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Review Article

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Deep Insights into Herbal Plants with Potential Anti-diarrheal Drug

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ABSTRACT

Millions of people throughout the globe rely on traditional medicines as part of their alternative health care systems. In contrast to contemporary pharmaceuticals, which are single molecules that have undergone extensive testing, structural optimization, and toxicological clearance, traditional herbal remedies are multi-constituent treatments whose safety and effectiveness is dependent on the experiences of practitioners. More than 80% of today's pharmaceuticals come from natural sources (plants, bacteria, cells, etc.), either as the original molecules or as synthetic versions of the original chemicals. Diarrhea and similar gastrointestinal diseases are treated using a wide variety of medicinal herbs used in traditional medicine. The effectiveness of several of these plants in treating diarrhea in animal models has been shown by science. Unfortunately, only a small fraction of these have been subjected to rigorous clinical trial testing. Several traditional anti-diarrheal medicinal herbs are discussed, and their effectiveness in in-vivo models is highlighted. While a small number of active phytomolecules have been isolated from these plants, their potential therapeutic use and safety have not been thoroughly investigated. The prospective herbal extracts that might be researched for the discovery of new active molecules against diarrhea and other gastrointestinal illnesses are also described in this study. The development of innovative, effective, and safe phyto-medicines for fighting diarrhea and related illnesses will need rigorous clinical studies of lead plants/phyto-molecules.

Keywords: Diarrhea, Herbal, Traditional medicines, Phytochemicals, Clinical trial, Mechanism of action

1. INTRODUCTION

One of the greatest causes of death and illness in children is diarrhea, a gastrointestinal condition characterized by the passing of three or more loose or watery feces daily. Depending on the severity and length of the symptoms, diarrhea has been classified into three clinical categories: acute watery, acute bloody, and chronic [1]. Diarrhea is responsible for around 8,000,000 fatalities of children under the age of five every year [2]. In the underdeveloped world, children in sub-Saharan and south Asian nations have a greater rate of diarrhea-related mortality (78%). Researchers have calculated that people aged 5 and above have more than 2.8 billion cases of diarrhoea each year [4]. Improper absorption, intestinal microbiota, gut motility, hypersensitivity, microbial infection, metabolic error, chemical irritation, immune system, genetic factors, and various secretory stimuli, such as bacterial enterotoxins, hormones generated by endocrine neoplasms, dihydroxy bile acids, hydroxylated fatty acids, and inflammatory mediators, all play a role in the pathophysiology of diarrheal disease [5]. Breastfeeding exclusively, zinc supplements, improved cleanliness, vaccination, oral rehydration therapy, and antibiotics are all effective ways to prevent and cure diarrheal illnesses [6]. Although though deaths have decreased worldwide by more than half (from 2000 to 2013), the illness still causes a great deal of suffering. antibiotics such as tetracycline, ciprofloxacin, norfloxacin, fleroxacin, cinoxacin, erythromycin, metronidazole, ampicillin, amoxycyline, doxycycline, vancomycin, and paromomycin are used to treat acute infectious diarrhea [1]. Use of antibiotics, however, is linked to issues including immune suppression [8], allergic responses [9], and a decline in beneficial gut and mucosal microorganism [7]. Long-term antibiotic usage is associated with the expansion and stability of resistant bacteria and resistance genes [10], as well as the emergence of antibiotic-resistant pathogenic strains. Antibiotic-associated diarrhea [11] may also be caused by an overgrowth of enteropathogens such Clostridium difficile.

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Several common diseases are becoming more resistant to conventional treatment medicines, and this has rekindled scientists' interest in natural product-based medication development. For thousands of years, people have turned to the healing properties of plants as a traditional remedy for a wide range of human health issues. In fact, many pharmaceuticals now in use are derived from plants [12,13]. Plants and plant products have a long history of usage in the treatment of diarrhea and its symptoms [14,15,16]. Traditional medicinal herbs, plant extracts, and phytochemicals have been the subject of a number of scientific validation studies that have shown their therapeutic potential. The mechanism of action of several herbs used in traditional medicine has also been studied. The most popular animal model is diarrhea caused by castor oil. Barium sulfate and the Vibrio cholerae-induced diarrhea model are two more methods used to determine the effectiveness of anti-diarrheal medications alongside Magnesium sulfate. There are three processes by which castor oil causes diarrhea. The first is via boosting calcium absorption in the intestines by producing nitric oxide. The second is an increase in fluid and electrolytes in the gut lumen caused by increased prostaglandin production. Castor oil also acts by stimulating the digestive system, which results in more peristalsis. Magnesium sulfate causes diarrhea because it stimulates duodenal mucosal cholecytokinin secretion, blocking the reabsorption of sodium chloride and water. The charcoal meal test is often used to evaluate gastrointestinal propulsive motility in anti-diarrheal medication investigations. Charcoal evacuation time is measured after a meal has passed through the digestive tract and into the small intestine [17]. For the temporary alleviation of diarrhea's unpleasant symptoms, many people turn to synthetic anti-diarrheal medications such loperamide, bismuth subsalicyclate, and diphenoxylate [18]. Loperamide is known to increase water absorption from feces by slowing the movement of intestinal contents [19]. Bismuth subsalicylate has anti-diarrheal effect [20], and this medication is known to coat tissues, therefore slowing the outflow of fluids in the intestinal lumen. As an added bonus, it promotes intestinal cell fluid and electrolyte absorption, has antimicrobial and antisecretory effects [21,22], and inhibits the growth of pathogenic bacteria. Diphenoxylate's ability to prevent diarrhea stems from its slowing impact on intestinal transit [23], which occurs as a result of the drug's influence on the circular muscle activity of the gut.

Using the charcoal meal test and castor oil induced diarrhea, the anti-diarrheal potential of a number of traditionally used herbs has been assessed. This review will focus on traditional anti-diarrheal medicinal herbs and the scientific findings that back up their traditional applications. Several promising medicinal plants have been proposed for further investigation and the discovery of active compounds based on the validation results. There aren't a lot of randomized controlled studies for plant-based preparations. The active phytomolecules in a number of traditional medicinal plants have been identified via in-depth research on just a small number of these plants. The therapeutic potential of these active compounds is also summarized in this paper.

2. CLINICAL TRIALS ON PLANT PREPARATIONS WITH ANTI-DIARRHEAL ACTIVITY

There have been hardly any clinical studies of therapeutic plant products. Randomized controlled studies have been used to evaluate the anti-diarrheal effectiveness of these medicines in a variety of diarrhoeal diseases, including acute diarrhoeal illness, IBS-associated diarrhoea, and HIV-associated diarrhoea (ADD). Medical preparations derived from plants have been the subject of a number of clinical trials; these preparations are often complicated combinations of several phyto-constituents. Certain inactive ingredients may have an enhancing function in the pharmacokinetics of the active component, which may explain why these mixes are used. This is a possible explanation for the medicinal effects of the herbal preparations. To ensure uniformity in the quality and effectiveness of herbal drugs, it is crucial to address the difficulties raised by standardization recommendations made in regulatory standards.

2.1. Croton lechleri

Croton lechleri, a South American plant, is often used as a folk remedy for the treatment of diarrhea. Prepared from the latex of Croton lechleri, SP303 is an oligomeric proanthocyanidin [46]. Patients with traveler's diarrhea were included in a double-blind, randomized, placebo-controlled trial with SP-303 (Provir). Over the course of two days, 184 people (aged 17 and above) were randomly assigned to receive either 125 mg, 250 mg, or 500 mg of SP-303 or a matched placebo four times daily. In 1 in 5 instances, researchers identified enterotoxigenic Escherichia coli as the cause. Throughout the 48 hours of treatment, the diarrheal episode duration was reduced by 21%. The highest rates of partial or total recovery after treatment with SV-303 were seen at doses of 125 mg and 250 mg [24]. Patients with AIDS with diarrhea participated in a phase II randomized, double-blind, placebo-controlled research assessing SP-303's safety and effectiveness when taken orally. For the course of the experiment, 26 participants took SP-303 and 25 took a placebo. Treatment consisted of 500 mg SP-303 or placebo every 6 hours for 96 hours (4 days). It was determined that the compound was risk-free to use. The intervention group also had a significant decrease in stool weight and irregular stool frequency compared to the placebo group [26].

2.2. Camellia sinensis

One of the most popular drinks in the world is black tea, or Camellia sinensis. A randomized, double-blind clinical

experiment was conducted to determine the effects of Camellia sinensis on nonbacterial diarrhea in children. The researchers looked at variables such the plant's influence on stool consistency, volume, and frequency of defecation. Children aged 2-12 years old were included in the trial, and all had acute nonbacterial diarrhea. Participants in the experimental group also got conventional medication, which included tablets containing 500 mg of dry black tea. Patients in the control group received just regular care. There were statistically significant variations in stool volume and frequency of defecation between the intervention group and the control group after 24 hours of therapy [39]. Studies have shown that black tea may stop diarrhea just as well as the medicine loperamide. Camellia sinensis leaves have been shown to contain many phytoconstituents, including 4HPyran-4-One, 1-methyl-5-mercaptotetrazole, n-hexa decanoic acid, nDecanoic acid, Phytol, Octadecanol, and Tetradecanol. While extensive examination against pathogenic organisms responsible for diarrhea and other gastrointestinal diseases has not been carried out to far [47], the plant has been reported to demonstrate anti-microbial action against Salmonella typhi, Staphylococcus aureus, and Pseudomonas aeruginosa. Both viral and noninfectious models of diarrhea might be used to investigate the potential anti-diarrheal function of plant extracts and their phytomolecules.

2.3. Mentha piperita

The effectiveness of Mentha piperita, or peppermint, in treating diarrhea was evaluated in a randomized, double-blind, placebo-controlled clinical trial. The intervention group took an enteric-coated peppermint oil formulation, which is a kind of peppermint oil that is designed to be absorbed more slowly (Colpermin). A total of 110 people with IBS symptoms participated in the study, comprising 66 men and 44 women aged 18 to 70. Colpermin (containing 187 mg peppermint oil) or a placebo was administered to individuals three to four times daily through a single capsule. The duration of the study lasted a whole month. For every 50 patients given a Colpermin pill, 43 (83%) saw a decrease in stool frequency, but for every 49 patients given a placebo, only 16 (32%) experienced a decrease in stool frequency. Those using the Colpermin pill also reported a reduction in additional IBS symptoms compared to those taking a placebo [30]. Many different types of microorganisms, such as bacteria (Escherichia coli, Pseudomonas aeruginosa, Bacillus subtilis, Staphylococcus aureus), fungus, and yeast, are killed by the essential oil of the M. piperita plant. Peppermint oil has around 47 different phyto-components. Menthol (19.1%), isomenthone (14.8%), limonene (10.6%), iso-menthanol (8.8%), menthyl acetate (6.6%), b-pinene (5.6%), a-pinene (4.8%), 1,8-cineole (3.5%), pulegone (3%), piperitone (2.1%), and b-phellandrene (2.8%) are the most abundant components [48]. Further research is needed to determine the activity and mechanisms of action of these phyto-compounds in the treatment of diarrhea.

2.4. Psidium guajava

Historically, Psidium guajava has been used to cure gastrointestinal issues such diarrhea, dysentery, gastroenteritis, stomach pain, and indigestion with the use of the plant's leaves. A phytodrug (QG-5 ®, with a standardized concentration of flavonoids, approximated as quercetin 1 mg/500 mg) was produced from guava leaves and examined in a randomized, double-blind, placebo-controlled clinical investigation to determine the efficacy and safety of its anti-diarrheal action. Fifty patients (20-59 years old) were given 500 mg capsules of the medication every 8 hours for three days. Those who took a guava product reported much less stomach discomfort and for a shorter time [34]. Another research looked at the effects of an aqueous P. guajava leaf extract made using a hot extraction technique on factors related to the infectiousness of diarrhea. S. flexneri and Vibrio cholerae were shown to be particularly susceptible to the drug's antibacterial effects. As shown by the results of Experiment 32, adhesion and invasion of enteropathogenic E. coli and enteroinvasive E. coli and S. flexneri by HEp-2 cells were inhibited by this treatment. As one method of anti-diarrheal action [35], P. guajava's antimicrobial activity was identified against the pathogens causing enteric fever. P. guajava leaves contain a number of phytoconstituents with antimicrobial activity; they include quercetin, quercetin-3-O-β-L-arabinofuranoside, quercetin-3-O—D-arabinopyranoside, quercetin-3-O—D-glucoside, and quercetin-3-O-β-D-galactoside. Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa have all been evaluated, However, future investigations against diarrhea producing organisms may be conducted to pinpoint the precise mechanism of action [49]. Other phytoconstituents found in the plant include guajanoic acid, β-sitosterol, uvaol, oleanolic acid, and ursolic acid, all of which could be investigated using a combination of computational prediction and wet lab models to determine their potential role in the plant's anti-diarrheal efficacy [50].

2.5. Tong-xie-ning

Tong-xie-ning (TXNG) is a traditional Chinese herbal combination made out of four different plants: Paeonia lactiflora (root), Atractylodes macrocephala (rhizome), Citrus reticulate (green unripe exocarp), and Allium macrostemon (bulb) (bulb). For the purpose of determining the safety and efficacy of TXNG, a randomized, placebo-controlled, double-blind clinical study was done over the course of 10 months with a total of 60 patients who had IBS with diarrhea as the primary symptom. Significant changes in stool frequency, stool consistency, and stool appearance were all noted. By comparing the TXNG group to the placebo

group, the treatment group's time to diarrhea relief was 47% shorter (7.6 4.6 days) compared to 14.4 4.3 days [36].

2.6. Entoban

Holarrhena antidysenterica, Berberis aristata, Symplocos racemosa, Querecus infectoria, and Helicteres isora are the active ingredients in the polyherbal compound known as Entoban. The effectiveness and safety of Entoban were tested in a randomized clinical study with 150 individuals suffering from persistent diarrhea (18 –60 yrs). Comparisons were made between the effectiveness of therapy and the synthetic antibiotic metronidazole. Each capsule of Entoban (400 mg) was given to the treatment group every 8 hours for five days, whereas each tablet of Metronidazole (400 mg) was given to the control group for the same time period. Participants were assessed for symptoms such as stomach discomfort, distention, stool consistency, and the perception of incomplete evacuation in addition to the number of times they had to use the restroom per day. Complete remission of diarrhea symptoms was seen in 84.78% of the test group and 78.72% of the control group after treatment. When compared to the synthetic medicine Metronidazole, the herbal version was also determined to be less dangerous (NCT02642250). The synergistic impact of the herbal blend may account for the anti-diarrheal effectiveness shown with Entoban. Holarrhena antidysenterica has been shown to have anti-microbial and gut-stimulating properties [40, 41]. These effects are thought to be mediated, in part, by the activation of histamine receptors and the blocking of Ca2+ channels. The antidiarrheal effects of Entoban may also be due to the presence of other components, such as Berberis aristata, Symplocos racemosa, Querecus infectoria, and Helicteres isora, which may have anti-microbial properties.

3. POTENT PHYTOMOLECULES WITH PROVEN ANTI-DIARRHEAL EFFICACY

A number of phytochemicals extracted from the plants were found and evaluated for their potential to treat diarrhea. Mentha longifolia, Artemisia dracunculus, Coriandrum sativum, Origanum vulgare, Rosmarinus officinalis, Thymus vulgaris, and Zingiber officinale are only few of the fragrant plants and spice oils that contain 1,8-cineole, either as a significant or minor ingredient. Diarrhea was caused by castor oil, and the effects of ingesting several dosages of this chemical (20, 60, 80, and 120 mg/Kg) were studied. In the trial, those who were given the medication had a 37% longer delay in the beginning of diarrhea than those who were given the placebo. The peristaltic index dropped by 20% after the chemical was given. 1,8-Cineole has been measured to have an LD50 of 1280 mg/Kg [51]. Friedelin was tested in both a castor oil-induced and a Magnesium sulfate-induced diarrhea model to determine its effectiveness as an anti-diarrheal agent. Several dosages of the chemical (5, 10, and 20 mg/Kg) were tried out. The chemical inhibited castor oil-induced diarrhea by 89% at a dosage of 20 mg/kg but only by 83% when used in conjunction with Magnesium sulfate. Furthermore, gastrointestinal motility was shown to decrease by 69% [52]. From the plant family Lamiaceae, Stachys parviflora, two diterpenoids were extracted and evaluated for their ability to stop diarrhea. These compounds were named Stachysrosane (1) and Stachysrosane (2). At 45 mg/Kg, Stachysrosane (1) completely prevented castor oil-induced diarrhea, but Stachysrosane (2) only prevented it by 70% [53]. Apigenin is a phytomolecule that exhibits several pharmacological properties, including those of being anti-metastatic, anti-osteoporotic, anti-inflammatory, anti-arthritic, etc. In a study comparing the treatment and control groups, it was shown that the substance isolated from Dracocephalum kotschyi (Lamiaceae) significantly reduced the beginning of diarrhea in the treatment group by 32%.

4. MECHANISM OF ACTION OF ANTI-DIARRHEAL MEDICINAL PLANTS

Most herbal extracts have been shown to have anti-diarrheal activity via one or more of the following mechanisms: suppression of intestinal secretions; improvement of intestinal absorption; inhibition of motility or peristaltic action; inhibition of microbial growth; and inhibition of spasms. Several in-vivo investigations have shown that treatment with herbal extracts (of different plant parts produced in different solvents) inhibits enteropooling/ intestinal fluid buildup, gastrointestinal transit, and reduces both the frequency and amount of fecal output. Traditional medicinal plants work through a variety of different mechanisms, including calcium channel blockage [67,68], anti-muscarinic mechanism, inhibition of butyrylcholinesterase [69], inhibition of phosphodiesterase enzyme [70], activation of adenosine triphosphate-sensitive K+ channels [71,72], enhanced activity of Na+-K+ ATPase in the small intestine, and attenuation of nitric oxide concentration. When it comes to the pathophysiology of gastrointestinal illnesses like diarrhea, changes in smooth muscle contractility are an important factor.

Ca2+ influx via voltage-dependent channels in the plasma membrane mediates contraction in smooth muscle and is controlled by changes in the membrane potential. Outward K+ currents, caused by activated K+ channels, hyperpolarize the membrane and dampen excitability and contractility in cells. Smooth muscle contraction is caused by membrane depolarization, which is triggered by the closing of K+ channels. Anti-diarrheal medication may include those that work by blocking calcium channels. Calcium channel blockers have a depressant impact [74] because they either

directly affect the contraction of gastrointestinal smooth muscles or interfere with cholinergic neurotransmission. Several plant extracts have been shown to have spasmolytic effects by blocking calcium channels. Examples of such plants include the Holarrhean antidysenterica [40], Elaeagnus umbellate [50], Buddleja polystachya [70], Morus nigra [67], Pistacia integerrima [75], Heliotropium strigosum [76], Trapa bicornis [77], and Rumex vesicarius [77]. The anticholinergic processes are at play in other cases. These plant extracts relax intestinal smooth muscle by inhibition of acetylcholinesterase (Polypodium vulgare, Morus nigra) or butylcholinesterase (Gaultheria trichophylla) enzymes [67,69,78]. Anti-spasmodic activities are shown by plants including Adiantum capillus-veneris, Polygonatum verticillatum, Matricaria chamomilla, and Symplocos paniculata via activating ATP-dependent K+ channels [55,56,64,68].

5. CONCLUSION

In terms of global health, diarrhea-related morbidity and death have been a big problem. Herbal remedies are gaining favor in the medical community as a safer alternative to pharmaceutical drugs. Phyto-preparations derived from traditionally used plants that have been shown to be effective in treating diarrhea and related symptoms are widely available but are not widely used. The anti-diarrheal benefits of these herbs are said to be mediated via their antisecretory, anti-peristaltic, anti-microbial, and anti-spasmodic properties, according to many scientific studies. There have been very few in-depth investigations of plants, however some have been done, and active phytoconstituents have been extracted and identified. Apart from their anti-secretory/antimotility action, several of the antidiarrheal phytoconstituents, such Apigenin and Friedelin, are recognized to have numerous therapeutic benefits. Apigenin is a chemical with various pharmacological properties that has been extracted from Dracocephalum kotschyi's aerial parts. Many studies have looked at the effectiveness of this molecule in treating cancer, arthritis, osteoporosis, inflammation, and other neurological disorders including Alzheimer's. Phytochemicals such 1,8-cineole (a terpenoid oxide), Stachysrosane, and prenylated flavanone Eriosematin E have not been studied extensively. Thus, the potential pharmacological effects of the lead plants and phytomolecules may be investigated further. However, only a small number of the traditionally used therapeutic herbs have been scientifically shown to be very effective against diarrhea. Leaves from plants like Mangifera indica, Vernonia amygdalina, and Cymbopogon citratus, as well as rhizomes, leaves, and stem bark from plants like Oxalis barrelieri, Pseudocedrela kotschyi, Maytenus erythroxylon, and Khaya senegalensis are used in various extracts. These possible herbal extracts may be used as a starting point for the development of novel herbal drugs; first, they can be used to isolate the active plant molecule(s), and then, after extensive pre-clinical and clinical testing, they can be tested for their effectiveness and safety in humans.

CONFLICTS OF INTEREST

No conflict of interest is declared.

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