

## ShigelDysent efficacy in alleviating clinical sign and symptoms prevailing in *Shigellosis*

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### Abstract

**Background:** Bacillary dysentery (*Shigellosis*) is an intestinal infection caused by the *Shigella* spp is potentially contagious for human health. The significant hallmark of *Shigellosis* is the bloody diarrhea particularly in developing countries with poor quality hygiene. *Shigella* species are accountable for a morbidity as well as mortality and poses threat to kids younger than five years and elder people with an undermined immune system. However, *Shigella* quickly spread in place having suffocated crowded dwellings and is transmitted directly by fecal material or through contaminated food or water.

**Methods:** A comparative study was undertaken to determine the efficacy of ShigelDysent (Test drug) in comparison with Ciprofloxacin (Control drug) in alleviating the clinical sign and symptoms of *Shigellosis*. The research was undertaken among age group 25-45 years in 2010-2013. *Shigellosis* was recorded in 250 patients dividing them into two parallel arm groups; 125 for test and 125 for control group each without consideration of the socio-economic status.

**Results:** Results showed that the medicinal plant coded formulation ShigelDysent exhibit significant ( $p < 0.029$ ) efficacy in relieving the clinical features for sign and symptoms of *Shigellosis* comparable with that of standard drug Ciprofloxacin.

**Conclusion:** ShigelDysent is effective in the in the treatment and management of *Shigellosis*. However further studies on large scale are suggested to find out the pharmacological action of ShigelDysent.

### Background

*Shigella* is entero-invasive bacteria which causes classical bacillary dysentery. The principal species causing gastroenteritis are *Shigella dysenteriae*, *Shigella flexneri* and *Shigella sonnei* which are found with varying epidemiological prevalence in different countries. All these species lead to a similar syndrome as a result of damage to the intestinal mucosa. Some strains of *Shigella dysenteriae* also secrete a cytotoxin affecting vascular endothelium. The organism is spread from person to person and only small numbers are afflicted and need to be taken to cure the illness for example  $<200$ , compared to 104 for *Campylobacter* and  $>105$  for *Salmonella*). Bacillary dysentery is far more prevalent in the developing world because of poor hygienic conditions [1-3]. The term dysentery is specifically used for the passage of stool with pain and cramps. Dysentery is of two kinds, one is limited to rectum while the other is confined to transverse colon, which is in contact or proximal to the rectum. Difference in both is obvious as dysentery occurs due to abrasion and muco-purulent discharge. There is no discomfort found in the rectum, tenesmus is less, excretion is possible by least tenesmus and patient remains asymptomatic. In rectal dysentery, defecation is painful with small fecal matter and tenesmus and patient suffer with fatigue easily [4]. It is colonic dysentery; sometimes inner portion of intestinal epithelial lining gets affected. In this case intestinal membrane becomes edematous that results in tissue death. These membranous scales are excreted out in stool [5]. Bacillary dysentery results from *Shigella species*, provokes passage of fecal blood and mucus. On reaching the large intestine the organism passes through the cell lining via M cells that superimpose the lymphoid nodules [6-8].

In view of the fact that due to bacterial resistance the current global trends and direction started to treat diarrheal diseases with herbal drugs. As such it is a need to strategically utilize efficacy based herbal

medicine to eliminate diarrhea. In order to prove the effectiveness of medicinal plants on scientific and clinical basis, we have designed and report here with the effectiveness of herbal coded formulation "ShigelDysent" for the eradication of *Shigella* species and it has shown significant results in a cited recent report [9]. In the present study, we have focused on the effectiveness of "ShigelDysent" in alleviating the clinical manifestations of *Shigellosis*.

### Materials and Methods

The research study is an experimental, randomized, clinical trial conducted during 2010-2013. The trials were executed in Shifa-ul-Mulk Memorial Hospital for Eastern Medicine (SUMMH), Hamdard University, Pehlwan Goth, Safoora Goth and Patel Para, Karachi, Pakistan. All patients were randomly assigned either Ciprofloxacin or ShigelDysent and divided into two groups according to treatment regimen i. e., test group and control group respectively. Clinical evaluation of the disease and also rectal swab cultures were made before and after treatment for seven days. Before starting the specific therapy, rectal swabs were obtained and transferred and immediately inoculated on to MacConkey and S.S. agar plates. Antimicrobial

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**Citation:** Qureshi T, Saeed A, Usmanhane K, Asif HM, Zaidi SF (2015) ShigelDysent efficacy in alleviating clinical sign and symptoms prevailing in *Shigellosis*. Int J Gastroenterol Disord Ther 2: 114. doi: <http://dx.doi.org/10.15344/2393-8498/2015/114>

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therapy was started without awaiting the results of stool cultures. Patients were withdrawn from the study if their stool cultures did not confirm the diagnosis of the presence of *Shigella organisms*. Research proforma was filled for documentation by the principal investigator that included the complete clinical data including the sign and symptoms of the bacillary dysentery (*Shigellosis*) and patient follow up to evaluate the drug efficacy.

### Sample size

Sample size comprises of 250 cases each of test group (125) and control group (125) prescribed and administered “ShigelDysent” as test and “Ciprofloxacin” as control drug.

### Selection of herbal drugs for *Shigellosis*

The medicinal plants effective for shigellosis were selected after thorough review of literature search on Herbal Pharmacopeias and research articles available in electronic journals. The medicinal plants showing remarkable ethno botanical and scientific evidences for the treatment of dysentery were selected namely *Phyllanthus emblica* L., *Aegle marmelos* L., *Holerrhena antidysenterica* L., *Myrtus communis* L., *Polygonum bistorta* L., *Citrus aurantifolia* L. in powder form to be used as capsules. All these phyto-pharmaceutical ingredients were grinded and aqueous alcoholic extract were filled in the capsule.

### Identification and preparation

The selected drugs for bacillary dysentery (*Shigellosis*) were purchased from the local market at Jodia Bazar. All the six herbal drugs were powdered separately into fine quality and filter through 100 number sieves in pharmacy at Hamdard Al-Majeed College of Eastern Medicine (HACEM), Hamdard University.

All the herbal drugs are separately weighed as per dosage in 500 mg capsule: *Myrtus communis* L. (Fruit of Hub-ul-Aas powder)-150mg, *Aegle marmelos* L. (Fruit of Belgiri powder)-100mg, *Polygonum bistorta* L. (Bikh Anjibar powder)-75mg, *Phyllanthus emblica* L. (Fruit of Aamla powder)-75mg, *Holarrhena antidysenterica* L. (Maroor phalli powder)-50mg, *Citrus aurantifolia* L. (Post Turang powder)-50mg. All the herbal drugs were cleaned and examined for their impurities and adulterations in pharmacy of HAMCEM. The herbal

drugs were weighed according to the dosage in formulation after powdered in grinding machine and filtered through 100 number sieves. The identity of the herbal drugs samples were identified and authenticated by Prof. Dr. Iqbal Azhar, Chairman, Department of Pharmacognosy, University of Karachi on 1st January 2010.

### Statistical analysis

The SPSS for windows version 17 was applied for the statistical analysis of data for verification and to check for range and consistency with customized data entry and XP software. After clinical follow-up the data so generated was included electronically and recorded. All the data was twice recorded in programs such as SPSS, XP Microsoft. Since the observation period was 7-10 days, current status of the disease along with new out comings of the disease episodes was also recorded. Non-parametric analysis was done by the use of the Wilcoxon rank sum test and Mann-Whitney test for assessment between the groups, to compare two paired groups proportion T-test, to compare three or more unmatched groups one way ANOVA was applied to assess the statistical significance. Clinical success for patients treated with ShigelDysent was predicted at 95%.

### Results

A total of 250 patients were assigned test and control therapy by dividing them into two groups i.e., test and control group. Patients in the test group were prescribed ShigelDysent (500mg) while patients in control group were given Ciprofloxacin (500mg) for 7days.

The major clinical manifestation of *Shigellosis* is the increase of stool frequency and disturbance in stool consistency. Patients in the test group showed marked improvement both in stool frequency and consistency which is comparable with that of standard drug Ciprofloxacin [Table 1 and 2], exhibiting that ShigelDysent is significant ( $p < 0.005$ ) in the treatment of clinical manifestation of *Shigellosis*.

Other clinical features including presence of blood in stool, presence of mucus in stool, abdominal pain, flatulence, tenesmus, nausea/vomiting and fever showed remarkable improvement in test group patients clearly display the result that ShigelDysent is significant in alleviating the clinical features of *Shigella* infection [Table 3].

Consistency of stool	Test group frequency			Control group frequency		
	Frequency	Percent	Cumulative Percent	Frequency	Percent	Cumulative Percent
Bloody mucoid	16	12.8	12.8	14	11.2	11.2
Watery	13	10.4	23.2	15	12	23.2
Soft	36	28.8	52	34	27.2	50.4
Semisoft	34	27.2	79.2	39	31.2	81.6
Mucoid	26	20.8	100	23	18.4	100
Total	125	100		125	100	
Outcome						
Firm Formed	87	69.6	69.6	73	58.4	58.4
Soft Formed	29	23.2	92.8	37	29.6	88
Unformed	8	6.4	99.2	15	12	100
Semiliquid	1	0.8	100	0	0	
Total	125	100		125	100	

Table 1: Consistency of stool in both groups.

Presence of blood	Test group frequency			Control group frequency		
	Frequency	Percent	Cumulative Percent	Frequency	Percent	Cumulative Percent
Pre treatment						
Trace	66	52.8	52.8	78	62.4	62.4
Fair	52	41.6	94.4	33	26.4	88.8
Significant	7	5.6	100	14	11.2	100
Total	125	100		125	100	
Post treatment						
Absent	119	95.2	95.2	82	65.6	65.6
Trace	4	3.2	98.4	41	32.8	98.4
Fair	2	1.6	100	2	1.6	100
Total	125	100		125	100	

Table 2: Frequency regarding presence of faecal blood.

Sign/Symptoms	Test		Control		p value
	Before treatment	After treatment	Before treatment	After treatment	
Abdominal Cramps					
Absent	74%	91%	77%	97%	
Mild	18%	9%	23%	3%	0.06
Moderate	9%	-	-	-	
Abdominal pain					
Absent	24%	97%	35%	82%	
Mild	34%	3%	51%	18%	0.00
Moderate	42%	-	14%	-	
Flatulence					
Absent	91%	98%	69%	95%	
Mild	6%	2%	25%	5%	0.31
Moderate	3%	-	6%	-	
Tenesmus					
Absent	5%	98%	51%	85%	
Mild	37%	2%	42%	15%	0.000
Moderate	58%	-	6%	-	
Nausea					
Absent	35%	92%	85%	90%	
Mild	54%	8%	5%	6%	
Moderate	11%	-	6%	4%	0.46
Severe	-	-	4%	-	
Anorexia					
Absent	32%	100%	70%	84%	
Mild	68%	-	12%	14%	
Moderate	-	-	14%	2%	0.000
Severe	-	-	4%	-	

Table 3: Clinical signs and symptoms before and after treatment in both groups.

## Discussion

A number of plant extracts and natural products have been shown to work synergistically like that antibiotic activity against resistant strains of *Shigella*. *Shigellosis* is one of the most common infections in developed countries where as in the developing countries undergoing industrialization usually exhibit with areas of poor and inadequate sanitation [10]. A three day

course of ciprofloxacin is the treatment currently recommended by the WHO for *shigellosis*, including *S. dysenteriae* type 1 infections. The WHO, after considering the risks and the benefits, has recommended ciprofloxacin as the primary treatment of shigellosis in adults and children [11-13]. The current knowledge of the mechanisms and the global distribution of *Shigella* with reduced susceptibility to ciprofloxacin remain limited. Therefore, due to the

ciprofloxacin resistance, alternative therapies could be the viable option to find out effective treatment of shigellosis. Etiological and clinical features elaborated with shigella infection consist of blood and mucus in stool, cramps, abdominal pain, tenesmus, fever and chills. The ciprofloxacin dose management consists of 500mg ODS for five days is the first line of diarrheal diseases. *Moringa stenopetala* was one of the said plants assessed for shigella treatment. It was reported that the biological active compounds isolated from both leaves and seeds of the plant by a bioassay guided fractionation exhibited antimicrobial activity against *Shigella*. In the late 1960s, *Shigella* suddenly reappeared in epidemic form in Central America and Mexico where it has again become a major public health problem and, more recently, in Asia and Africa including Pakistan the *shigella* infection is on rise [14]. Inflammatory diarrhea occurs with inflammation of bowel mucosa, which limits its ability to reabsorb fluid and it can occur with *Shigella*. Until recently, several studies have been conducted on the antimicrobial properties of the leaf and stem extracts of *Myrtus communis* (myrtle) against pathogenic bacteria and good results have been obtained about its effects on *Shigella* [15]. The minimum bactericidal concentration (MBC) of Myrtle for most tested microorganisms was similar to the MBC i.e. 0.5 mg/ml for *Salmonella aureus*, 2.5 mg/ml for *Pseudomonas mirabilis* and *Pseudomonas vulgaris*, 15 mg/ml for *Klebsiella* spp, *Salmonella typhi*, and 20 mg/ml for *Pseudomonas aeruginosa*. The MBC of Myrtle for the two relatively least sensitive species, *Shigella* and *E. coli* was 40 mg/ml and 45 mg/ml of media, respectively. The antibacterial activity of Myrtle was markedly increased by 18 times after it has been autoclaved at 121°C for 15 minutes [16]. The isolated lectin from the fruit pulp of *Aegle marmelos* exhibited its effect against *Shigella dysenteriae* infection. The effect of *Aegle marmelos* fruit lectin on the adherence of *Shigella dysenteriae* to human colonic epithelial cells (HT29 cells) was evaluated by Enzyme Linked Immune Sorbent Assay and invasion was analyzed. The protective nature of the *Aegle marmelos* lectin was assessed by analyzing apoptosis through dual staining method. *Aegle marmelos* lectin significantly inhibited hemagglutination activity of *Shigella* and its minimum inhibitory concentration is 0.625 µg/well [17].

The anti-diarrheal effect of ethanol extract of the dried fruit pulp of *Aegle marmelos* was studied on various intestinal pathogens. It showed excellent activity against *Shigella boydii*, *S. sonnei* and *S. flexneri* whereas the activity was found to be moderate against *S. dysenteriae*. The minimum inhibitory concentration against the strains of *Shigella* was recorded between 250 to 500 µg/ml [18]. Aqueous extract of *Aegle marmelos* enhanced the susceptibility of beta-lactam resistant *Shigella flexneri* and *Shigella dysenteriae* towards beta-lactam antibiotics by altering poring channels. Antimicrobial activity has been shown in the leaves of *Aegle marmelos* and this study is in consistence with the differential expression of *ompC* and *ompF* in multi-drug resistant *Shigella dysenteriae* and *Shigella flexneri* [19]. As cited the research work performed in vitro and in vivo anti-diarrheal potential of chloroform extract of the root of *Aegle marmelos* and was found that the extract was comparable to that of ciprofloxacin and mostly active against the strains of *Vibrio cholerae*, followed by *Escherichia coli* (*E. coli*) and *Shigella* spp [20]. *Phyllanthus emblica* anti-microbial and cytotoxic activities was reported with the alkaloids fraction showed the strongest inhibitory effect against *Bacillus subtilis* and moderate inhibitory activity against *Salmonella typhi*, *Bacillus cereus*, *Pseudomonas aeruginosa*, *Shigella boydii* and *Shigella dysenteriae* [21].

The antimicrobial property of aqueous extracts of *Aloe vera*, *Aloe babrbadensis*, *Daucus carota*, *Emblica officinalis*, *Punica granatum* was carried out and to assessed the reason for inhibition of growth of pathogenic organisms by DNA and protein analysis. The effect of four citrus fruit peels extract was compared with antibiotics and the ethanol extract concentrate of *Citrus aurantifolia* and *Citrus limon* showed a better inhibitory effect on *E. coli* and *Shigella* spp. [22]. As such the coded herbal drug ShigelDysent also contains the above mentioned plants which adequately have been shown to inhibit the *Shigella* spp. Therefore, herbal formulation based on these medicinal plants upon comparison with ciprofloxacin was found to be effective for the treatment of Shigellosis. However, ShigelDysent showed lesser effects as compared with ciprofloxacin but it does not elaborate side or adverse drug reaction.

## Conclusion

In the present study the predominate species was found to be *Shigella sonnei* due to contaminated drinking water, then *Shigella flexneri* and lastly *Shigella boydii*. ShigelDysent (herbal formulation) is effective in alleviation of clinical features of shigellosis comparable with that of standard drug Ciprofloxacin.

## Competing Interests

The authors have no competing interests with the work presented in this manuscript.

## Author Contributions

All the authors substantially contributed to the study conception and design as well as the acquisition and interpretation of the data and drafting the manuscript.

## Acknowledgement

The authors are thankful to the clinical and non-clinical staff of Shifa-Ul-Mulk Memorial Hospital for Eastern Medicine for the help and support in the collection of data.

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