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A Literature Review—*Khaya senegalensis*, *Anacardium ouest* L., *Cassia sieberiana* DC., *Pterocarpus erinaceus*, *Diospyros mespiliformis*, *Ocimum gratissimum*, *Manihot esculenta*, *Vernonia amygdalina* Delile, *Pseudocedrela kotschyi* and *Daniellia oliveri* Possess Properties for Managing Infectious Diarrhea

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Abstract

The rise in antimicrobial resistance increases researchers' interest in medicinal plants used for traditional treatment of infectious diseases. The study is based on ten (10) medicinal plants mostly cited in the treatment of diarrhea in West Africa: *Khaya senegalensis*, *Anacardium ouest* L., *Cassia sieberiana* DC., *Pterocarpus erinaceus*, *Diospyros mespiliformis*, *Ocimum gratissimum*, *Manihot esculenta*, *Vernonia amygdalina Delile*, *Pseudocedrela kotschyi*, *Daniellia oliveri*. The objective is to make a review on ethnopharmacological, pharmacological, toxicological and chemical data that enhance these medicinal plants in the fight against diarrheal infections. Specific keywords were used for bibliographic research in Google Scholar, Science Direct, PubMed Directory of Open Access Journals (DOAJ) and other databases. Generalities relating to diarrheal infections and scientific data on the ten selected plants in the fight against diarrheal infections were sought. From the results, it emerges that each of the ten plants has been listed as useful in the traditional treatment of diarrheal infections. Antibacterial tests showed their effectiveness on

several bacterial strains responsible for bacterial infections. The chemical components identified as responsible for the activity of medicinal plants belong to the groups of saponins, flavonoids, alkaloids, tannins and others. An optimal use of these medicinal plants in the fight against diarrheal infections requires deep pharmacological, chemical and toxicological studies.

Keywords

Infectious Diarrhea, West Africa, Medicinal Plants

1. Introduction

World Health Organization (WHO) defined diarrhea as "the passage of three or more loose or liquid stools per day (or more frequent passage than is normal for the individual)". Diarrhoeal diseases are one of the major causes of malnutrition and the second leading cause of death among children under five, with nearly 525,000 child deaths each year [1]. Diarrhoea is usually part of the symptoms of a gastrointestinal infection, which can be caused by a bacterium, virus or parasite. In sub-Saharan Africa, infectious diarrhoea is a major cause of morbidity and mortality [2].

A priori, most cases of bacterial gastroenteritis do not require antimicrobial treatment, but there is a high level of antimicrobial use [3]. In "WHO guidelines for the clinical management of childhood diarrhea" [4], Antibiotics are only necessary in cases of bloody diarrhoea, suspected cholera or associated septicaemia. However, this prescription is not formally respected as there is an increase in the use of antibiotics in the treatment of diarrhoea. In a study in the Central African Republic, 40% of children before arrival and 70% during hospitalization received antibiotic treatment [2]. This situation is likely to lead to problems of antimicrobial resistance. Many enteric bacteria became resistant to antibiotics [5], which seriously hampers the management of infectious diarrhea.

Medicinal plants, therefore, constitute a precious heritage for humanity and more particularly for the majority of poor communities in developing countries. More than 80% of the population continues to treat themselves with medicinal plants in Africa. This situation leads to the consideration of medicinal plants as an alternative to antibiotics, and as a solution against antimicrobial resistance.

Khaya senegalensis [6] [7] [8], *Anacardium occidentale* L. [9] [10], *Cassia sieberiana* DC [11] [12], *Pterocarpus erinaceus* [13] [14], *Diospyros mespiliformis* [15], *Ocimum gratissimum* [16], *Manihot esculenta* [17] [18], *Vernonia amygdalina Delile* [19], *Pseudocedrela kotschyi* [20] and *Daniellia oliveri* [21] are ten plants from West African Pharmacopoeia, cited in several works for their usefulness in the treatment of infectious diarrhea. A synthesis of their monographs will make it possible to review the available data, which will allow research perspectives to emerge and points to be explored in greater depth in order to valorize

them in the fight against infectious diarrhea.

2. Overview about Infectious Diarrhea

2.1. Definition

Diarrhea is defined as "the passage of three or more loose or liquid stools per day (or more frequent passage than the normal for the individual)" [1]. It is simply a modified movement of ions and water along an osmotic gradient. Under normal conditions, the gastrointestinal tract absorbs large amounts of fluids and electrolytes. It is estimated that 100 to 200 ml of fluids and electrolytes are excreted in the stool from the 8 to 9 litres of fluid presented in the intestine each day. Pathogens in the intestine (bacteria, viruses, parasites, etc.) can, for one reason or another, contribute to altering this balance towards a net secretion: this is called diarrhoeal disease [22]. Most of these pathogens responsible for diarrhoeal diseases are spread by faeces contaminated water.

2.2. Causes and Pathophysiology of Infectious Diarrhea

Infections are more frequent when there is a lack of sanitation and/or hygiene and safe water [1]. Infection with bacteria such as enterotoxigenic and enteropathogenic *E. coli*, *Salmonella*, *Shigella* and V. *cholerae*, is one of the main causes of diarrheal diseases in developing countries [5]. *Rotavirus*, *Escherichia coli*, *cryptosporidium* and *Shigella* species are among the most reported pathogens [1] [23]. In a study performed in Bangui, including 333 cases and 333 controls, the most attributable cases of hospitalized diarrhea were due to *rotavirus*, *Shigella/EIEC*, *Cryptosporidium parvum/hominis*, *astrovirus* and *norovirus* [2]. Two or more pathogens may be involved at the same time: this is called polymicrobial infection. For a micro-organism to be pathogenic, several conditions must be met: 1) the need to ingest a minimal inoculum infecting; 2) fighting the barrier flora with which it competes; 3) crossing the mucus film and adhering to enterocytes (by various ways) [24]. After this step, the enteric pathogens, in depending on the genetic information they have, will interfere with the physiologically normal mechanisms for regulating the movement of water and electrolytes by taking over intracellular control of the regulation of the concentration of cyclic adenosine monophosphate (cAMP), cyclic guanosine monophosphate (cGMP), intracellular Ca^{2+} ion concentration, or by modifying the architecture of the enterocyte cytoskeleton. In addition, there are several particularities depending on the microorganisms involved [25].

2.2.1. *Escherichia coli*

Escherichia coli represents 80% of the aerobic intestinal flora of humans. It is both a commensal bacterium and an enteropathogenic bacterium through the expression of acquired and/or constitutive virulence factors. There are six *E. coli* pathovars capable of enteropathogenic potential: 1) Enterotoxigenic *E. coli* (ETEC) responsible for childhood diarrhea in developing countries and trav-

eler's diarrhea; 2) Entero-invasive *E. coli* (EIEC), responsible for dysentery close to shigellosis, 3) Enterohemorrhagic *E. coli* (EHEC), found in hemorrhagic colitis and typical hemolytic uremic syndrome (HUS), 4) Enteropathogenic *E. coli* (EPEC) are the cause of persistent childhood diarrhea which is often epidemic in developing countries, 5) Diffuse adhesion *E. coli* (DAEC) and 6) *E. coli* enteroaggregative (EAggEC) which cause persistent watery diarrhea in children [26].

2.2.2. *Salmonella spp.*

Non-typhoid *Salmonella* species are invasive bacteria that use a type III secretion system to deliver a variety of effectors into intestinal epithelial cells [27]. They are one of the 4 main causes of diarrhoeal diseases in the world [28].

2.2.3. *Shigella spp.*

Shigella produces Shiga toxins and stimulates an inflammatory infiltrate and watery and/or bloody diarrhea [29].

Shigella species cross the epithelial barrier by M cells. After elimination of the microphages, they bind lipoprotein to TLR2 (a Toll-like receptor encoded by the TLR2 gene and involved in bacterial recognition), resulting in the production of IL-1β (a chemo-attractor). Following translocation through M cells, LPS can bind to basolateral TLR4, resulting in the production of IL-6 and IL-8. IL-8 is a potent chemo-attractor for polymorphonucleocytes (PMN). PMNs are responsible for the secretion of Cl^- and can also cause ulceration of the epithelium, resulting in a decrease in the surface area for absorption but also maximizing permeability and allowing easy access of the intestinal flora to the basolateral surface of the cells, thus promoting inflammation [30] [31] (**Figure 1**).

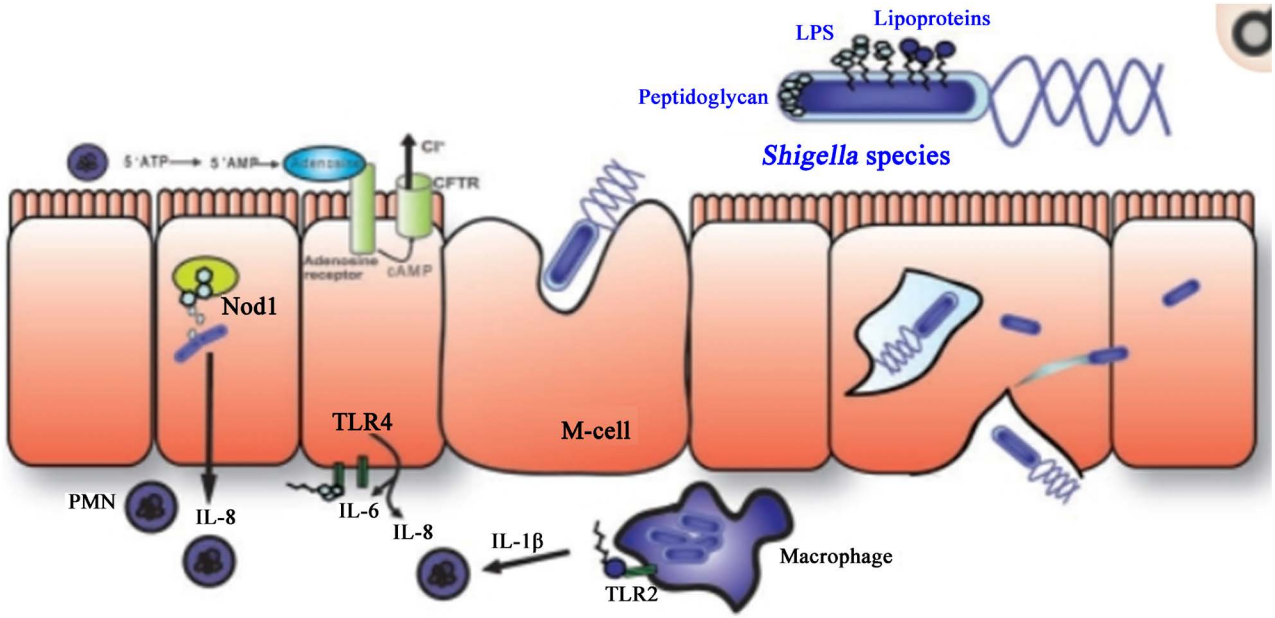

Figure 1. Invasion and inflammation caused by *Shigella* [5].

2.2.4. *Vibrio cholerae*

V. cholerae causes diarrhea using its major virulence factor (cholera toxin (CT)), which binds to apical GM1 receptors on host epithelial cells, thereby allowing translocation of the toxin into the cell [32]. One of the sub-units of the TC causes the production of cAMPs. cAMP activates PKA which phosphorylates the cystic fibrosis transmembrane conductance regulator (CFTR) domain. There is then an increase in Cl secretion, a decrease in Na^+ absorption, where the activity of NHE2 and NHE3 (both apical sodium transporters) is reduced together, resulting in increased levels of NaCl in the intestinal lumen, either by increasing secretion or decreasing absorption [33] [34] [35] [36] (**Figure 2**).

2.2.5. *Clostridium difficile*

C. difficile often causes debilitating diarrhea. *C. difficile* produces toxins A and B (TcdA and TcdB), as well as an additional toxin called binary toxin [37].

TcdA alters the cytoskeleton and disrupts tight junctions, resulting in loss of epithelial barrier function. TcdA and TcdB thus pass easily through the epithelium with the preferential binding of TcdB to the basolateral cell membrane. They induce the production of pro-inflammatory cytokines, increased vascular permeability, recruitment of monocytes and neutrophils, apoptotic cell death of epithelial cells and connective tissue degradation. All this leads to pseudomembrane formation and diarrhea. In addition, the toxin-induced release of certain neuropeptides stimulates the central nervous system to induce fluid secretion, which is responsible for diarrhea [22] (**Figure 3**).

2.2.6. Viral Diarrhea

Viral diarrhoea is watery and often leads to dehydration that needs to be compensated for with oral rehydration solutions [38]. The main pathogens responsible

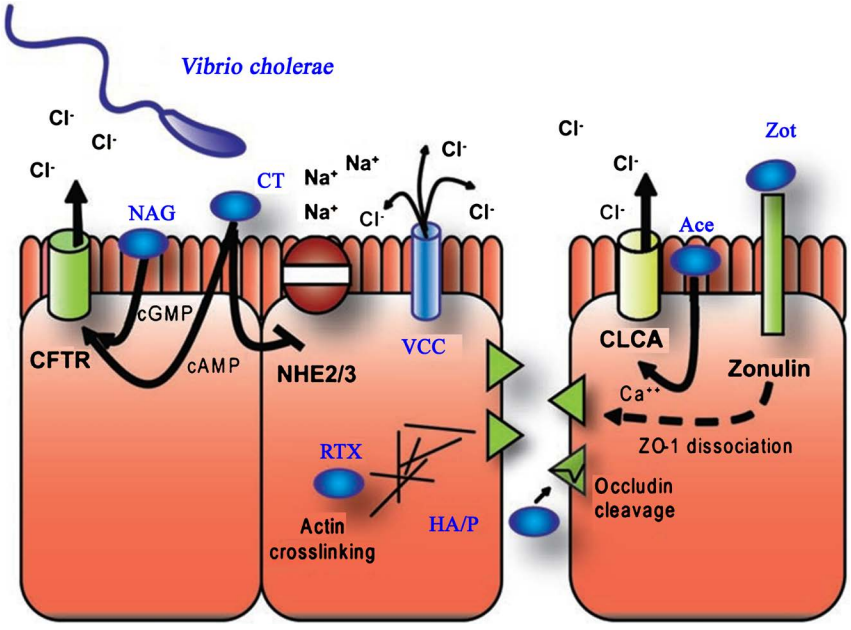

Figure 2. Mechanisms underlying *V. cholerae*-induced diarrhea [22].

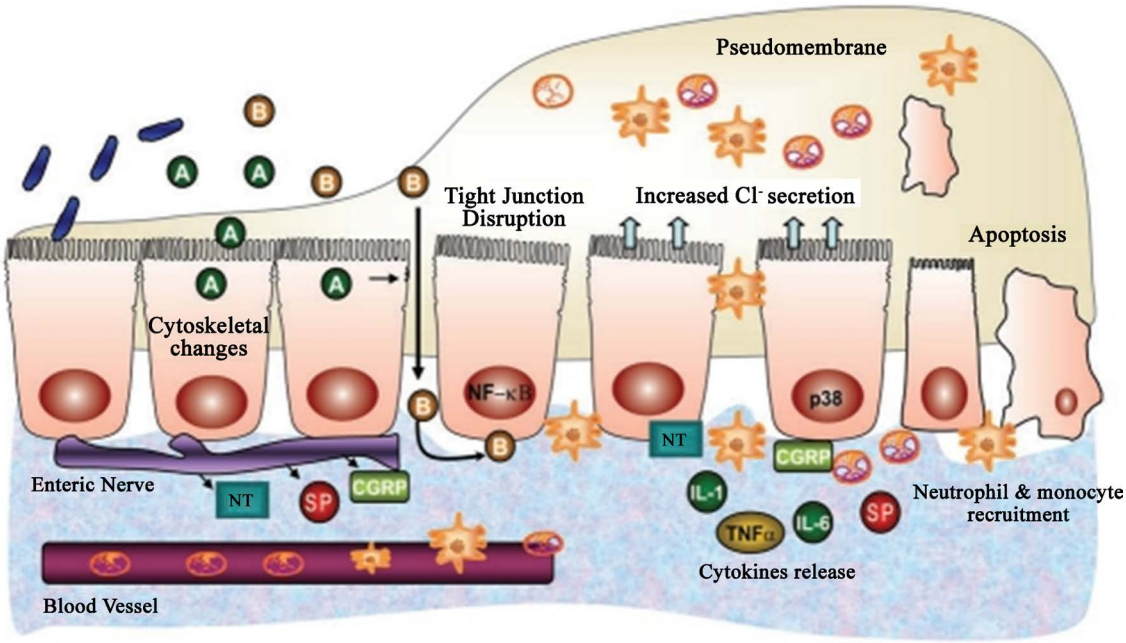

Figure 3. Pathogenesis of *C. diffcile*-associated diarrhea [22].

for infectious diarrhea *are rotaviruses*, *noroviruses*, *sapoviruses*, *adenoviruses*, and *astroviruses*. Among them, rotaviruses are the most important, causing severe diarrhea and mortality in children worldwide [5] [39]. They probably account for 50% of viral causes [38].

2.2.7. Parasite-Mediated Diarrhea

Parasite such as *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum* are common causes of water-borne diarrhea. For example, *Giardia* tropozoites use a ventral adhesive disc to adhere strongly to the epithelial surface of the intestine. In this way, they decrease the surface area for absorption. Absorption of NaCl and glucose due to this are therefore minimized, resulting in diarrhea [22] [40].

3. Management of Infectious Diarrhea

The management strategy for diarrhea must give priority to the assessment of the level of dehydration and its correction, using oral rehydration solutions with low osmolarity. Zinc supplementation is recommended for children with gastroenteritis living in poor conditions. It is only for moderate to severe bloody diarrhoea that antimicrobial therapy is sought in children. Breastfeeding is fundamental for the prevention of infectious diarrhoea but also during diarrhoea [23].

According to "Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea", the empiric antimicrobial therapy in adults should be either a fluoroquinolone such as ciprofloxacin, or azithromycin, depending on the local susceptibility patterns and travel history (strong, moderate). Empiric therapy for children includes a third-generation cephalosporin for infants < 3 months of age and others with

neurologic involvement, or azithromycin, depending on local susceptibility patterns and travel history (strong, moderate) [41].

4. Involvement of Medicinal Plants in the Management of Infectious Diarrhea

In the African context, traditional medicine can be defined as a set of knowledge, preparation techniques and uses of natural substances. It is based on the socio-cultural and religious foundations of African communities, more specifically the experience of using and transmitting knowledge from generation to generation. It is used for the diagnosis, prevention or treatment of an imbalance in physical, mental or social well-being [42]. Diarrheal infections are among the many diseases treated by traditional medicine.

Khaya senegalensis [6] [7] [8], *Anacardium occidentale* L. [9] [10], *Cassia sieberiana* DC [11] [12], *Pterocarpus erinaceus* [13] [14], *Diospyros mespiliformis* [15], *Ocimum gratissimum* [16], *Manihot esculenta* [17] [18], *Vernonia amygdalina Delile* [43], *Pseudocedrela kotschyi* [20] and *Daniellia oliveri* [21] are ten plants from West African Pharmacopoeia, cited in several works for their usefulness in the treatment of infectious diarrhea.

4.1. *Khaya senegalensis*

4.1.1. Bioactives Compounds

Saponin, Flavonoids, alkaloid, and tannin were found in Water and ethanol extract of stem (bark) and leaf of *Khaya senegalensis* [6]. *K. senegalensis* also contain glycosides, steriods, terpenoids and anthraquinones [44] [45]. Celestine *et al.* [46] identified by Gas Chromatography-Mass Spectrometry (GC-MS) oleic acid, 1,2,3-benzenetriol, 1-flourodecane, n-Hexadecanoic acid, 1,E-11,Z-13-octadecatriene in aqueous stem bark extract.

4.1.2. Toxicity Study

According to Nwosu *et al.* [7], the aqueous extract of the leaves of *Khaya senegalensis* is not toxic. According to a study carried out by these authors in Nigeria on rats, the LD50 of the extract is higher than 3000 $mg{\cdot}kg^{-1}$ body weight. Although other studies revealed that chronic treatment rather induces an increase of these parameters [47]. Long treatments also cause elevation of serum creatinine and blood urea [7] which reflects renal dysfunction. Adakole and Balogun suspected a risk of acute ecotoxicity of crude (ethanol and aqueous) leaves of *K. senegalensis* [8]. The study focused on the sensitivity of chironomid larvae to extracts in the aquatic environment. LC_{50} of 1.39 g/L and 1.20 g/L were obtained (for aqueous and ethanol extracts, respectively). In addition, deformations of mouthparts and other morphological changes were observed [48].

4.1.3. Antibacterial Properties

Scientific data reported that leaves and stem-bark of *K. senegalensis* were used for the cure of diarrhea [49]. Extracts were active on *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Streptococcus spp.*, *Salmonella spp.*

and *Bacillus subtilis*. Aliyu *et al.* [45] reported an Minimal Inhibitory Concentration (MIC) of 50 mg/ml for *K. senegalensis* extract on *E. coli*. The medicinal plant thus has a potential to be valorized in the fight against the diarrhoeic infections.

4.2. *Anacardium occidentale L.*

4.2.1. Bioactives Compounds

Ethanol extracts of the leaves, stem bark, and flowers are rich in bioactive secondary metabolites [9]. They contain phenolic compounds, saponins, alkaloids, and tannins [10] [50] [51].

4.2.2. Toxicity Study

According to Nzi *et al.* [52] which conducted 30-day subacute toxicity tests, the crude extract did not produce toxic symptoms in rats at doses up to 2000 mg/kg. Significant biochemical changes were not observed.

4.2.3. Antibacterial Properties

Folk medicine in West Africa as well as in South America uses decoction or the leaves infusion to treat gastrointestinal disorders (acute gastritis, diarrhea), mouth ulcers, throat problems [53]. The antimicrobial effect of an 80% ethanol extract on cashew leaves, has been described by Goncalves *et al.* [53]. Another study carried out by da Silva *et al.* [9] confirmed antimicrobial activity. 16 mg/ml of leaf methanol extract of *A. occidentale* inhibited *Salmonella* Typhi and *E. coli*, with inhibition diameters of 17 and 20 mm, respectively [51].

4.3. *Cassia sieberiana* DC

4.3.1. Bioactives Compound

Methanol extract of *C. sieberiana* leaves contains flavonoids, saponins, tannins, phenols alkaloids, carbohydrates, steroids/triterpenoids, cardiac glycosid, cyanogenic glycosides, reducing sugars and Anthraquinones [54] [55].

4.3.2. Toxicity Study

According to Kelechi and Favour [11] the acute toxicity test showed neither death nor sign of acute toxicity. in other respects, Toma *et al.* [55] reported that the use at a high dose (400 - 1600 mg/kg body weight) of *C. sieberiana* for a long period can cause liver damage.

4.3.3. Antibacterial Properties

Kelechi [11] reported that all doses of the methanol extract of *C. Sieberiana* significantly ($p < 0.05$) reduced the castor oil-induced enteropooling. Dichloromethane and methanol extracts of *C. sieberiana* have good antibacterial activity of *E. coli* [54].

4.4. *Pterocarpus erinaceus*

4.4.1. Bioactive Compounds

Aqueous and methanolic stem bark extract contain tannins, Saponins, alkaloid,

flavonoids, and phenols [13] [56]. Glycosides were absent in both extract while terpenoids and steroids were absent in aqueous and methanol extract respectively [13].

4.4.2. Toxicity Study

Tittikpina carried out a cytotoxicity assay of the raw extract on a human non-cancerous cell (namely MRC-5) and reported that the extracts were not toxic to MRC-5 cells [57]. Olafadehan [58] reported that a dietary tannin concentration of 60 g/kg and intake of 1.4 g/kg b.m. have no threat on animal health.

4.4.3. Antibacterial Properties

Pterocarpus erinaceus is used Nigeria and in other African savanna countries for traditional treatment of diarrhea, urethral discharges, fever and dysentery [59]. According to Tittikpina [57], All extracts and fractions tested show good activity against Gram-positive bacteria (including methicillin-resistant *Staphylococcus aureus*, MRSA) and *Pseudomonas aeruginosa* with MIC values ranging from 32 μg/mL to 256 μg/mL Methanol extract caused a significant ($p < 0.01$) reduction in wet faeces in mice in castor oil-induced diarrhea [14].

4.5. *Diospyros mespiliformis*

4.5.1. Bioactives Compound

The stem bark of *D. mespiliformis* contains alkaloids, flavonoids, Steroids, triterpenes, saponins, tannins and anthraquinones [15] [60].

4.5.2. Toxicity Study

The effects of medium term administration of crude *Diospyros mespiloformis* root extracts on some biochemical parameters were investigated in mice [61]. The outcomes are early indications that long term consumption of *D. mespiliformis* could predispose to adverse tissue effects.

4.5.3. Antibacterial Properties

Leaf decoctions are used against fever, whooping cough and wounds [62]. Barks and roots are used to treat malaria, pneumonia, syphilis, leprosy, dermatomycoses, diarrhea, facilitation of delivery and as psycho-pharmacological drug [63]. Leaf and the stem-bark extracts are effective against *Escherichia coli*, *Pseudomonas aeruginosa*, *Streptococcus pyogenes* and *Salmonella* Typhi, *Shigella spp*, *Staphylococcus aureus*, *Streptococcus pneumonia*, [64].

4.6. *Ocimum gratissimum*

4.6.1. Bioactives Compound

The chemical screening revealed the presence of phenolic mixtures, nitrogen mixtures, steroids and terpenoids. Phenolic molecules include catechin tannins, gallic tannins, flavones, free anthracene derivatives, and combined anthracenic derivatives specifically reducing mixtures [16].

4.6.2. Toxicity Study

According to Ajayi *et al* [65] the phenolic extract of *O. gratissimum* leaf had no cytotoxic effect against brine shrimp eggs and CHO-k1 cells.

4.6.3. Antibacterial Properties

Ocimum gratissimum leaves are used in the treatment of diarrhea and respiratory tract infections [66]. The essential oils extracted from fresh leaves of *Ocimum gratissimum* showed strong antibacterial activities against *Salmonella enterica* serotype Oakland and *Salmonella enterica* serotype Legon [67]. Essential oil also inhibited Klebsiella *sp*, *Salmonella enteritidis*, *Shigella flexineri* and *Escherichia coli* [68].

4.7. *Vernonia amygdalina*

4.7.1. Bioactives Compound

The leaves of *Vernonia amygdalina* contain alkaloids, gallic and cathechic tannins, flavonoids, anthocyanins, mucilages, coumarins, quinone derivatives, reducing compounds, saponins, traces of steroids and cyanogenic derivatives [43].

4.7.2. Toxicity Study

A larval cytotoxicity assay carried out by Agbankpe *et al.* [43] revealed the extracts *Vernonia amygdalina* is not cytotoxic (LC50 > 0.01 mg/ml).

4.7.3. Antibacterial Properties

Vernonia amygdalina belongs to the vegetable species most cited and used by traditional healers in the treatment of bacterial diarrhoea [43]. Extracts were active on *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Staphylococcus aureus* and *bacillus* [69].

4.8. *Manihot esculenta*

4.8.1. Bioactives Compound

Manihot esculenta contains tannins, oxalates, phytates [17].

4.8.2. Toxicity Study

Cassava (*Manihot esculenta* Crantz) contains cyanogenic glycosides. The toxic effects of the ingestion of cassava leaves are due to the action of cyanide released from these cyanogenic glycosides [18].

4.8.3. Antibacterial Properties

Various studies reported that *M. esculenta leaves* extract can be used as antibacterial agent [70].

4.9. *Pseudocedrela kotschyi*

4.9.1. Bioactives Compound

The phytochemical analysis revealed the presence of carbohydrates, reducing sugars, glycosides, flavonoids, steroids, saponins, tannins and alkaloids [20].

4.9.2. Toxicity Study

The 28-day acute oral toxicity study of *P. kotschyi* demonstrated a lack of methanol extract toxicity. Behavioral, biochemical, hematological and weight data showed no toxicity [71].

4.9.3. Antibacterial Properties

The root bark of *P. kotschyi* is used in management of gastro-intestinal diseases, fever and rheumatism in Togo and [72]. In Nigeria, the roots and leaves are used in the treatment of rheumatism and dysentery. The results of the antimicrobial activity showed that the ethyl acetate extract was effective on *Staphylococcus aureus*, *Salmonella* Typhi, *Streptococcus pyogenes*, *Candida albicans* and *Escherichia coli* [20].

4.10. *Daniellia oliveri*

4.10.1. Bioactives Compound

The phytochemical analysis revealed the presence of Steroids/terpenes, Carbohydrates/Sugars, Flavonoids and Tanins [21].

4.10.2. Toxicity Study

The acute toxicity studies for the N-butanol extract in mice (i.p) was found to be 1141.4 mg/kg and >4000 mg/kg *D. oliveri* [21].

4.10.3. Antibacterial Properties

Among the Hausa people in northern Nigeria, *D. oliveri* Hutch and Dalz (Fabaceae) is used for the treatment of diarrhoeal infections. Experimentally, in castor-oil-induced diarrhoea, variable protection between 80% and 60% has been observed for several doses. The antidiarrheal activity was comparable to that of loperamide at 5 mg/kg [21].

5. Conclusion

Due to their low toxicity, their antibacterial activity and their chemical composition, the ten plants studied have a definite potential for the fight against infectious diarrhea. However, more in-depth work is needed. It is necessary to evaluate the efficacy of the plants selected for diarrheal infections and propose galenitic formulations from the most effective plants, for the medical management of infectious diarrhea.

Consent for Publication

All authors have read and gave their consent for publication.

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Authors' Contributions

DV, HE, LBB, B-ML and DJ wrote the protocol, collected the information and did the synthesis. DV got the funding. FK, SK, AA, AM, DV and KJR wrote the draft of the manuscript. DV, BH and DJ reviewed the manuscript. All authors read and approved the final manuscript.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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