage (*Salvia officinalis* L.), rosemary (*Rosmarinus officinalis* L.), juniper (*Juniperus communis* L.), lavender (*Lavandula officinalis* Chaix), *Myrtus communis* L., *Laurus nobilis* L., pine oil (*Pinus brutia*) [55], *Juniperus excelsa* M.Bieb. [56], *Inula helenium* L [52], marigold (*Calendula officinalis* L.), ginger (*Zingiber officinale* L.), patchouli (*Pogostemon cablin*), gardenia (*Gardenia jasminoides* (Blanco) Benth.), cedarwood (*Cedrus atlantica* (Endl.) Manetti ex Carrière), carrot seed (*Daucus carota* L.), celery seed (*Apium graveolens* L.), mugwort (*Artemisia vulgaris* L.), spikenard (*Nardostachys jatamansi* (D.Don) DC.), orange bitter oils (*Citrus* x *aurantium* subsp. *amara* (Link) Engl.), etc [47].

Terminalia macroptera Guill. & Perr. has been used for treating various infectious diseases in West Africa. Silva et al. subjected 100 clinical isolates of *C. jejuni* to the ethanolic extract of *T. macroptera* and recorded a MIC value as low as 6.25 µg/mL, which was similar to that of co-trimoxazole, used as the positive control, therefore suggests a therapeutic potential of *T. macroptera* in foodborne disease caused by *C. jejuni* [57]. In South Africa, Samie et al. conducted a study on clinically isolated *C. jejuni* from stool samples (n = 110) to find a complementary therapeutic remedy for this infection. They tested extracts of 18 plants i.e., *Annona* sp., *Bauhinia galpinii* N.E.Br., *Bridelia micrantha* (Hochst.) Baill.,

Carissa edulis (Forssk.) Vahl, *Cissampelos torulosa* E.Mey. ex Harv. & Sond., *Elaeodendron transvaalensis* (Burtt Davy) R.H.Archer, *Ficus sycomorus* L., *Lippia javanica* (Burm.f.) Spreng., *Momordica balsamina* L., *Mucuna coriacea* Baker, *Peltophorum africanum* Sond., *Pouzolzia mixta* Solms, *Pterocarpus angolensis* DC, *Rhoicissus tridentate* (L.f.) Wild & R.B.Drumm., *Sida alba* L., *Syzygium cordatum* Hochst. ex Krauss, *Ximenia caffra* Sond. and *Zornia milneana* Mohlenbr. on these isolated bacterial strain. All the extracts were active, but potent activity was observed with the extracts of *P. angolensis* and *L. javanica* having an MIC of 90 µg/mL [58]. The extract of *Cryptolepis sanguinolenta* (Lindl.) is used traditionally for treating different infections in Guinea Bissau. An alkaloid cryptolepine has been isolated from this plant. When tested on a collection of 106 clinical strains of *C. jejuni* by Paulo et al. in Portugal, it was found to be very effective. They recorded MIC_{50} of this alkaloid was equal to that of ampicillin in their study [59]. Jarriyawattanachaikul et al. in Thailand, evaluated 26 Thai plants against *C. jejuni* in search of complementary therapy for infection caused by this bacterium. They found 7 active plants, i.e., taew kaao (*Cratoxylum formosum* (Jacq.) Benth. & Hook.f. ex Dyer), golden shower (*Cassia fistula* L.), mangosteen (*Garcinia mangostana* L.), ginger (*Zingiber officinale* Roscoe), garlic (*Allium sativum* L.), onion (*Allium cepa* L.) and shallot (*Allium ascalonicum* L.), among which *C. formosum* possesses the strongest antibacterial activity as observed from its MIC of 0.3 mg/mL [60]. A traditional beverage, kombucha, showed strong activity against *C. jejuni* [61]. Black and green tea, which are the most widely consumed beverages in the world also have confirmed antibacterial propensity against *C. jejuni* [62]. Aslim et al. have obtained convincing results of the essential oil of *Origanum minutiflorum* O.Schwarz & P.H.Davis against a ciprofloxacin-resistant strain of *C. jejuni*. [63]. Many Australians plants possess antimicrobial properties and have been utilized by the native populations for centuries as traditional medicines for GIT diseases. In a study by Kurekci et al., 109 plants from Australia were tested against *C. jejuni*. Most of these plants were active as their MICs fall between 32 and 1024 µg/mL. *Eucalyptus occidentalis* Endl. was the most active plant reported with MIC of 32 µg/mL [64].

3.2. *Salmonella*

Salmonella is a rod-shaped, Gram-negative, motile, non-spore-forming bacteria belonging to family Enterobacteriaceae. Members of this genus are facultative anaerobes, oxidase negative and catalase-positive bacteria [65]. *Salmonella* species exist everywhere in nature, however, the gastrointestinal tracts of mammals, reptiles, birds and insects and environment polluted with humans or animals' excreta are the main reservoirs [66]. Their characteristic to survive and grow over a wide range of temperature (2–54 °C) and pH (3.6–9.6) makes them difficult to control [67]. Salmonellosis, which is an infection caused by *Salmonella* species is one of the leading causes of foodborne diseases [68]. Transmission to humans occurs via consumption of contaminated food, mostly of animal origins such as milk, eggs and meat. The antibiotics ampicillin, chloramphenicol and co-trimoxazole were once considered as the mainstay treatments for *Salmonella* infection but are largely replaced by fluoroquinolones due to bacterial resistance to antibiotics. Recently, resistance to fluoroquinolones has also emerged [69], thus necessitating the use of traditional medicines for *Salmonella* infections.

Extracts of *Acacia nilotica* L. have been tested against *Salmonella* species in which the extract disrupted the cell wall of bacteria with consequent release of electrolytes and cellular constituents [70]. Another study conducted by Khan et al. in India has also confirmed the potential use of *A. nilotica* against *Salmonella*. They recorded MIC as 9.75 µg/mL in their study [71]. Sugarcane bagasse has also been tested for anti-*Salmonella* activity. It was found to be bacteriostatic and caused leakage of electrolytes [72]. In South Africa, herbs are used as traditional medicine for the treatment of GIT disorders, e.g., stomach pain, diarrhea, etc. Bisi-Johnson et al. conducted a comprehensive study to scientifically prove the effectiveness of traditional plants for treating Salmonella infection. These plants include *Aloe arborescens* Mill., *Acacia mearnsii* De Wild., *Aloe striata* Haw., *Eucomis autumnalis* (Mill.) Chitt., *E. comosa* (Houtt.) Wehrh., *Cyathula uncinulata* (Schrad.) Schinz, *Hydnora africana* Thunb., *Hermbstaedtia odorata* (Bur ch. ex Moq.) T. Cooke, *Hypoxis latifolia* Wight, *Psidium guajava* L., *Pelargonium sidoides* DC., *Schizocarphus nervosus* (Burch.) van der Merwe. Although most of the studied plants

were active in the study, but *A. arborescens*, *A. striata*, *C. uncinulata*, *E. autumnalis*, *E. comosa* and *P. guajava* were particularly potent. The *Salmonella* species used in this study was extended spectrum beta-lactamase positive (ESBL) [73]. In another study from South Africa, the potent antibacterial activity of medicinal was been reported which include *Hypericum roeperianum* Schimp. ex A.Rich., *Cremaspora triflora* (Thonn.) K.Schum., *Heteromorpha arborescens* (Spreng.) Cham. & Schltdl., *Pittosporum viridiflorum* Sims, *Bolusanthus speciosus* (Bolus) Harms, *Calpurnia aurea* (Aiton) Benth., *Maesa lanceolata* Forssk., *Elaeodendron croceum* (Thunb.) DC. and *Morus mesozygia* Stapf. All the plant extracts used were active against *Salmonella* isolates, but *Cremaspora triflora* and *Maesa lanceolata* were very potent having MIC of 0.12 and 0.13 mg/mL, respectively [74]. *Entada abyssinica* A.Rich. is traditionally used in bacterial infections of the gastrointestinal tract (GIT). A total of 8 compounds were isolated from this plant including flavonoids and terpenoids and tested for anti-Salmonella activity. Entadanin was found to be the most potent compound having a MIC of 1.56 µg/mL [75]. *Leea indica* (Burm. f.) Merr. from Saudi Arabia [76], *Leea indica*, *Sclerocarya birrea* (A.Rich.) Hochst. from South Africa [77,78], *Lawsonia inermis* L. from Pakistan [79], *Rhus succedanea* L. from India [80], *Achillea clavennae* L., *Achillea holosericea* Sm., *Achillea lingulata* Waldst. & Kit. and *Achillea millefolium* L. from Japan [81], *Butomus umbellatus* L., *Polygonum amphibium* L. and two species of the genus *Sparganium* (*S. erectum* L. and *S. emersum* Rehmann) from Turkey [82], *Spathodea campanulata* P.Beauv., *Ficus bubu* Warb., *Carica papaya* L., *Cissus aralioides* (Welw. ex Baker) Planch., *Piptadeniastrum africana* (Hook.f.) Brenan, *Hilleria latifolia* (Lam.) H.Walter, *Gladiolus gregarious* Welw. ex Baker and *Phyllanthus muellerianus* (Kuntze) Exell from Cameroon [83,84], persimmon (*Diospyros lotus* L.), guava (*Psidium guajava* L.), sweetsop (*Annona squamosal* Linn.) and *Cichorium intybus* L. from China [85,86], *Anisophyllea laurina* R. Br ex Sabine from Guinea [87], *Sambucus australis* Cham. & Schltdl. from Brazil [88], *Terminalia avicennioides* Guill. & Perr., *Momordica balsamina*, *Combretum paniculatum* Vent., *Trema guineensis* (Schum. & Thonn.) Ficalho, *Morinda lucida* Benth. and *Ocimum gratissimum* L. from Nigeria [89] were reported to have strong antibacterial activity against *Salmonella* species. It has been observed that EO disrupt and increase the permeability of bacterial cell walls, therefore causing the release of intracellular organelles and proteins. The end result is inactivation and death of the microbes as reviewed by Franklyne et al. [90]. Most of the spices contain EO and consumption of spices has additional health benefits. The common spice ingredients like black pepper, fennel, coriander, cardamom are rich in EO [91].

Biosynthesized nanoparticles of metals (metals + natural materials) are frequently reported to have enhanced pharmacological activities. A newly emerged concept is nano-antibiotics [92], which use plants mediated biogenic nanoparticles with improved antimicrobial, chemotherapeutic and biologic properties [93,94]. Using this approach, several metals are reduced using aqueous extracts of medicinal plants [95] and then used as antimicrobial agents with advanced drug delivery and therapeutic outcomes [96]. Silver (Ag) nanoparticles of aqueous leaf extract of *Eupatorium odoratum* L. were shown to have high anti-*Salmonella* activities than the aqueous leaf extract of *E. odoratum* and also $AgNO_3$ [97]. Silver nanoparticles using the aqueous leaf extracts of *Lippia citriodora* (Palau) Kunth have also been proved to be active against *Salmonella* species [98]. Other authors have also applied nanoparticles of phytoconstituents against *Salmonella* and obtained potent antibacterial activity [99–101].

3.3. Escherichia coli

Escherichia coli (*E. coli*), Gram-negative rods, belongs to *Enterobacteriaceae* family. They represent a vital part of human intestinal normal flora [102]. Enterohemorrhagic *E. coli* (EHEC) produces verotoxin which causes gastrointestinal cramps and diarrhea [103]. The most prevalent serotype O157:H7 which can lead to HUS followed by neurological disorders and kidney failure. Consumption of unhygienic foods including meat, unprocessed milk, fruits, vegetables can transmit the microbes [104]. This important pathogen involved in foodborne diseases was once highly responsive to fluoroquinolones and beta-lactams, but now is resistant to these antibiotics [105]. Therefore, alternative strategies, e.g., traditional medicines as such and compounds derived from such sources are used to treat foodborne diseases caused by *E. coli*. *Acacia nilotica* (L.) Del has been found to disintegrate the cell wall of *E. coli* and

release nucleic acids, proteins with a reduction in viable cell growth [70]. In an in vitro study by Elisha et al., nine plants (*Hypericum roeperianum* Schimp. ex A.Rich., *Cremaspora triflora* (Thonn.) K.Schum., *Heteromorpha arborescens* (Spreng.) Cham. & Schltdl., *Pittosporum viridiflorum* Sims, *Bolusanthus speciosus* (Bolus) Harms, *Calpurnia aurea* (Aiton) Benth., *Maesa lanceolata* Forssk., *Elaeodendron croceum* (Thunb.) DC. and *Morus mesozygia* Stapf) were selected for antibacterial activity against *E. coli*. All were found to be active against *E. coli* and thus could be used in the therapeutic management of *E. coli* infection. The lowest MIC was observed for *Maesa lanceolata* as 0.04 mg/mL [74]. *Wasabia japonica* (Miq.) Matsum. is an edible plant that grows at shady, humid and cool places in Japan, China, New Zealand and Korea, and possesses many medicinal properties. This plant inhibits *E. coli* strain O157:H7 which is widely responsible for diarrhea in foodborne diseases [106]. *Punica granatum* L. (pomegranate) is a well-known fruit and is abundantly used throughout the world. It is widely used in traditional medicine for a variety of indications including anti-angiogenic, anti-cancer and antimicrobial [107,108]. Pomegranate contains a variety of phytochemicals (ellagitannins and gallotannins, catechins, procyanidins, flavonoids, anthocyanins and anthocyanidins) [109]. Its antimicrobial activity against *E. coli* has been reported by several researchers [110–112]. Traditional healers of the Limpopo province of South Africa use a variety of medicinal plants for treating diarrhea [113]. Mathabe et al. performed antibacterial experiments to scientifically validate the traditional use of plants against diarrhea/foodborne disease-causing bacteria, i.e; *E. coli*. Their findings confirmed the potential action of *Gymnosporia senegalensis* (Lam.) Loes., *Indigofera daleoides* Harv., *Ozoroa insignis* Delile, *Punica granatum* L., *Spirostachys africana* Sond. and *Syzygium cordatum* Hochst. ex Krauss in limiting *E. coli* infection [114]. Similarly, in Puerto Rico, traditional medicines are used as an alternative therapy for GIT infections. *Tamarindus indica* L., *Phyllanthus acidus* (L.), *Punica granatum* L., *Citrus aurantifolia* (Chrism.) Swingle, *Citrus aurantium* L. were active against *E. coli* [115].

3.4. Staphylococcus aureus

Staphylococcus aureus (*S. aureus*), a Gram-positive, coagulase producing facultative anaerobe is a major cause of foodborne diseases and hospitalization [104]. In addition to causing clinical infections, *S. aureus* also causes food poisoning (a foodborne disease). Individuals suffering from *Staphylococcal* food poisoning are presented with diarrhea, abdominal cramps, nausea and profuse vomiting usually between 1–8 h after food consumption [116]. This pathogen produces exoproteins that are heat stable and are known as *Staphylococcal* enterotoxins (SEs). These toxins act as virulence factors [117] and are mostly responsible for food poisoning and are grouped into five toxin groups designated classically as SEA to SEE. Other *Staphylococcal* enterotoxins (SEG to SER and SEU) have also been described recently [118–120]. *Staphylococcal* foodborne disease outbreak without harboring enterotoxins has also been reported [121]. Traditional medicine is widely practiced in South Africa for treating GIT problems. Bisi-Johnson et al. evaluated the anti–staphylococcal activity of plants used in traditional medicine for GIT related problems including diarrhea and vomiting which are indication of food poisoning. They found that the medicinal plants including *Aloe arborescens* Mill., *Aloe striata* Haw., *Cyathula uncinulata* (Schrad.) Schinz, *Eucomis autumnalis* (Mill.) Chitt., *Eucomis comosa* (Houtt.) Wehrh., *Hypoxis latifolia* Wight, *Hermbstaedtia odorata* (Burch. ex Moq.) T.Cooke, *Scilla nervosa* (Burch.) J.P.Jessop, *Pelargonium sidoides* DC., *Psidium guajava* L. and *Hydnora africana* Thunb. possess strong antibacterial potential towards *S. aureus* and validates the scientific evidence of the use of these plants for food poisoning caused by *S. aureus* [73]. The plant extracts of *Aristolochia indica, Cuscuta pedicellata, Melilotus indicus* and *Tribulus terrestris* fruit which are traditionally used in Pakistan for various ailments including diarrhea have anti–staphylococcal activity [122]. From Togo, anti–staphylococcal activity has been reported for *Holarrhena floribunda* (G.Don) T.Durand & Schinz [123], from Cameroon, for *Vismia rubescens* Oliv., *Vismia laurentii* De Wild [124,125], from South Africa, *Chrysophyllum albidum* G. Don-Holl., *Terminalia ivorensis* A.Chev. [126,127], from Sudan, *Combretum hartmannianum* Schweinf., *Combretum pentagonum* M.A.Lawson, *Anogeissus schimperi* Hochst. ex Hutch. & Dalziel and *Terminalia arjuna* (Roxb. ex DC.) Wight & Arn. [128], from Egypt, clove (*Syzygium aromaticum*), cress (*Lepidium sativum* L.), lemongrass

(*Cymbopogon citratus* (DC.) Stapf.), Oregano (*Origanum vulgare* L.), rosemary (*Rosmarinus officinalis* L.), sage (*Salvia officinalis* L.) [129], from Algeria, *Stachys guyoniana* Noë ex Batt. and *Mentha aquatic* L., *Centaurea diluta* Ait. subsp. *algeriensis*, *Ferula vesceritensis* Coss. & Durieu ex Trab., *Genista saharae* Coss. & Durieu and *Zilla macroptera* Coss. [130–132] and *Clerodendrum myricoides* (Hochst.) R. Br. ex Vatke from Kenya, [133].

Juglone is a natural compound occurring in plants such as black walnut (*Juglans nigra* L.). This compound has antibacterial property and inhibits *S. aureus* by binding to DNA and disrupts cell wall synthesis, thus stressing the bacterial cells to increasing peroxidative environment [134]. Tetrandrine is an alkaloid isolated from the radix of *Stephania tetrandra* S. Moore. It inhibits *S. aureus* by binding to the peptidoglycan [135]. *Fraxinus rhynchophylla* Hance and its active constituent fraxetin is antibacterial to *S. aureus* via inhibition of essential proteins synthesis. It also decreases the activity of topoisomerase I and topoisomerase II [136]. Several researchers have reported active compounds from medicinal plants that are active against staphylococcal bacteria [137–139]. Essential oils are also utilized against *S. aureus* and studies have shown potential benefits of essential oils derived from *Petroselinum crispum* (Mill.) Fuss, *Cuminum cyminum* L, white mustard (*Sinapis alba* L.), *Chamaecyparis obtusa* (Siebold & Zucc.) Endl. [140–143].

3.5. Shigella

Shigella is a genus of Gram-negative bacteria. It has four species, *S. flexneri, S. sonnei, S. dysenteriae* and *S. boydii*. These are rod-shaped, non-motile, non-spore forming and facultative anaerobic bacteria [144]. They cause diseases commonly known as shigellosis, characterized by profuse watery diarrhea, fever, abdominal cramps and also bloody dysentery. Ingestion of as low as 100 numbers of these bacteria can cause foodborne disease. These bacteria attack the epithelial cells of the colon of primates only. The resultant inflammation causes high intestinal motility and diarrhea which even leads to dysentery [145]. The virulence of Shiga toxin is like that of verotoxin of *E. coli*, which halts protein synthesis in the host cells [104,146]. In Iran, pomegranate (*Punica granatum*) is commonly used to treat diarrhea. Mahboubi et al. reported that the the extracts of pomegranate were active against *Shigella* [147]. Another study has reported the anti-*Shigella* activity of five plants, e.g., *Thymus vulgaris* L., *Thymus carmanicus* Jalas, *Zataria multiflora* Boiss., *Ziziphora clinopodioides* Lam. and *Ziziphora tenuior* L. Among these *Thymus caramanicus* and *Zataria multiflora* were found comparatively more active having MIC values of 0.78 and 1.56 mg/mL, respectively [148]. In a study by Vuuren et al. 23 traditionally used plants for various ailments including diarrhea, were subjected to antibacterial activity against *Shigella* bateria. Although, all the plants had antibacterial property, *Acacia burkei* Benth. (MIC 0.25 mg/mL), *Acanthospermum glabratum* (DC.) Wild (0.44 mg/mL), *Brachylaena transvaalensis* Hutch. ex E.Phillips & Schweick. (0.5 mg/mL), *Catharanthus roseus* (L.) G.Don (0.41 mg/mL), *Chenopodium ambrosioides* L. (0.5 mg/mL), *Cissampelos hirta* Klotzsch (0.38 mg/mL), *Gymnosporia senegalensis* (Lam.) Loes. (0.63 mg/mL), *Lippia javanica* (0.5 mg/mL), *Mangifera indica* L. (0.25 mg/mL), *Melia azedarach* L. (0.57 mg/mL), *Psidium guajava* L. (0.33 mg/mL), *Sarcostemma viminale* (L.) R.Br. (0.5 mg/mL), *Schotia brachypetala* Sond. (0.58 mg/mL), *Sclerocarya birrea* (A.Rich.) Hochst. (0.34 mg/mL), *Syzygium cordatum* Hochst. ex Krauss (0.43 mg/mL) and *Terminalia sericea* Burch. ex DC. (0.04 mg/mL) were particularly potent [149]. Essential oils are also utilized for foodborne infections caused by *Shigella* [150,151].

3.6. Listeria monocytogenes

Listeria monocytogenes (*L. monocytogenes*), a Gram-positive, non-spore-forming, facultative anaerobe widely affecting food, meat, poultry and seafood [152]. This pathogen grows between 0.4 and 50 °C [104]. The virulence factors of *L. monocytogenes* include the production of beta hemolysin, catalase and superoxide dismutase. It has been implicated in foodborne outbreaks [153]. This microbe can survive refrigeration, high salt content and low pH [154]. These properties enable *L. monocytogenes* to contaminate food even after food postprocessing [155]; *L. monocytogenes* being a foodborne pathogen is

challenged with extracts and compounds derived from medicinal plants. In a study by Yoon et al. in South Korea, 69 herbal extracts were tested for inhibition of *L. monocytogenes*. Psoraleae Semen and Sophorae Radix extracts were found potent in their study [156]. Attachment of *L. monocytogenes* to the human intestinal epithelium and its subsequent invasion results in listeriosis. Motility, lecithinase and hemolysin production are the major virulence factors of this pathogen. The virulence factors, i.e., motility, lecithinase and hemolysin production were also decreased. Furthermore, the expression of the virulence genes was downregulated by cinnamaldehyde, carvacrol and thymol more than 3-folds [157,158]. The essential oils are reported to possess antilisterial activity. Essential oils of *Zataria multiflora* Boiss. from Turkey [159], *Carum copticum* (L.) Benth. & Hook.f. ex C.B.Clarke from Iran [160], *Thymus capitatus* (L.) Hoffmanns. & Link from Tunisia [161], *Cymbopogon citratus* D.C. Stapf. from Brazil [162], *Eryngium foetidum L.* from Italy [163] have been reported to have the potential of inhibiting *L. monocytogenes*.

3.7. Clostridium spp.

Clostridium botulinum (*C. botulinum*) is a Gram-positive, rod-shaped, motile, obligate anaerobe [164]. It is a spore-forming bacterium and produces a neurotoxin known as botulinum [165]. It causes a foodborne disease known as foodborne botulism. This happens after ingestion of the preformed toxin produced by *C. botulinum*. The major virulence factor is toxin production [166]. Seven types of toxins have been identified. These are named as A–G. Among these, A, B and E toxin types are associated with foodborne illness. The symptoms of foodborne botulinum are blurred vision, dry mouth, nausea, vomiting, abdominal cramps and difficulty in swallowing [167,168]. Toosendanin, a natural compound, prevents botulinum in animals [169].

C. perfringens, a Gram-positive, spore-forming bacteria has a widespread anaerobic environmental distribution including soil, foodstuff and is part of human flora [170]. Extracts from traditionally important medicinal plants including *Psidium guajava* L., *Haematoxylum brasiletto* H.Karst. and *Euphorbia prostrata* Aiton were found highly effective against *C. perfringens* type A [171]. Likewise, essential oils from *Satureja montana* L. tested against *C. perfringens* type A at a concentration of 1.56%, showed inhibitory activity causing structural damage and cell lysis. Moreover, a synergistic effect between $NaNO_2$ and *Satureja montana* EOs was observed and the findings suggest the potential combined use of savory essential oil and minimal amounts of the synthetic additive, $NaNO_2$ to control *C. perfringens* [172]. The natural product, berberine demonstrated efficacy towards the *C. perfringens* disease based on significantly decreased mortality and lesion scores at 1.0 mL/L, in vitro [173]. Extracts from several plants *Pueraria thunbergiana* (Siebold & Zucc.) Benth., *Astragalus membranaceus* (Fisch.) Bunge, *Eucommia ulmoides* Oliv., *Coptis japonica* (Thunb.) Makino, *Akebia quinata* (Houtt.) Decne. and *Rhus chinensis* Mill. exhibited considerable activity against *C. perfringens* [174].

3.8. Bacillus cereus

B. cereus, a Gram-positive spore-forming bacterium, is frequently implicated in foodborne infections. Among the pathogenic aspects of the bacterium is the production of tissue-damaging exo-enzymes. The bacterium secretes toxins including hemolysins, phospholipases, emesis-inducing toxins and proteases [175]. In the in vitro antibacterial assay against *B. cereus*, the extract of *Dryopteris erythrosora* (D.C. Eaton) Kuntze exhibited an MIC of 0.0156 mg/mL, followed by *Siegesbeckia glabrescens* (SG) Makino leaf (0.0313 mg/mL), *Morus alba* L. bark (0.0313 mg/mL), *Carex pumila* Thunb. root (0.0625 mg/mL) and *Citrus paradisi* Macfad. seed (0.0625 mg/mL) extracts. The combined inhibitory effects of extracts against *B. cereus* were also determined. A combination of *D. erythrosora* and *C. pumila* extracts showed a partial synergistic inhibition, with a fractional inhibitory concentration index of 0.75. The single and combined inhibitory activities of selected plant extracts against *B. cereus* in reconstituted infant rice cereal were also investigated and showed the MICs of *S. glabrescens*, *M. alba*, *D. erythrosora* and *C. pumila* extracts against *B. cereus* as 1.0, 2.0, 2.0 and 8.0 mg/mL, respectively [176]. The plant extracts of *Rhus coriaria* L. and *Hipiscus sabdariffa* L. were investigated against six presumptive *Bacillus*

cereus isolates that were isolated from 49 samples of food, soil, manure and eggshells in Amman, Jordan. It was observed that the inhibition of the growth of bacteria was proportional to the increase in extract concentrations. Complete inhibition of the growth was demonstrated at the highest concentrations. The authors concluded that *Rhus coriaria* and *Hibiscus sabdariffa* have the potential to be used as food preservatives against wider spectra of spoilage microorganisms in food [177].

3.9. Vibrio cholerae

V. cholerae, a Gram-negative curved rod from family *Vibrionaceae* has two major virulence factors including cholera toxin, causing profuse rice-watery diarrhea and toxin-coregulated pilus that is mediated in intestinal colonization [178]. Cholera caused by toxigenic *V. cholerae* is a major public health problem particularly in less developed regions of the world with poor sanitation facilities [179]. The extracts of *Ocimum basilicum* L., *Opuntia ficus-indica* (L.) Mill., *Acacia farnesiana* (L.) Willd. and *Artemisia ludoviciana* Nutt. were found active against *V. cholera*, with MBCs values ranging from 0.5–3.0-mg/mL [180]. Recently, solvent-based extracts from red chili, sweet fennel and white pepper were reported to inhibit cholera toxin production. Further, capsaicin the active ingredient of chili prevented the synthesis of cholera toxin in different strains of *V. cholerae*. Capsaicin declined the expression of virulent genes (*ctxA, tcpA* and *toxT)* yet increased the expression of *hns* gene that transcribes a global prokaryotic gene regulator (H-NS) [181]. Solvents based extracts from 32 Mexician plants were evaluated for their inhibitory effects against *V. cholera* strains (O1, O139). Among these, *Acacia farnesiana* and *Artemisia ludoviciana* ethanolic extracts were more effective with minimum Bactericidal Concentrations of 4.0–7.0 and 4.0–6.0-mg/mL respectively [182]. In another study, the extracts of *Terminalia chebula* Retz. and *Syzygium cumini* (L.) Skeels exhibited considerable activity against *V. cholerae*, *Aeromonas hydrophila* and *Bacillus subtilis*, with MBCs (0.25–4 mg/mL). These results favor the use of ethnopharmacological important plants in the management of diarrhea, especially those associated with cholera [183].

4. Plant Extracts and Phytochemicals against Viruses Causing Foodborne Diseases

4.1. Norovirus

Norovirus is single-stranded, positive-sense RNA and non-enveloped virus which is also known as winter vomiting bug [184]. It is a major cause of acute gastroenteritis affecting people of all ages. The transmission of the virus occurs via contaminated food. After entry into the body, the virus replicates in the intestines. It takes one to two days for symptoms to appear. The major symptom reported is gastroenteritis [185]. Other symptoms include watery diarrhea, abdominal cramps, nausea and vomiting. The infection is self-limiting, and recovery occurs within two to three days. There is no specific treatment for norovirus infection. Supportive therapy includes maintaining fluid and electrolyte balance [186]. A combination of juice and polyphenols from pomegranate is effective for eradicating norovirus infection [187]. Chinese galls and pomegranate significantly reduces the attachment of norovirus P protein to their receptors (human histo-blood group antigens) which is an important step for this pathogen virulence. Along with other phytochemicals, tannic acid is responsible for this blocking action [188]. Similarly, grape (*Vitis vinifera* L.) seed extract is used in GIT diseases and has been proved to have potential anti-norovirus activity [189]. Allspice oil and lemongrass oil can reduce viral infection by degrading the capsid of the virus [190]. Curcumin, a natural compound from *Curcuma longa* L. and juice of mulberry (*Morus alba* L.) were tested for anti-noroviral activity and were found to have good inhibitory activity on norovirus.

4.2. Astrovirus

Astroviruses are non-enveloped, positive-sense single-stranded RNA viruses causing GIT disorders particularly pediatric diarrhea. The astrovirus capsid acts as enterotoxin and thus disrupts gut epithelial barrier [191]; *Achyrocline bogotensis* (Kunth) DC. extracts were evaluated for their

antirotavirus (RRV) and anti-astrovirus (Yuc8) activities. The nontoxic concentrations displayed considerable antiviral potentials against both viruses. The activity can be attributed to the presence of steroids, sterols, terpenes, phenols, flavonoids and sesquiterpene lactones [192]. *Spirulina platensis* ethanolic extract was tested and revealed a considerable decline in vitro for infectious units of various types of viruses including adenovirus (type 7), astrovirus (type 1), Coxsackievirus B4, rotavirus (Wa strain) and adenovirus (type 40) [193]. Northern Nigerian plants have been investigated against poliovirus, astrovirus, herpes simplex viruses and parvovirus. The obtained results showed that the test samples showed considerable activity against viruses at 100–400 mg/100 mL dose [194].

4.3. Hepatitis-A Virus

The hepatitis A virus (HAV), a picornavirus is a widespread cause of hepatitis and is transmitted via oral intake of contaminated food, water and blood transfusion [195]. Medicinal plants including *Alnus japonica* (Thunb.) Steud. have revealed significant virucidal activity against HAV and at a concentration of 50-µg/mL has reduced HAV titer by 3.43 ± 0.24 logs. Similarly, *Artemisia annua* L., *Allium sativum* L., *Allium fistulosum* L. and *Agrimonia pilosa* Ledeb. extracts exhibited 2.33 ± 0.43, 2.10 ± 0.41, 2.07 ± 0.60 and 2.03 ± 0.26-log reductions, respectively [196]. It has been observed that green tea extract has a strong anti-HAV activity with a direct effect on the viral particles. Supplementing tap water with the extract with continuous shaking every 15 min for 1 h caused a significant reduction in the percentage of HAV plaque counts. There is a strong recommendation of supplementing water with a small concentration of green tea extract that does not cause an observed change in its color and taste for 1 h with persistent shaking before usage in endemic areas for HAV infections [197].

4.4. Rotavirus

Rotavirus infections represent the leading cause of dehydrating gastroenteritis among children less than 5 years of age. Despite the worldwide vaccinations against rotavirus, it is still a major cause of fatality (>200,000 deaths annually) especially in low-income countries [198]. These viruses usually infect enterocytes, thus induce diarrhea via the decline in the absorptive capacity of enterocytes, increase intestinal secretion stimulated by viral non-structural protein 4 and activation of the enteric nervous system [199]. It has been observed that supplementation *Nelumbo nucifera* Gaertn., *Aspalathus linearis* (Burm.f.) R.Dahlgren, *Urtica dioica* L., *Glycyrrhiza glabra* L. and *Olea europaea* L. extracts are effective in the managment of rotavirus induced diarrhea [200,201]. Moreover, aqueous extracts from *Nelumbo nucifera*, *Urtica dioica*, *Aspalathus linearis*, *Glycyrrhiza glabra* and *Olea europaea* leaves were reported to exhibit substantial antiviral potentials with IC_{50} of <300 µg/mL. Likewise, 18β-glycyrrhetinic acid and luteolin isolated from *G. glabra* and *A. linearis* exhibited IC_{50} of 46 µm and 116 µm, respectively [201]. *Rubia cordifolia* L. extracts, isolated compounds including xanthopurpurin and vanillic acid were quite effective against rotavirus and inhibited its multiplication by augmenting virus-mediated apoptosis in MA-104 cells [202]. The antirotavirus activity of *Bauhinia variegata* L. was examined, which showed antiviral activity against rotavirus in vitro with therapeutic index ranged from 0.2 to 23 and a reduction in virus titers ranged from 0.25 $\log_{10}$ to 4.75 $\log_{10}$. These results demonstrated that *B. variegata* has a potential for the pharmacotherapeutic management of rotavirus induced gastroenteritis [203]. The antiviral activity of different extracts from *Calliandra haematocephala* Hassk. leaves against rotavirus (RV) infection was evaluated both in vitro and in vivo. *C. hematocephala* at non-cytotoxic concentrations exhibited antirotavirus activities at a different magnitude of potency with therapeutic index ranging from 1.3 to 32 and a reduction in virus titer ranging from 0.25 $\log_{10}$ to 5.75 $\log_{10}$. In the in vivo study, oral administration of the methanol extract at 50 mg and 100 mg/kg/day significantly reduced mortality, virus titers, duration and severity of diarrhea, as well as alleviation of lesion in the small intestine in rotavirus infected mice [204]. The leaf of Japanese big-leaf magnolia (*Magnolia obovate* Thunb.) has long been used as a natural packaging material for traditional foods in Japan. The extract significantly inhibited cytopathic effects and mRNA expression of rotaviral proteins in SA11-infected MA104 cells

and thus can be used as a medicine or food additive to prevent and ameliorate rotavirus-induced diarrhea in individuals that may have difficulty in benefitting from the rotavirus vaccines [205].

5. Plant Extracts and Phytochemicals against Parasites Causing Foodborne Diseases

5.1. Giardia lambia

Giardiasis is a human parasitic infection most commonly transmitted through the ingestion of infected food and is associated with significant morbidity [206]. The most common cause of giardiasis is the protozoan, *Giardia lamblia* commonly called *G. intestinalis* and *G. duodenalis*. Several treatment strategies are devised for its eradication which includes nutritional intervention, ingestion of probiotics and phytotherapeutic agents [207]. Several natural products including *Allium sativum*, berberine and flavonoid-rich herbs, *Piper longum* L., *Butea monosperma* (Lam.) Taub. and various isolated compounds have been found effective in the eradication of giardiasis [208,209].

Natural products based therapeutics play a significant role in the treatment and management of giardiasis, mediated through eradication of parasite and thus relieving the unwanted symptoms of infection. Several herbs are extensively reported for their effectiveness in *Giardia* infections; *Allium sativum* is a well-known household remedy against numerous human diseases including microbial and parasitic infections [210]. In a study, Harris et al. reported the anti-giardial potentials of crude *A. sativum* and its isolated compounds; A. *sativum* crude extract exhibited IC_{50} of 0.3-mg/mL against *Giardia intestinalis*, whereas, the isolated compounds allyl mercaptan, diallyl disulfide, diallyl sulfide, allyl alcohol and dimethyl disulfide showed IC_{50} values of 0.037, 0.1, 1.3, 0.007 and 0.2 mg/mL, respectively [33].

Furthermore, the incubation of *Giardia* trophozoites in the presence of whole *A. sativa* exhibited considerable decline in the parasite motility, flagellar movement and ultimate swelling of the trophozoite. The mechanisms underlying these events involve the loss of osmoregulation of parasite and loss of transmembrane electrochemical gradient. Microscopic studies revealed morphologic changes in the ventral disc of the parasite which can be responsible for its inability to attached to its host cell [33]. In another clinical study, Soffar and Mokhtar administered fresh *A. sativum* distilled water extract (5 mL) or 0.6 mg commercially available capsules to 26 children infected with *G. lamblia* for three days and observed its beneficial effects against giardiasis [211]. The symptoms of giardiasis were effectively subsided in all the groups of children with thirty-six hours of therapy and the stool examination revealed complete eradication of parasite [211]. Allicin isolated from *A. sativum* is reported to mediate its action against the parasite via inhibition of giardia's cysteine proteases and inhibition of products responsible for unwanted symptoms of giardiasis [212,213]. Moreover, *A. sativa* also increases the mucosal nitric oxide (NO) production via stimulation of nitric oxide synthase, which subsequently increases the liberation of NO from enterocytes and exhibits direct giardicidal effects [33].

Piper longum L. is a well-known folk medicine for the treatment of gastrointestinal disorders and helminthesis [214]. In a study, Tripathi et al. investigated the giardicidal actions of crude extracts of *P. longum*. Treatment with crude ethanolic extract (125 µg/mL) and aqueous extracts (250 µg/mL) showed 100% lethality against *Giardia lamblia*. In an animal model of giardiasis, *P. longum* crude ethanolic extract, aqueous extract and fruit powder at doses of 250, 450 and 900 mg/kg, respectively significantly (75%) diminished the live trophozoites count in the intestinal mouse aspirates after five days of therapy [215]. The two important gastroprotective herbs including *Piper longum* and *Butea monosperma* have been combined in a traditional herbal formulation called Pippali rasayana (PR). This formulation is very famous in folk medicine for the treatment of helminthesis and chronic dysentery. In a study, Agarwal et al. reported the anti-giardial effects of PR formulation in an animal model. The in vivo study revealed that PR administration in doses of 225, 450 and 900 mg/kg exhibited 62%, 79% and 98% parasitic clearance, respectively. Moreover, PR significantly augmented the macrophage phagocytic activity and macrophage migration index at all the tested doses. As the PR formulation is inactive against the parasite in vitro, so it was proposed that the formulation may

mediate its anti-giardial activity through boosting of host immune system and thereby increasing clearance mechanisms [216]. To further explore the clinical significance of PR formulation, Agarwal et al. extended the study and included fifty human subjects with all signs and symptoms of giardiasis including cysts and Giardia trophozoites in the stool samples. The subjects were divided into two groups; the treated group was maintained on PR (1 g T.D.S) for fifteen days, whereas the second group served as a placebo control. After the completion of therapy, stool samples were analyzed for *G. lamblia*, frequency of diarrhea and mucous content of the stool. In the treated group, 92% inhibition of *Giardia* and a significant decline in diarrhea and mucous were observed. A boost in the cell-mediated immune system indicated by a decline in leukocyte migration was also observed [217].

In a study, Miyares et al. evaluated the giardicidal potential of propolis in 136 subjects with well-known symptoms of giardiasis. In the five days' trials, propolis was administered in 20, 30% solutions (adults) and 10% solution (children) and duodenal aspirates were evaluated for giardicidal activity. Results of the study revealed 60% giardicidal activity for 30% solution and 40% giardicidal activity for 20% solution in adults whereas, 52% giardicidal activity was observed in children after administration of 10% solution. The standard drug, tinidazole exhibited a 40% efficacy [218]. Several studies have confirmed the efficacy of berberine and berberine rich plants including *Coptis chinensis* Franch., *Berberis vulgaris* L., *Berberis aquifolium* Pursh, *Berberis aristata* DC. and *Hydrastis canadensis* L. in the management of gastrointestinal disorders like parasitic infestation and diarrhea [219,220]. Berberine is highly effective against Giardia trophozoites and mediates its beneficial effects via morphologic changes in the trophozoites including changes in the shape of vacuoles, trophozoites swelling and deposition of glycogen deposits [221]. Berberine hydrochloride at a dose of 5 mg/kg showed a 68% decline in the stool–*Giardia* content and a significant decline in giardiasis symptoms in a clinical study [222]. In a clinical trial, berberine administered in doses of 5, 10 mg/kg for 5–10 days showed a 47%, 55%, 68% and 90% decline in the Giardia content in all the treated groups of children. The standard drugs, furazolidone and metronidazole exhibited a 92% and 95% efficiency against *Giardia* [223]. In vitro studies have revealed high efficacy of crude extracts from these plants in comparison to pure berberine, which can be attributed to the synergistic interactions of berberine with other isoquinoline alkaloids present in these plants [224]. Natural flavonoids including epicatechin, quercetin, epigallocatechin, apigenin and kempferol, which are abundant in several natural products like *Quercus robur* L., *Hamamelis virginiana* L. and *Croton lechleri* Müll.Arg. are extensively reported for giardicidal potentials [225–227]. In a study, flavonoids and tannins rich plants including *Origanum vulgare* L., *Psidium guajava* L., *Mangifera indica* L. and *Plantago major* L. showed high anti-giardial activity in comparison to the standard drug, tinidazole [228]. Barbosa E et al. reported the antigiardial activity of flavonoids isolated from *Geranium mexicanum* Kunth, *Helianthemum glomeratum* (Lag.) Lag. ex Dunal, *Cuphea pinetorum* Benth. and *Rubus coriifolius* Liebm. Among the isolated compounds, kempferol, tiliroside and epicatechin exhibited IC_{50} values of 2.057, 1.429 and 0.072 µmol/kg, respectively against *G. lambia* [229].

5.2. *Entamoeba histolytica*

Amoebiasis is a ubiquitous gastrointestinal disorder most prevalent in less developed countries with poor sanitation and socioeconomic status, affecting about 12% of global population [230]. It is known to be the third leading cause of mortality [231–233]. The causative agent of amoebiasis is *Entamoeba histolytica,* which is associated with typical symptoms of amoebic dysentery, abdominal cramps, bloating or tenderness and stomachache [234,235]. Among the currently available chemotherapeutics, metronidazole is an effective amoebicide, but is associated with unwanted side-effects like carcinogenesis, mutagenesis, nausea and vomiting [236,237]. The stratagem of utilizing natural drugs in antiamoebic therapy traces back to the pre-historic era. For instance, emetine isolated from *Cephaelis ipecacuanha* (Brot.) A.Rich. is used as a front line anti-amoebic drug [238]. Currently, a large population is dependent on traditional therapeutics for the management of various diseases [18,25,239]. Medicinal plant and herbal drugs represent an indispensable part of the traditional

medicine practiced in many countries owing to low costs, frequent availability, biosafety and ancestral knowledge [240–242]. Hence, in search of more effective drugs, traditionally used natural products are of great importance. Several natural products and isolated compounds have been scientifically validated for effective eradication of *Entamoeba histolytica*, for potential drug development. For instance, bruceantin, a potent amoebicide from *Brucea antidysenterica* J.F.Mill. exhibited IC_{50} of 0.018 µg/mL [243], parthenin from *Parthenium hysterophorus* L. [244], extracts and isolated compounds from *Brucea javanica* (L.) Merr. fruits and *Simarouba amara* Aubl. [245] and alkaloids from *Alstonia angustifolia* Wall. ex A.DC. roots [246] were extensively studied against *E. histolytica*. Cimanga et al. investigated the effect of *Morinda morindoides* (Baker) Milne-Redh. leaves extracts and isolated compounds against *E. histolytica* [247]. The crude methanolic extract and aqueous decoction showed significant anti-amoebic action with IC_{50} values of 1.7 and 3.1 µg/mL, respectively. Among the isolated compounds, kempferol, apigenin, luteolin, apigenin-7-*O*-glucoside and luteolin-7-*O*-glucoside exhibited IC_{50} values of 10.3, 12.7, 17.8, 22.3 and 37.4 µg/mL, respectively against *E. histolytica*.

Tona et al. evaluated forty-five Congolese plant extracts used in traditional medicine against *E. histolytica*. Among the tested samples, *Mangifera indica* L., *Rauwolfia obscura* K.Schm., *Carica papaya* L., *Euphorbia hirta* L., *Hymenocardia acida* Tull., *Jatropha curcas* L., *Maprounea africana* Mull. Arg., *Paropsia brazzeana* Baill., *Psidium guajava* L., *Cryptolepis sanguinolenta* (Lindl.) Schltr. and *Quassia africana* (Baill.) Baill. were highly active with IC_{50} values of 7.81, 31.5, 7.81, 31.25, 31.25, 31.25, 31.25, 7.81, 7.81, 7.81 and 31.5 µg/mL, respectively [248]. In another study, Sohni et al. investigated the antiamoebic potentials of an herbal formulation containing *Zingiber officinale*, *Berberis aristata*, *Boerhavia diffusa* L., *Tinospora cordifolia* (Willd.) Miers and *Terminalia chebula* extracts. Among these plant extracts, *Berberis aristata* and *Tinospora cordifolia* showed IC_{50} values of 100 and 1000 µg/mL, respectively. All these plants in a combined formulation exhibited an IC_{50} of 1000 µg/mL. The herbal formulation was also tested against some enzymes of *E. histolytica* including DNase, RNase, aldolase, alkaline, acid phosphatases and α-amylase that are known to play a significant role in the virulence and invasiveness of the parasite. Results confirmed various degrees of inhibition of these enzymes [249]. Owing to the traditional use of *Salvia polystachya* Cav. for the treatment of dysentery in the Mexican traditional medicine, Calzada et al. investigated various isolated compounds from *Salvia polystachya* against *E. histolytica* and *G. lamblia* trophozoites. Among the tested compounds, Linearolactone was most active showing IC_{50} value of 22.9 and 28.2 mM against *E. histolytica* and *G. lamblia*, respectively. Whereas, polystachynes A, B and D, exhibited modest antiprotozoal potentials with IC_{50} values ranging from 117.0–160.6 mM against *E. histolytica* and 107.5–134.7 mM against *G. lamblia* [250].

In the search for new antiprotozoal drugs from natural products, Calzada et al. studied the inhibitory effects of twenty-six traditional Mexican drugs against *E. histolytica* and *G. lamblia*. Among the tested samples, *Chiranthodendron pentadactylon* Larreat., *Annona cherimola* Mill., *Punica granatum*, *Dichondra argentea* Humb. & Bonpl. ex Willd., *Chenopodium ambrosioides* L. and *Chrysactinia mexicana* A.Gray were most active showing IC_{50} values of 2.5, 14.8, 29.5, 38.3, 45.2, 45.3 µg/mL, respectively against *E. histolytica*. Whereas, *Dorstenia contrajerva* L., *Senna villosa* (Mill.) H.S. Irwin & Barneby, *Ruta chalepensis* L., *Cocos nucifera* L. and *Chiranthodendron pentadactylon* Larreat. exhibited IC_{50} values of 23.3, 32.1, 37.8, 44.1, 44.2 µg/mL, respectively against *G. lamblia* [251]. In another study, the same group investigated the antiprotozoal efficiency of crude extracts and isolated compounds from the roots of *Geranium mexicanum* against *E. histolytica* and *G. lamblia*. Among the crude samples, dichloromethane–methanol, ethyl acetate, fraction 13 (from ethyl acetate) and aqueous fractions showed IC_{50} values of 79.2, 66.7, 51.5 and 221.6 µg/mL, respectively against *E. histolytica* and 100.4, 63.7, 59.7 and 215.9 µg/mL, respectively against *G. lamblia*. Among the isolated compounds, epicatechin, catechin, β-sitosterol 3-O-β-D-glucopyranoside and tyramine revealed IC_{50} values of 1.9, 65.6, 82.2 and 54.2 µg/mL, respectively against *E. histolytica* and 1.6, 33.9, 61.5 and 68.9 µg/mL, respectively against *G. lamblia* [252]. The antiprotozoal potential of another traditional plant, *Rubus coriifolius* and its isolated compounds were investigated by Alanís et al. against *E. histolytica* and *G. lambia*. In the crude fractions, dichloromethane–methanol was most active with IC_{50} values of 11.6 and 55.6 µg/mL, respectively

against *E. histolytica* and *G. lamblia*. Whereas, the isolated compounds including epicatechin, catechin, nigaichigoside, *β*-sitosterol-3-*O*-*β*-D-glucopyranoside, hyperin, gallic acid and ellagic acid exhibited IC_{50} value of 1.9, 65.5, 111.9, 82.16, 143.6, 220 and 56.5 µg/mL, respectively against *E. histolytica* and 1.6, 34.0, 123.6, 61.5, 49.2, 70.3 and 24.9 µg/mL, respectively against *G. lamblia* [253].

5.3. Toxoplasma gondii

Toxoplasmosis is a parasitic infection caused by *Toxoplasma gondii* and transmitted from infected pregnant women and contaminated food and is a major cause of foodborne hospitalization and death [254]. Meat from various sources including pork, cattle, wild game meat, poultry meat, lamb if not properly cooked and vegetables contaminated with oocysts, infected water and feces can cause transmission of toxoplama infection [255]. Proper cleansing, cooking of meat and washing of fruits and vegetables can significantly reduce the risk of toxoplasmosis. Immunocompromised and organ transplant individuals are at more risk to develop this infection. Several toxoplasmosis outbreaks in Korea are reported to be linked with the use of uncooked pork [256]. Toxoplasmosis is reported as a major cause of neurologic infections in HIV infected individuals [257]. Toxoplasmosis is reported as the second major cause of foodborne infections and the fourth major cause of hospitalization and deaths in the United States [4]. In Greece, toxoplasmosis has been reported among the top five contributors of foodborne infections, leading to major disabilities and deaths [258].

Several studies regarding the efficacy of natural products against toxoplasmosis have been reported. In a study, Youn et al. reported the antiparasitic potentials of traditionally used plant extracts against *Toxoplasma gondii* and *Neospora caninum* [259]. Solvent extracts of *Sophora flavescens* Aiton, *Torilis japonica* (Houtt.) DC., *Ulmus macrocarpa* Hance, *Sinomenium acutum* (Thunb.) Rehder & E.H.Wilson and *Pulsatilla koreana* (Yabe ex Nakai) Nakai ex T. Mori collected from South Korea were tested. Among the tested herbs, *T. japonica* exhibited significant inhibitory potential against *T. gondii* by inhibiting parasite proliferation from 54% to 99% at 19.5–156 ng/mL; S. *flavescens* extracts restrain *T. gondii* growth by 27.2–98.7% at a concentration ranging from 39-ng/mL to 156 ng/mL. Extracts from other plants including *Pulsatilla koreana*, *U. macrocarpa* and *S. acutum* showed moderate antiparasitic activity against *T. gondii*. Wright et al. tested the effectiveness of isolated compounds from *Simarouba amara* and *Brucea javanica* fruits against *Toxoplasma gondii*, *E. histolytica* and *Giardia intestinalis*. Among the tested compounds, ailanthinone, bruceantin, bruceine B, bruceine C, bruceine D, brusatol, glaucarubinone and quassin exhibited IC_{50} values of 0.0251, 0.0115, 0.75, 0.842, 7.56, 0.179, 0.374 and 111 µM, respectively [260].

In a study, Choi et al. tested methanolic extracts from fifteen traditional herbs against *T. gondii*. Among the tested samples, *Sophora flavescens*, *Zingiber officinale*, Meliae Cortex, *Acorus gramineus* Aiton, *Dryopteris crassirhizoma* Nakai and *Glycyrrhiza glabra* were potent and exhibited EC_{50} values of 0.20, 0.18, 0.77, 0.11, 0.15 and 0.13 mg/mL, respectively against *Toxoplasma gondii* [261].

5.4. Cryptosporidium

Cryptosporidium spp. belongs to the family, *Cryptosporidiidae*. The most common species that cause human infection are the *Cryptosporidium parvum* and *Cryptosporidium hominis*. They can be transmitted from animals, human-to-human, water, food, and tend to cause waterborne outbreaks. The clinical manifestation in immunocompetent patients is self-limiting when compared to immunocompromised individuals where it causes chronic diarrhea not responding to treatment [262]. *Cryptosporidium* spp. are well recognized as causes of diarrheal disease and is increasingly identified as an important cause of morbidity and mortality worldwide [263]. The ethanolic extract from olive (*Olea europaea*) pomace, after oil pressing and phenol recovery, reproducibly inhibited *Cryptosporidium parvum* development (MIC = 250–500 µg/mL, IC_{50} = 361 (279–438) µg/mL, IC_{90} = 467 (398–615) µg/mL) [264]. In an in vivo study, the extract of *Curcuma longa* L. had the highest effect on *Cryptosporidium* oocysts shedding. The inhibitory effect was observed at a rate of 100% on the 7th day of treatment at 750 mg/kg and on the 5th day at 1000 mg/kg in the watery extracts. At a rate of 100% on the 4th day at 1000 mg/kg

in alcoholic extracts [265]. Potential cryptosporicidal effects have been observed for blueberry with its polyphenolic compounds, cinnamon with its phenolic compounds and onion with its flavonoids and sulfide compounds, garlic with its allicin, mango with its mangiferin, olive pomace with its oleuropein, pomegranate with its polyphenols and tannins and oregano with its carvacrol especially against *Cryptosporidium parvum* and *Cryptosporidium hominis* [266]. The anti-*Cryptosporidium* efficacies of various plant extracts were evaluated in four groups of age-matched neonatal Swiss albino mice. There was a 100% reduction in *Cryptosporidium* oocyst excretion in stool and copro-DNA of *O. europaea*-treated infected mice after 2 weeks. Thus, the plant of *O. europaea* is a promising natural therapeutic for cryptosporidiosis [267].

A detailed list of antiprotozoal activity of important medicinal plant extract and phytochemicals against foodborne parasites is provided in Table 1. Chemical structures of some of the plants derived bioactive compounds are given in Figure 1.

Table 1. Summary of effects of plant extracts and phytochemicals against foodborne parasites.

Plant Source	Part Used	Effective against	Mechanism/IC_{50}	Reference
Allium sativum	Crude methanolic eextract	*G. intestinalis*	300 µg/mL ↓ Parasite motility ↓ Flagellar movement ↑Trophozoite swelling ↓Transmembrane electrochemical gradient ↓ Osmoregulation ↑ Morphologic changes in the ventral disc	[33]
	Allyl mercaptan Diallyl disulfide Diallyl sulfide Allyl alcohol Dimethyl disulfide	*G. intestinalis*	37 µg/mL 100 µg/mL 1300 µg/mL 7 µg/mL 200 µg/mL	[33]
	Aqueous extract commercial capsule	*G. lamblia*	↓Giardiasis symptoms ↓*Giardia* stool content	[211]
	Allicin	*G. lamblia*	↓ Cysteine proteases ↓ *Giardia* waste products	[212,213]
Piper longum	Crude ethanolic extract and aqueous extract of fruit powder	*G. lamblia*	100% Lethality ↓ Trophozoites count	[215]
Piper longum and *Butea monosperma*	Pippali Rasayana Formulation at 225, 450, 900 mg/kg	*G. lamblia*	62%, 79%, 98% Parasite clearance ↑ Macrophage phagocytic action ↑Macrophage migration index ↑Host immune system ↑Clearance of parasite wastes	[216]
	Pippali Rasayana Formulation 1 g T.D.S	*G. lamblia*	↑Giardia inhibition (92%) ↓Diarrhea frequency ↓Stool mucous content ↓Leukocyte migration	[217]
Coptis chinensis, *Berberis vulgaris*, *Berberis aristata*, *Berberis aquifolium*, *Hydrastis canadensis*	Crude extracts, Berberine	*G. lamblia*	↑Morphologic changes in trophozoites ↑ Trophozoites Swelling ↑Glycogen deposition ↓Giardia stool content	[221–224]
Quercus robur, *Hamamelis virginiana*, *Croton lechleri*	Epicatechin, Quercetin, Epigallocatechin, Apigenin, Kempferol	*G. lamblia*	↑Giardia inhibition	[225–227]
Origanum vulgare, *Psidium guajava*, *Mangifera indica*, *Plantago major*	Flavonoids and tannins rich crude extracts	*G. lamblia*	↑Antigiardial activity	[228]

Table 1. *Cont.*

Plant Source	Part Used	Effective Against	Mechanism/IC_{50}	Reference
Geranium mexicanum, Helianthemum glomeratum, Cuphea pinetorum and *Rubus coriifolius*	Kempferol Tiliroside Epicatechin	*G. lamblia*	2.05 µmol/kg 1.42 µmol/kg 0.07 µmol/kg	[229]
Geranium mexicanum	Dichloromethane-methanol extract	*E. histolytica* *G. lamblia*	79.2 µg/mL 100.4 µg/mL	[252]
	Ethyl acetate extract	*E. histolytica* *G. lamblia*	66.7 µg/mL 63.7 µg/mL	
	Aqueous extract	*E. histolytica* *G. lamblia*	221.6 µg/mL 215.9 µg/mL	
	Epicatechin	*E. histolytica* *G. lamblia*	1.9 µg/mL 1.6 µg/mL	
	Catechin	*E. histolytica* *G. lamblia*	65.6 µg/mL 33.9 µg/mL	
	β-Sitosterol 3-*O*-β-D-glucopyranoside	*E. histolytica* *G. lamblia*	82.2 µg/mL 61.5 µg/mL	
	Tyramine	*E. histolytica* *G. lamblia*	54.2 µg/mL 68.9 µg/mL	
Rubus coriifolius	Dichloromethane-methanol extract	*E. histolytica* *G. lamblia*	11.6 µg/mL 55.6 µg/mL	[253]
	Epicatechin	*E. histolytica* *G. lamblia*	1.9 µg/mL 1.6 µg/mL	
	Catechin	*E. histolytica* *G. lamblia*	65.5 µg/mL 34.0 µg/mL	
	Nigaichigoside	*E. histolytica* *G. lamblia*	111.9 µg/mL 123.6 µg/mL	
	β-Sitosterol 3-*O*-β-D-glucopyranoside	*E. histolytica* *G. lamblia*	82.16 µg/mL 61.5 µg/mL	
	Hyperin	*E. histolytica* *G. lamblia*	143.6 µg/mL 49.2 µg/mL	
	Gallic acid	*E. histolytica* *G. lamblia*	220.1 µg/mL 70.3 µg/mL	
	Ellagic acid	*E. histolytica* *G. lamblia*	56.5 µg/mL 24.9 µg/mL	
Allium sativum	Methanolic extract	*E. histolytica* *G. lamblia*	61.8 µg/mL 64.9 µg/mL	[251]
Aloysia triphylla	Methanolic extract	*E. histolytica* *G. lamblia*	113.4 µg/mL 106.9 µg/mL	
Annona cherimola	Methanolic extract	*E. histolytica* *G. lamblia*	14.8 µg/mL 146.0 µg/mL	
Artemisia absinthium	Methanolic extract	*E. histolytica* *G. lamblia*	72.3 µg/mL 135.4 µg/mL	
Artemisia ludoviciana	Methanolic extract	*E. histolytica* *G. lamblia*	82.2 µg/mL 95.1 µg/mL	
Bocconia frutescens	Methanolic extract	*E. histolytica* *G. lamblia*	96.4 µg/mL 79.3 µg/mL	
Cesalpinia pulcherrima	Methanolic extract	*E. histolytica* *G. lamblia*	182.2 µg/mL 49.9 µg/mL	
Carica papaya	Methanolic extract	*E. histolytica* *G. lamblia*	153.0 µg/mL 128.8 µg/mL	
Cocos nucifera	Methanolic extract	*E. histolytica* *G. lamblia*	59.6 µg/mL 44.1 µg/mL	
Chenopodium ambrosioides	Methanolic extract (Green plant) Methanolic extract (Red Plant)	*E. histolytica* *G. lamblia*	45.2 µg/mL 106.5 µg/mL	
Chenopodium murale	Methanolic extract	*E. histolytica* *G. lamblia*	90.3 µg/mL 99.8 µg/mL	
Chiranthodendron pentadactylon	Methanolic extract	*E. histolytica* *G. lamblia*	2.5 µg/mL 44.2 µg/mL	
Chrysactinia mexicana	Methanolic extract	*E. histolytica* *G. lamblia*	45.3 µg/mL 106.5 µg/mL	

Table 1. *Cont.*

Plant Source	Part Used	Effective Against	Mechanism/IC_{50}	Reference
Dorstenia contrajerva	Methanolic extract	*E. histolytica*	47.1 µg/mL	
		G. lamblia	23.3 µg/mL	
Dichondra argentea	Methanolic extract	*E. histolytica*	38.3 µg/mL	
		G. lamblia	284.7 µg/mL	
Geranium mexicanum	Methanolic extract	*E. histolytica*	139.9 µg/mL	
		G. lamblia	267.1 µg/mL	
Hippocratea excelsa	Methanolic extract	*E. histolytica*	233.2 µg/mL	
		G. lamblia	72.7 µg/mL	
Lippia alba	Methanolic extract	*E. histolytica*	58.1 µg/mL	
		G. lamblia	109.4 µg/mL	
Lygodium venustum	Methanolic extract	*E. histolytica*	178.4 µg/mL	
		G. lamblia	74.3 µg/mL	
Matricaria recutita	Methanolic extract	*E. histolytica*	102.1 µg/mL	
		G. lamblia	67.1 µg/mL	
Ocimum basilicum	Methanolic extract	*E. histolytica*	41.7 µg/mL	
		G. lamblia	79.4 µg/mL	
Punica granatum	Methanolic extract	*E. histolytica*	29.5 µg/mL	
		G. lamblia	198.5 µg/mL	
Ruta chalepensis	Methanolic extract	*E. histolytica*	61.9 µg/mL	
		G. lamblia	37.8 µg/mL	
Schinus molle	Methanolic extract	*E. histolytica*	82.4 µg/mL	
		G. lamblia	154.7 µg/mL	
Senna villosa	Methanolic extract	*E. histolytica*	133.1 µg/mL	
		G. lamblia	32.1 µg/mL	
Thymus vulgaris	Methanolic extract	*E. histolytica*	90.9 µg/mL	
		G. lamblia	68.7 µg/mL	
Sophora flavescens	Alcoholic extracts	*T. gondii*	99.7%	[259]
Torilis japonica, *Ulmus macrocarpa*, *Sinomenium acutum*			99.9%	
			99.8%	
Pulsatilla koreana			99.7%	
Sophora flavescens			99.6%	
Meliae cortex	Methanolic extracts	*T. gondii*	0.20	[261]
Acorus gramineus			0.77	
Dryopteris crassirhizoma			0.11	
Glycyrrhiza glabra			0.15	
Zingiber officinale			0.13	
			0.18	
Brucea javanica *Simarouba amara*	Ailanthinone	*T. gondii*	0.02 µM	[260]
	Bruceantin		0.01 µM	
	Bruceine A		NT	
	Bruceine B		0.75 µM	
	Bruceine C		0.84 µM	
	Bruceine D		7.56 µM	
	Brusatol		0.17 µM	
	Glaucarubinone		0.37 µM	
	Quassin		11 µM	
	Ailanthinone	*E. histolytica*	0.13 µM	[260]
	Bruceantin		0.03 µM	
	Bruceine A		0.22 µM	
	Bruceine B		0.63 µM	
	Bruceine C		0.49 µM	
	Bruceine D		0.06 µM	
	Brusatol		0.32 µM	
	Glaucarubinone		1130 µM	
	Ailanthinone	*G. intestinalis*	45.44 µM	[260]
	Bruceantin		1.20 µM	
	Bruceine A		8.84 µM	
	Bruceine B		NT	
	Bruceine C		NA	
	Bruceine D		NA	
	Brusatol		6. I7 µM	
	Glaucarubinone		12.42 µM	
Brucea antidysenterica	Bruceantin	*E. histolytica*	0.01 µg/mL	[243]
Brucea javanica, *Simarouba amara*	Bruceantin	*E. histolytica*	0.01 µg/mL	[245]
	Glaucarubol		5 µg/mL	

Table 1. *Cont.*

Plant Source	Part Used	Effective Against	Mechanism/IC_{50}	Reference
Morinda morindoides	Quercetin	*E. histolytica*	105.2 µg/mL	[247]
	Quercetin-7,4-dimethylether		70.3 µg/mL	
	Quercetin-3-*O*-rutinoside		120.7 µg/mL	
	Quercetin-3-*O*-rhamnoside		93.2 µg/mL	
	Kempferol-3-*O*-rhamnoside		64.7 µg/mL	
	Kempferol-3-*O*-rutinoside		72.5 µg/mL	
	Kempferol-7-*O*-rhamnosyl-sophoroside		>125 µg/mL	
	Chrysoeriol-7-*O*-neohesperidoside		>125 µg/mL	
	Apigenin-7-*O*-glucoside		22.3 µg/mL	
	Luteolin-7-*O*-glucoside		37.4 µg/mL	
	Kempferol		10.3 µg/mL	
	Apigenin		12.7 µg/mL	
	Luteolin		17.8 µg/mL	
	Gaertneroside		4.3 µg/mL	
	Gaertneric acid		7.1 µg/mL	
	Methoxygaertneroside		2.3 µg/mL	
	Epoxygaertneroside		1.3 µg/mL	
Justicia insularis	Leaves water extract	*E. histolytica*	>500 µg/mL	
Draceana reflexa	Leaves water extract	*E. histolytica*	62.5 µg/mL	
Costus afer	Juice	*E. histolytica*	125 µg/mL	
Vitex madiensis	Leaves water extract	*E. histolytica*	>500 µg/mL	
Cissius areloides	Leaves water extract	*E. histolytica*	>500 µg/mL	
Datura arborea	Leaves water extract	*E. histolytica*	125 µg/mL	
Morinda morindoides	Leaves water extract	*E. histolytica*	15.62 µg/mL	
Nauclea latifolia	Root-bark water extract	*E. histolytica*	125 µg/mL	[248]
	Laves water extract		>500 µg/mL	
Heinsia pulchella	Root-bark water extract	*E. histolytica*	15.62 µg/mL	
Crossopteryx febrifuga	Laves water extract	*E. histolytica*	125 µg/mL	
Pteridium aquilinum	Twigs water extract	*E. histolytica*	>500 µg/mL	
Phytollaca dodecandra	Laves water extract	*E. histolytica*	>500 µg/mL	
Mangifera indica	Stem-bark water extract	*E. histolytica*	7.81 µg/mL	
Rauwolfia obstura	Root-bark water extract	*E. histolytica*	31.5 µg/mL	
Voacanga africana	Root-bark water extract	*E. histolytica*	62.5 µg/mL	
Tithonia diversifolia	Leaves water extract	*E. histolytica*	62.5 µg/mL	
Ceiba pentandra	Stem-bark water extract	*E. histolytica*	125 µg/mL	
Dialum englerianum	Stem-bark water extract	*E. histolytica*	62.5 µg/mL	
Carica papaya	Immature seeds water extract	*E. histolytica*	62.5 µg/mL	
	Mature seeds water extract		<7.81 µg/mL	
Garcinia kola	Stem-bark water extract	*E. histolytica*	125 µg/mL	
Tetracera poggei	Leaves water extract	*E. histolytica*	>500 µg/mL	
Alchornea cordifolia	Leaves water extract	*E. histolytica*	125 µg/mL	
Bridelia ferruginea	Root-bark water extract	*E. histolytica*	62.5 µg/mL	
Euphorbia hirta	Leaves water extract	*E. histolytica*	250 µg/mL	
Hymenocardia acida	Stem-bark water extract	*E. histolytica*	31.25 µg/mL	
	Root-bark water extract		250 µg/mL	
Jatropha curcas	Leaves water extract	*E. histolytica*	31.25 µg/mL	
Maprounea africana	Leaves water extract	*E. histolytica*	62.5 µg/mL	
	Root-bark water extract		31.25 µg/mL	
Cajanus cajan	Leaves water extract	*E. histolytica*	>500 µg/mL	
Paropsia brazzeana	Root-bark water extract	*E. histolytica*	<7.81 µg/mL	
Harungana madagascariensis	Stem-bark water extract	*E. histolytica*	62.25 µg/mL	
Sida rhombifolia	Leaves water extract	*E. histolytica*	62.5 µg/mL	
Pentacletra macrophylla	Stem-bark water extract	*E. histolytica*	250 µg/mL	
Myrianthus arboreus	Leaves extract	*E. histolytica*	>500 µg/mL	
Psidium guajava	Leaves extract	*E. histolytica*	62.5 µg/mL	
	Stem-bark water extract		<7.815 µg/mL	
Ongokea gore	Stem-bark water extract	*E. histolytica*	>500 µg/mL	
Ryptolepis sanguinolenta	Root-Bark water extract	*E. histolytica*	<7.815 µg/mL	
Zingiber officinale	Ethanolic extract	*E. histolytica*	>1000 µg/mL	[249]
Boerhavia diffusa	Ethanolic extract	*E. histolytica*	>1000 µg/mL	
Tinospora cordifolia	Ethanolic extract	*E. histolytica*	1000 µg/mL	
Terminalia chebula	Ethanolic extract	*E. histolytica*	>1000 µg/mL	
Berberis aristata	Ethanolic extract	*E. histolytica*	100 µg/mL	

Table 1. *Cont.*

Plant Source	Part Used	Effective Against	Mechanism/IC_{50}	Reference
Salvia polystachya	Polystachyne A	*E. histolytica*	153.8 µg/mL	[250]
		G. lamblia	134.7 µg/mL	
	Polystachyne B	*E. histolytica*	117.0 µg/mL	
		G. lamblia	107.8 µg/mL	
	Polystachyne D	*E. histolytica*	160.6 µg/mL	
		G. lamblia	107.5 µg/mL	
	Linearolactone	*E. histolytica*	22.9 µg/mL	
		Giardia lamblia	28.2 µg/mL	
	Kaempferol	*E. histolytica*	27.7 µg/mL	
		G. lamblia	30.5 µg/mL	

NT: not tested, **NA:** not active, **↑:** Increase/activate, **↓:** decrease/inhibit, **↔:** no effect/not modulate, **CDT:** cytolethal distending toxin, **EO:** essential oils.

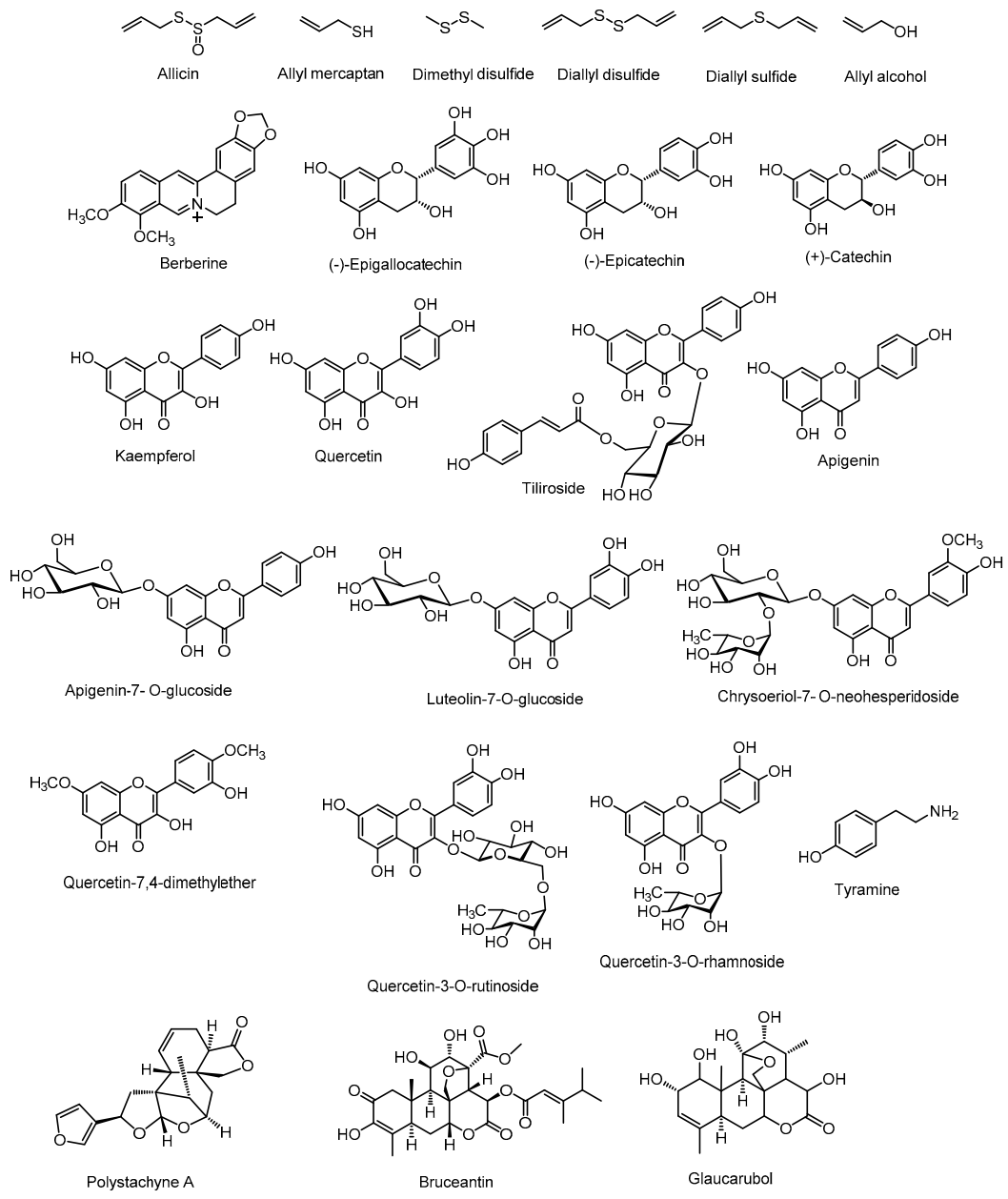

Figure 1. Chemical structures of some of the phytochemicals discussed in this manuscript.

6. Mechanisms of Antimicrobial Activity

Various mechanisms have been reported for the antimicrobial activities of medicinal plants and isolated natural antimicrobials. These natural products affect those pathways of macromolecular metabolism which are proven targets for antibiotic intervention. Among the existing antibacterial agents, it is clear that protein and cell wall biosynthesis are the targets of the widest variety of natural products [34]. The pathways of macromolecular metabolism as antimicrobial targets of natural products include inhibition of protein synthesis, inhibition of cell wall synthesis, disruption of membrane integrity, inhibition of RNA synthesis, inhibition of DNA synthesis, dysfunction of microtubules, inhibition of lipid synthesis, inhibition of cell division, dysfunction in ion uptake, reduction in protein secretion, dysfunction of RNA processing and inhibition of DNA methylation. These mechanisms have been investigated for the antimicrobial properties of medicinal plants and natural products including *Hemidesmus indicus* (L.) R. Br. ex Schult., *Leucas aspera* (Willd.) Link, *Plumbago zeylanica* L., *Tridax procumbens* (L.) L. [268], *Syzygium cumini* (L.) Skeels [269], *Combretum albidum* G.Don, *Hibiscus acetosella* Welw. ex Hiern, *Hibiscus cannabinus* L., *Hibiscus furcatus* Willd., *Punica granatum* L. and *Tamarindus indica* L. [270], 5,6,7-trihydroxyflavone (baicalein) [271], flavones [272], *Hibiscus sabdariffa*, *Rosmarinus officinalis*, *Syzygium aromaticum*, *Thymus vulgaris* [273], linalyl acetate, (+)menthol, thymol [274], *Origanum vulgare* [275], essential oils [276], caffeine [277], allspice oil, lemongrass oil, citral [278], alkaloids [279], *Boerhaavia diffusa* [280], paeonol (PA) and 1,2,3,4,6-penta-*O*-galloyl-*β*-D-glucopyranose (PGG) from *Paeonia lactiflora* Pall. [281], *Aristolochia bracteolata* Lam. [282], *Rhizophora apiculate* Blume, *Phyllanthus niruri* L., *Scutellaria baicalensis* Georgi, *Geum japonicum* L. and *Momordica charantia* L. [283]. Plants being mixture of numerous compounds can act on several targets like, inhibition of bacterial cell wall synthesis, protein synthesis and interference with microbial metabolic pathways. Hence, as a whole, the activity of crude extracts may be due to more than one antibacterial mechanism. Further, different compounds in the extract can act synergistically as well as can antagonize the effect of each other depending upon their respective concentrations. Considering the presence of large number of chemical compounds present in the extracts of medicinal plants, it is most likely that their antimicrobial activity can be attributed to more than a single specific antimicrobial mechanism.

7. Persisting Challenges

However, many plant extracts and their isolated phytochemicals have been reported to show potent activity against foodborne illness causing agents, there have not been detailed studies about their mechanism using in vivo studies. As the systematic treatment, use of oral rehydration salts and antibiotics are also of great concern for their use in foodborne illness in children and their efficacies [17], alternative therapies like herbal extracts and compounds should be used with proper caution and with the support of scientific evidence regarding the other dosage forms of these herbal products. Human gut microbiota plays a vital role in sustaining gastrointestinal health via inhibition of pathogenic microbes. The use of broad-spectrum antibiotics causes inhibition of normal flora beside pathogenic bacteria, thus provide the opportunity to other pathogens and secondary infections emerge [284,285]. On the other hand, herbal products like tea and many herbs and vegetables are also reported to be the source of foodborne microorganisms [286,287]. Herbal products contaminated with mycotoxins, bacterial toxins, as well as bacterial strains are reported to cause foodborne infections. For instance, herbs contaminated with *Salmonella* is a major cause of foodborne infections in North America and Europe [286]. Subsequently, several approaches were adopted to decontaminate these products including irradiation which effectively eradicate *Salmonella, S. aureus, Comphylobacter* sp., *Listeria and E. coli* without affecting nutritional properties of these products [288].

Natural product research has broadly emerged into two major fields including ethnopharmacology and toxicology. However, both strategies were successful regarding the discovery of numerous drugs against several diseases, yet the development of antimicrobial agents from these sources is limited [289]. To augment the development of antimicrobial agents from the herbal source it is important to elucidate exact molecular antimicrobial mechanisms of these products. This information will enable researchers

not only to have better control of these microbes but will use modern technologies to synthesize more potent and effective derivatives. Moreover, studies regarding the efficacy of these agents in combination with other herbs and drugs is limited. For instance, a combination of several EOs in combined form does not produce the synergistic antimicrobial effect and subsequently their use as a food preservative is limited. These agents can also interact with food ingredients which significantly affect their quality. Like, EOs beside their great beneficial effects has limited efficacy as a food preservative due to the intense aroma and toxicity issues. EOs used as preservatives in food are reported to change organoleptic properties of foodstuff and their higher doses can produce severe toxicological responses [290,291].

8. Conclusions

Foodborne diseases are one of the main causes of morbidity and mortality, especially in low-income countries having poor sanitation and inadequate healthcare facilities. Several plant extracts and phytochemicals including catechin, epigallocatechin, apigenin, kempferol, berberine, tiliroside and quercetin were found to be highly effective to control the growth of these foodborne pathogens causing infections in in vitro systems. Various mechanisms have been reported for the antimicrobial activities of medicinal plants and they affect those pathways of macromolecular metabolism which are the proven targets for antibiotic intervention. Medicinal plants can impact more than a single specific antimicrobial target as they contain a large number of biochemical phytoconstituents. Once utilized, natural products with antimicrobial properties can be effective for the prevention and treatment of foodborne diseases and can increase the shelf life of food products. However, most of the studies covered in this review are performed using in vitro assays. Further detailed in vivo studies for exploration of effectiveness and mechanism of their activities are necessary. Along with that, most of these studies were performed in the in vitro systems without the addition of food, simulated gastric and/or intestinal juice. Various such factors may alter the activity of these extracts and compounds when used in complex biologic systems such as in vivo and human studies. Future studies should also focus on the pharmacokinetic and toxicological aspects of plant extracts and phytochemicals.

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