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Der Pharma Chemica, 2010, 2(2): 66-93
(http://derpharmachemica.com/archive.html)

ISSN 0975-413X

Pharmacological review on natural antidiarrhoel agents

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Abstract

Diarrhoea refers to an increase in the frequency, fluidity and/or volume of faeces, greater than normal for an individual, resulting from an imbalance between the secretory and absorptive forces in the intestines. The World Health Organization (WHO) estimates that 3–5 billion cases occur each year (1billion in children less than 5 years of age), and that approximately 5 million deaths are due to diarrhoea annually (2.5 million in children less than 5 years of age). The incidence of diarrhoeal diseases still remains high despite the efforts of many governments and international organisations to curb it. Many synthetic chemicals like diphenoxylate, loperamide and antibiotics are available for the treatment of diarrhoea but they have some side effects and increasing resistance of pathogen to the common antibiotics. In recent years, special attention is being given on alternative safe natural bio-remedies to cure the infectious diseases because of their less or no side effects, high efficacy, less cost. In this paper an attempt has been made to give an overview of certain plants with their phytoconstituents and mechanism of action which have been studied for their antidiarrhoel activity.

Key Words: Castor oil-induced diarrhoea, Tannin, Diarrhoea, Flavonoids, Anti-diarrhoeal drugs

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INTRODUCTION

Diarrhoea (Greek and Latin: dia, through and rheein: to flow or run) is characterized by increased frequency of bowel movement, wet stool and abdominal pain.[1] In most cases of diarrhoea result from disorders of intestinal water and electrolyte transport.[2] There are numerous causes of diarrhoea including infectious agents, toxins, anxiety, drugs, and so forth.[3] Diarrhoea is a major health problem especially for children under the age of 5 years. Worldwide distribution of diarrhoea accounts for more than 5-8 million deaths each year in infants. According to W.H.O. estimates for 1998, about 7.1 million deaths were caused by diarrhoea. The incidence of diarrhoeal diseases still remains high despite the efforts of many governments and international organisations to curb it.[4] In recent times, emphasis has been focused on the use of oral rehydration solution (ORS) as a replacement therapy to replenish the lost fluid and electrolytes in diarrhoeic cases.[5] Generally, the treatment of diarrhoea is non-specific, and is

usually aimed at reducing the discomfort and inconvenience of frequent bowel movements.[6,7] Many synthetic chemicals like diphenoxylate, loperamide and antibiotics are available for the treatment of diarrhoea but they have some side effects and increasing resistance of pathogen to the common antibiotics.[1,8-12]

Table 1: Classification of antidiarrhoel drugs

Class	Drug	Adverse affect
Antisecretory	Sulfasalazine	Rashes, fever, join Pain, haemolysis, blood dyscrasias
	Bismuth subsalicylate	None at therapeutic dose
	Atropine	Dry mouth, blurd vision
	Mesalazine	Nausea, Abdominal pain, headache
	octreotide	
Antimotility	Codeine	Nausea, vomiting, dizziness
	Diphenoxylate atropine	Apnoea, sedation, mental clouding
	loperamide	Abdominal cramps, rashes

In recent years, special attention is being given on alternative safe natural bio-remedies to cure diseases because of their less or no side effects and resistance in microbes against them.[9]

Natural Products

To combat the problem of diarrhea in developing countries, the world health organization (WHO) has constituted a diarrhea disease control programme (DDC) which includes studies of traditional medicine practices together with the evaluation of health education and prevention approaches.[13, 14]

Therefore, the search for safe and more effective agents has continued to be an important area of active research.[13] It is therefore important to identify and evaluate available natural drugs as alternatives to currently used anti-diarrhoeal drugs, which are not always free from adverse effects.[4] A detailed account from various plant derived product are described in the given table 2.

Table 2: Antidiarrhoel properties of plant-products

Plants name	Part used	Chemical Constituents	Solvent system	Method used	Ref.
Acacia catechu (leguminosae)	Bark	Flavonoids	Ethyl acetate, Petroleum ether, chloroform, methanol and aqueous extracts	Castor oil-induced diarrhoea in rats, Against pathogenic *escherichia coli*	15 9
Acacia nilotica	Bark	Tannin	Petroleum ether, chloroform, methanol and aqueous extracts	Against pathogenic *escherichia coli*	9
Acorus calamus	Rhizome	-	Aqueous and methanolic	Castor-oil induced diarrhoea in mice	16

Aegle marmelos (Rutaceae)	Unripe fruit, Fruit pulp	Glycosides, amino acids, proteins, tannins, flavanoids, phytosterols, coumarins such as marmelosin and marmelide	Aqueous and methanolic, Petroleum ether, chloroform, Ethanol extract	Castor-oil induced diarrhoea in mice, Against pathogenic *escherichia coli*, Colonization, production and action of enterotoxins. Activity against 4 strains of shigella	16 9 17 18
Alhagi maurorum	-	Flavonoids, tannins, sterols, triterpenes, saponins and anthraquinones.	Methanol extract	Castor oil-induced diarrhoea,	19
Alternathera repens (Amaranthaceae)	Dried powdered plant	-	Hexane, chloroform, methanol and aqueous extracts	Diarrhoea induced by castor oil and $MgSO_4$ in mice	20
Andrographis paniculata (Acanthaceae)	Whole plant parts	Diterpenes, Andrographolide, neoandrographolide, deoxyandrographolide and andrographiside	Alcoholic extract	*E. coli* enterotoxin-induced secretory response causing diarrhoea syndromes	8,21
Annona senegalensis (Annonaceae)	Stem-bark extract	Flavonoids, tannins, alkaloids, saponins, glycosides and sterols/triterpenes	Methanol	Charcoal meal in order to investigate intestinal transit time	22
Annona squamosa	Leaves	Alkaloid, tannins	Petroleum ether, chloroform, methanol and aqueous extracts	Against pathogenic *escherichia coli*	9
Anthocephalus cadamba (Rubiaceae)	Flowering tops	Indole alkaloids, secoiridoids, triterpenes and saponins	Hydroethanolic extract	Castor oil-induced diarrhoea in mice	23
Aristea spp.	Stem	-	Aqueous extract Aqueous and methanolic extracts	Castor oil-induced diarrhoea in rats Castor-oil treated rats, anti-microbial activity against different pathogenic microorganisms that	13 24

				cause diarrhoea	
Artemisia ludoviciana	-	Nonanal, flavonoids	Essential oil	Castor oil-, magnesium sulphate-, arachidonic acid- and PGE_2 -induced diarrhoea in CD1 mice	25
Azadirachta indica	Leaves	-	Petroleum ether, chloroform, methanol and aqueous extracts	Against pathogenic *escherichia coli*	14
Asparagus racemosus	Root extracts	Alkaloids, saponins, flavonoids, sterols, terpenes and sugars	Ethanol and aqueous extracts	Castor oil-induced diarrhoea model in rats	26
Baphia nitida (Papilionaceae)	Fresh leaves	Flavonoids, isoflavonoids, isoflavones, saponins, tannins, and alkaloids	Ethyl acetate extract	Castor oil-induced diarrhoea, Castor oil-induced intestinal transit,	27
Bridelia micrantha	Bark	-	Aqueous and methanolic extracts	Castor oil-induced diarrhoea in rats Castor-oil treated rats, anti-microbial activity against different pathogenic microorganisms that cause diarrhoea	13 24
Bidens bipinnata	Aerial parts	-	-	Castor oil-induced diarrhoea, gastrointestinal movement in rats (charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits	28
Butea monosperma (Fabaceae)	Stem bark	Steroids, flavonoids, phenolic compounds, tannins and glycosides	Ethanolic extract	Castor oil induced diarrhoea and PGE_2 induced enteropooling in rats, gastrointestinal motility after charcoal meal administration	29

Byrsocarpus coccineus (Connaraceae)	Leaf extract	Alkaloids, saponins, tannins, anthraquinones, glycosides, simple sugars	Aqueous	Normal and castor oil-induced intestinal transit, castor oil-induced diarrhoea, enteropooling and gastric emptying.	30
Calotropis gigantean (Ascelpiadaceace)	Aerial parts	Sugars, flavonoids, flavonol glycosides, terpenes, terpene derivatives, pentcyclic triterpenoids and triterpenoids	Hydroalcoholic extract	Castor oil-induced diarrhoea in rats	31
Calotropis procera	Aerial parts	-	Latex	Castor oil-induced diarrhoea in animals	32
Cassia fistula coleusforskohlii	-	-	Alcohol, hexane, chloroform, butanol and aqueous extracts	*Escherichia coli* enterotoxin-induced secretion in rabbit and guinea pig ileal loop models	21
Cleome viscosa (Capparidaceae)	Entire plant	Tannins, steroids, and flavonoids	Methanol extract	Castor oil-induced diarrhoea and PGE_2-induced enteropooling in rats.	33
Clerodendrum phlomidis (Verbenaceae)	Leaf extract	Steroid, alkaloid, flavanoids	Methanolic extract	Castor oil induced diarrhoea and PGE_2-induced enteropooling in rats	34
Cinnamomum tamala	Dried leaves	Germacrene A, *a*-gurjunene, 1-8-cineole, p-cymene, methyl eugenol and eugenol acetate, Tannins	50% aqueous ethanol.	Castor oil-induced diarrhoea in rats	35
Costus lucanusianus (Costaceae)	Leaves extract	Tannins, saponins, reducing sugars and carbohydrate	Aqueous	Castor oil-induced diarrhoea and small intestinal transit in mice	2
Combretum sericeum	Roots	Alkaloids, glycosides, saponins, tannins anthraquinones and	Aqueous extract	Castor oil induced diarrhoea, gastrointestinal motility and castor oil induced fluid accumulation	36

		flavonoids			
Convolvulus fatmensis	Aerial parts	-	-	Castoroil-induced diarrhoea, gastrointestinal movement in rats (charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits	28
Commelina coelestis (Commelinaceae)	Dried powdered plant	-	Hexane, chloroform, methanol and aqueous	Mice with diarrhoea induced by castor oil and $MgSO_4$	20
Conyza dioscoridis	-	-	Methanol extract	Castor oil-induced diarrhoea	19
Cynachum acutum	Aerial parts	-	-	Castor oil-induced diarrhoea, gastrointestinal movement in rats (charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits	28
Cylicodiscus gabunensis (Mimosaceae)	Stem bark	Tannins, alkaloids, saponins, flavonoids, sterols, triterpenes and reducing sugars	Ethyl acetate extract	Castor oil-induced diarrhoea	4
Dalbergia lanceolaria (Fabaceae)	Bark	-	Ethanol extract	Castor oil, magnesium sulphate induced diarrhoea in albino mice.	37
Dalbergia sissoo (Fabaceae)	leaves	Carbohydrates, glycosides, proteins, amino acids, phytosterols, saponins, flavonoids, alkaloids, and tannins.	Aqueous	colonisation to intestinal epithelial cells and production/action of enterotoxins	38
Diplotaxis acris	Aerial parts	-	-	Castor oil-induced diarrhoea, gastrointestinal movement in rats	28

				(charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits	
Eleutherina bulbosa	Bulb	-	Aqueous and methanolic extracts	Castor-oil treated rats, anti-microbial activity against different pathogenic microorganisms that cause diarrhoea	24
Emilia coccinea	Leaves	Tannins, alkaloids, saponins, flavonoids, steroids and or terpenoids	Methanol and aqueous extracts	Castor oil-induced diarrhoea	39
Eremomastax speciosa (Acanthaceae)	Ground leaves	Tannins and flavonoids	Aqueous extract	Castor oil induced diarrhoea in mice	40
Eugenia jambolana	Bark	Alkaloids, steroids and tannins	Ethanol extracts	Castor oil-induced diarrhoea and PGE_2-induced enteropooling in rats	41
Euphorbia paralias	Aerial parts	-	Methanol	Castor oil-induced diarrhoea, gastrointestinal movement in rats (charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits	28
Ficus bengalensis (Moraceae)	Hanging roots	Alkaloids, steroids and tannins	Ethanol extracts	Castor oil-induced diarrhoea and PGE_2-induced enteropooling in rats	41
Ficus hispida	Leaf extract	Tannins triterpenoids, alkaloid and saponin	Methanol extract	Castor oil-induced diarrhoea and PGE_2-induced enteropooling rats.	42
Ficus racemosa (Moraceae)	Bark	Alkaloids, steroids and tannins	Ethanol extracts	Castor oil-induced diarrhoea and PGE_2-induced enteropooling in rats.	41
Gentianopsis paludosa (Gentianaceae)	Whole herb	Xanthones, terpenoids and flavonoids	Ethanol extract	Castor oil-induced diarrhoea and gastrointestinal motility in the	43

				charcoal meal test in mice	
Guiera senegalensis (Combretaceae)	Root	Tannins, flavonoids, anthraquinones, polyphenols, quinic acid gallates, alkaloids and ascorbic acid	Aqueous	Castor oil-induced diarrhoea in mice.	44
Geranium incanum (Geraniaceae)	Leaf	Tannins, saponins flavonoids, Gallic acid	Aqueous extract	Castor oil induced diarrhoeal, charcoal meal test	45
Holarrhena antidysenterica	Bark	-	Petroleum ether, chloroform, methanol and aqueous extracts	Against pathogenic *escherichia coli*	9
Jatropha curcus (Euphorbiaceae)	Root extract	-	Methanol extract	Castor oil induced diarrhoea	46
Juniperus phoenicia (Cupressaceae)	Leaves	Flavonoids, alkaloids and tannins	Aqueous extract	Castor oil induced diarrhoea in rats	47
Leucas lavandulaefolia	Aerial parts	Alkaloids, steroids and tannins	Ethanol extracts	Castor oil-induced diarrhoea and PGE_2-induced enteropooling in rats.	41
Litsea polyantha (Lauraceae)	Dried bark and aerial parts	Alkaloids, carbohydrate, flavonoids and saponins	Methanol extract	Castor oil-induced diarrhoea and propulsive gut motility in mice	48
Ludwigia hyssopifolia (Onagraceae)	Whole plant parts	Terpenoid and alkaloid	Methanol Extract	Castor oil and serotonin induced diarrhea	49
Mezoneuron Benthamianum (Caesalpiniaceae)	Whole plant	Tannins, flavonoids	Aqueous extract	Castor oil-induced diarrhea, Castor oil-induced enteropooling	50
Momordica cymbalaria (Cucurbitaceae)	Fruit extract	Tannins, alkaloids, sterols, terpenes and flavanoids.	Methanol Extract	Castor oil-induced diarrheal model in rats, Gastrointestinal tract motility after charcoal meal administration and PGE_2 induced intestinal fluid accumulation.	51
Mangifera indica	Seed	-	Methanolic and	Castor oil and	52

			aqueous extract	magnesium sulphate in mice.	
Nelumbo nucifera	Rhizome extract	-	Methanolic extract	Castor oil induced diarrhoea and PGE_2 enteropooling in rats	53
Ocimum basilicum	Leaves	-	Petroleum ether, chloroform, methanol and	Against pathogenic *escherichia coli*	9
Ocimum gratissimum (Labiatae)	Leaves	Thymol eugenol, xanthones, terpenes and lactone	aqueous extracts Aqueous Extract	Castor oil –induced diarrhoea in Wistar albino rats	54
Ocimum selloi (Lamiaceae)	Leaves	Methyl chavicol or estragole, trans-anethole, cis-anethole, and caryophyllene	Essential oil	Castor oil in mice	55
Plantago major	Leaves	-	Methanol	Castor oil-induced diarrhoea, gastrointestinal movement in rats (charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits	28
Papaver somniferum	-	-	Alcohol, hexane, chloroform, butanol and aqueous extracts	Escherichia coli enterotoxin-induced secretion in rabbit and guinea pig ileal loop models	22
Parkia biglobosa (Leguminosae)	Stem bark	-	Aqueous	Castor-oil-induced diarrhoea	56
Paullinia pinnata (Sapindaceae)	Leaves	Carbohydrates, reducing sugars, saponins, tannins cardiac glycosides and anthracene derivatives.	Methanolic extract	Castor oil induced diarrhoea model	47
Pentaclethra macrophylla	Leaf extracts	-	Aqueous and ethanol	Castor oil-induced diarrhoea in rats	57

Phoenix dactylifera	-	-	Aqueous extract	Castor oil-induced diarrhoea, enteropooling and gastrointestinal transit test in rats	58
Plantago major	Leaves	-	Methanol	Castor oil-induced diarrhoea, gastrointestinal movement in rats (charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits	28
Pongamia glabra	Leaves	-	Aqueous and methanolic	Castor-oil induced diarrhoea in mice.	16
Psidium guajava (Myrtaceae)	Fresh leaves	Quercetin, tannins, polyphenolic compounds, pentacyclic triterpenoids	Aqueous and methanolic extracts	Castor oil-induced diarrhoea in rats Castor-oil treated rats, anti-microbial activity against different pathogenic microorganisms that cause diarrhoea	13 24
Punica granatum (Punicaceae)	Seed extract	Steroid, flavonoids and tannin	Methanol extract	Castrol oil induced diarrhoea and PGE_2 induced enteropooling in rats.	59
Rhus javanica (Anacardiaceae)	Fruit extract	-	Methanolic extract	Castor oil-induced diarrhoea ,Gastrointestinal transit test, Enteropooling assay, Measurement of faecal output	60
Rumex maritimus (Polygonaceae)	Root	-	Partitioned n-hexane, ethylacetate and residual methanol extracts	Castor oil and serotonin induced diarrhoea and also charcoal motility test	61
Saccharum spontaneum (Gramineae)	Whole plant	-	Methanolic extract	Castor oil-induced diarrhoeal model in mice	62
Sanseviera liberica (Agavaceae)	Root extract	Reducing sugars, alkaloids, saponins,	Aqueous	Castor oil induced diarrhoea, enteropooling, and gastric	63

		anthraquinones, and tannins		emptying methods	
Securinega virosa (Euphorbiaceae)	Leaves, stem bark and root bark	Flavonoids	Methanolic Extracts	Castor oil-induced diarrhoeal model in mice	64
Schouwia thebaica	Aerial parts	-	-	Castor oil-induced diarrhoea, gastrointestinal movement in rats (charcoal meal) and on the motility of duodenum isolated from freshly slaughtered rabbits	28
Sphaeranthus senegalensis (Asteraceae)	Whole plant	Tannin	Aqueous extract	Castor oil-induced diarrhoea and fluid accumulation and on gastrointestinal (charcoal meal) test	65
Spondias mangifera	Bark	-	Methanolic extract	Castor-oil induced diarrhoeal activity	66
Strychnos nux-vomica	Root bark	-	Aqueous and methanolic	Castor-oil induced diarrhoea in mice	16
Strychnos Potatorum (Loganiaceae)	Seed extract	Steroids, alkaloids, tannins and reducing sugars.	Methanol extract	Castor oil-induced diarrhoea, effects on gastrointestinal motility and on PGE_2-induced gastric enteropooling	67
Stereospermum kunthianum (Bignoniaceae)	Stem bark	-	Aqueous extract	Castor oil-induced intestinal transit in mice	68
Swietenia macrophylla (Meliaceae)	Seed	Steroids and triterpenes	Petroleum ether extract	Castor oil induced diarrhoea in Wister albino rats	1
Strychnos nux-vomica	Root bark	-	Aqueous and methanolic	Castor-oil induced diarrhoea in mice	16
Thespesia populnea (Malvaceae)	Stem barks	-	Aqueous and alcoholic extracts	Castor oil induced diarrhea, Prostaglandin-E_2 induced Diarrhea and Charcoal meal test	69
Trachyspermum ammi	Seeds	-	Petroleum ether, chloroform, methanol and aqueous extracts	Against pathogenic *escherichia coli*	9
Tridex	-	-	Alcohol,	*Escherichia coli*	21

procumbens			hexane, chloroform, butanol and aqueous extracts	enterotoxin-induced secretion in rabbit and guinea pig ileal loop models	
Vitex doniana	Fruits	Flavonoids, tannins	Aqueous extract	Castor oil–induced diarrhea in mice	3
*Xanthium Indicum(*Compositae)	Leaves	Flavonoids, Tannins	Hydromethanolic	Castor oil and $MgSO_4$-induced diarrhoeal model and charcoal induced gastrointestinal motility test in mice.	70
*Xylocarpus moluccensis (*Meliaceae)	Barks	-	Methanol extract	Castor oil- and magnesium sulphate-induced diarrhoea models in mice	71
Xylocarpus granatum	Bark	Anthraquinones, flavonoids, tannins and saponins	Methanol extract	Castor oil and magnesium sulphate in mice	72
Zizyphus spinachristi (Rhamnaceae)	Stem bark	Tannins	Methanol extract	Castor oil induced diarrhoea, intraluminal fluid accumulation, and	73
Ziziphus mauritiana	Root extract	Alkaloids, glycosides, saponins and volatile oils and or flavonoids	Methanolic extract	Gastrointestinal transit time Castor oil induced dirrhoea and castor oil induced fluid accumulation,	74
*Zingiber officinale (*Zingiberaceae*)*	Rhizomes	Tannins, flavonoids, essential oil, sulphonatated compounds and pungent principles like zingerone, gingerols and shogaols	Water	Colonization of epithelial cells and production of enterotoxins.	75.76

Mechanism through which natural products act as antidiarrhoeal agents

Acacia catechu

Acacia catechu commonly known as Catechu or cutch (katha in Hindi and Manipuri) *Acacia catechu* significantly decreased the number of stool passed ($p<0.001$). *A. catechu* at a dose of 250 mg/kg, p.o., (single dose) has been found to possess highly significant antidiarrhoel property ($p<0.001$) in respect of latent period of onset of diarrhoea, average number of stool passed and purging index.[15]

Aegle marmelos

Aegle marmelos (Rutaceae) commonly known as *Bael*/*Bilva*.[17] Methanol extract of *Aegle marmelos* was very effective at higher doses ($P<0.001$) than the aqueous extract. The unripe fruit of *A. marmelos* is used as an astringent and is said to be an excellent remedy for diarrhoea, owing to the presence of tannin or mucilaginous substance. Marmelosin isolated from the plant *A. marmelos* also showed antihelmintic activity. Methanol extracts of the plants used significantly reduced the total weight of wet faeces in a dose dependent manner. Aqueous extract also showed some effect by the lowering of faecal weight.[16]

The decoction of the unripe fruit pulp of *A. marmelos*, despite having limited antimicrobial activity, affected the bacterial colonization to gut epithelium and production and action of certain enterotoxins.[17]

Acorus calamus

An aqueous and methanolic extract of *Acorus calamus* at lower doses were less effective, but at higher doses the extracts were very effective. Methanolic extract of *A. calamus* was more effective at higher doses than aqueous extract. The essential oil, aqueous and alcoholic extract of *A. calamus* relaxed the tone of isolated intestine of guinea pigs. For gastro-intestinal disorders or in diarrhoeal diseases the lower dose (7.5 mg and below) of *A. calamus* is useful. *A. calamus* is a common drug given for the relief of abdominal complaints in children.[16]

Alhagi maurorum

Oral administration of methanol extract from *Alhagi maurorum* in a 200 mg/kg dose exhibits a significant antidiarrhoel effect against castor oil-induced diarrhoea, In a dose of 400 mg/kg, *A. maurorum* produced a significant (less than 0.01) effect. *A. maurorum* increased the contractile force in concentrations between 0.4 and 1.6 mg/ml. Higher concentrations (>3.2 mg/ml) caused a rapid depressant effect.[19]

Alternanthera repens

The methanolic extracts and the water extract of *Alternanthera repens* showed dose related antidiarrhoeic activity at doses of 12.5-50 mg/kg on diarrhoea induced by castor oil or magnesium sulphate. *A. repens* at dose of 50 mg/kg, the maximum inhibition (75.93%) is observed when administered 60 min. before the $MgSO_4$ and 58.2% when administered 30 min. before castor oil.[20]

Anthocephalus cadamba

The dry hydroethanolic extract (250-500 mg/kg body mass, *p.o.*) of *Anthocephalus cadamba* (Rubiaceae) exhibited a dose-dependent decrease in the total number of faecal droppings in castor oil-induced diarrhoea in mice. The extract also produced a significant ($p < 0.01$) and dose-dependent reduction in intestinal fluids accumulation and in the gastrointestinal transit from 64.59 % and 71.19% at doses of 250 and 500 mg/kg. The reduction rates were 37.85% and 74.91%, respectively, with the control and standard drug group.[23]

Andrographis paniculata

The alcoholic extract of *Andrographis paniculata* (Acanthaceae) exhibited significant antidiarrhoel activity against *E. coli* enterotoxins in animal models. Andrographolide was found to be superior against heat stable; enterotoxin, the most common cause of epidemics of neonatal diarrhoea. Alcoholic extract of *A. paniculata* inhibits the intestinal secretory response induced by heat labile enterotoxins, which are known to act through the stimulation of adenylate cyclise and they do not cause any structural damage to the enterocytes. It also inhibits the secretion induced

by *E. coli* heat stable enterotoxins, which act through activation of guanylate cyclase. When the alcoholic extract of *A. paniculata* was given simultaneously with enterotoxins the inhibition was found to be dose dependent. Andrographolide may act as a biochemical step after cyclase activation or it may act non-specifically to increase the intestinal absorption.[8]

Annona senegalensis

The antidiarrhoel effect of *Annona senegalensis* (Annonaceae) at a dose of 10 mg/kg was found to be similar to loperamide. The extract of *A. senegalensis*, at the dose rate of 10 mg/kg, significantly (p<0.05) reduced the length covered by the standard charcoal meal in the gastrointestinal tract (GIT) of mice by 23.70%. This value was higher than that of 19.69% produced by administration of loperamide (a standard antidiarrhoel agent) at a dose of 1mg/kg. The extract was acting as an antagonist of either neurotransmitter to block their effect by preventing the release of Ca^{2+} from the cisternae and hence its entry into the cell to activate smooth muscle contraction.[22]

Artemisia douglasiana

Dehydroleucodine, a sesquiterpene lactone of the guaianolide type isolated from *Artemisia douglasiana* prevented the damage and inflammation in acetic acid-induced colitis in rats and TNBS-induced colitis in mice; accompanied by significant decreases in diarrhoea. The α_2-adrenergic receptor antagonist yohimbine and phentolamine effectively antagonized the effect of dehydroleucodine, when given subcutaneously (1 mg/kg) 10 min before administration of dehydroleucodine. This inhibitory effect on small intestinal transit induced by dehydroleucodine could be at least in part responsible of its antidiarrhoel activity. Dehydroleucodine given orally at dose of 10 and 80 mg/kg reduced in dose-related manner diarrhoea induced by castor oil when given 60 min before oil challenge. Dehydroleucodine produces an inhibitory action on gastrointestinal functions, motility and secretion, and this effect is mediated, at least in part, through the α_2-adrenergic system.[77]

Artemisia ludoviciana

Nonanal showed a significant inhibitory effect on mice with diarrhoea induced with castor oil, $MgSO_4$ and arachidonic acid. However, with the PGE_2- induced diarrhoea model, the effect was smaller. It also showed an important delayed the intestinal transit activity 30 min after its administration. The Nonanal isolated from *A. ludoviciana* showed symptomatic relief of induced diarrhoea.[25]

Asparagus racemosus

Asparagus racemosus (Liliaceae), the extracts had a similar activity as loperamide, when tested at 200 and 250 mg/kg and statistically significant reduction in the frequency of defecation and the wetness of the faecal droppings when compared to untreated control rats. Anti-diarrhoeal effect of ethanol and aqueous extracts may be due to the inhibition of prostaglandin biosynthesis. The plant extracts showed significant ($P < 0.05$) inhibitor activity against castor oil induced diarrhoea and PGE_2 induced enteropooling in rats when tested at 200 mg/kg. Both extracts also showed significant ($P < 0.001$) reduction in gastrointestinal motility in charcoal meal test in rats.[26]

Baphia nitida

In the castor oil-induced diarrhoea test, *Baphia nitida* (Papilionaceae) produced a significant increase in onset of diarrhoea (103.40 ± 8.74, 138.80 ± 17.04 and 174.8 ± 29.04 min, 100 to 400 mg/kg, vs. 47.60 ± 8.76 min for control and 226.10 ± 12.57 min for morphine). The severity of diarrhoea (diarrhoea score) was dose dependently reduced (19.00 ± 2.26, 17.04 ± 1.89, 15.00 ±

2.05, 100 to 400 mg/kg, vs. 31.40 ± 2.11 for control and 7.7 ± 2.2 for morphine). *B. nitida* also reduced the number and weight of wet stools. Ethyl acetate leaf extract of *B. nitida* possesses antidiarrhoel property possibly mediated by interference with the L-arginine nitric oxide pathway and synergistic with antagonistic action on muscarinic receptors.[27]

Butea monosperma

Ethanolic extract of *B. monosperma* possesses significant anti-diarrhoeal activity due to its inhibitory effect both on gastrointestinal propulsion and fluid secretion. The extract appears to act on all parts of the intestine. Thus, it reduced the intestinal propulsive movement in the charcoal meal treated model; at 800 mg/kg, the extract showed activity similar to that of atropine. The extract at doses of 400 and 800 mg/kg reduced diarrhoea by inhibiting gastrointestinal motility and PGE_2 induced enteropooling. The extract of *B. monosperma* exhibited significant anti-diarrhoeal activity against castor oil induced diarrhoea in rats. The extract had a similar activity as loperamide, when tested at 400 and 800 mg/kg and significantly inhibited the frequency of defecation and the wetness of the faecal droppings when compared to control rats.[29]

Byrsocarpus coccineus

The *Byrsocarpus coccineus* extract (50, 100, 200 and 400 mg/kg, p.o.) produced a significant ($P < 0.05$) dose dependent decrease in propulsion in the castor oil-induced intestinal transit in mice. In a dose dependent manner, it delayed the onset of diarrhoea, produced a significant decrease in the frequency of defecation, severity of diarrhoea and protected the mice treated with castor oil. Mean diarrhoea scores were 30.83 ± 1.72, 22.40 ± 1.71, 21.43 ± 1.32, 13.80 ± 0.33, 18.00 ± 3.94 and 7.67 ± 2.41 for control, extract (50, 100, 200 and 400 mg/kg) and morphine, respectively. The extract (400 mg/kg) significantly decreased the volume (ml) of intestinal fluid secretion induced by castor oil (0.60 ± 0.23) compared with 1.27 ± 0.12 for control. *B.coccineus* possesses antidiarrhoel activity due to its inhibitory effect on gastrointestinal propulsion, mediated through α_2 adrenoceptors, and also inhibition of fluid secretion.[30]

Calotropis gigantea

Like atropine (3 mg/kg, i.p.) there were significant reductions in fecal output and frequency of droppings when *Calotropis gigantea* extracts of 200 and 400 mg/kg doses were administered intraperitoneally compared with castor oil treated rats. All doses of plant extract also significantly retarded the castor oil induced enterpooling and intestinal transit. The dose 100 ($P < 0.01$), 200 and 400 mg/kg significantly inhibited ($P < 0.01$) weight and volume of intestinal content. Probably extract increased the reabsorption of NaCl and water by decreasing intestinal motility as observed by the decrease in intestinal transit by charcoal meal. The antidiarrhoeal activity of the extract may also be due to the presence of denature proteins forming protein tannaates, protein tannates make the intestinal mucosa more resistant and reduce secretion.[31]

Calotropis procera

Dry latex of *Calotropis procera* possesses significant anti-diarrhoeal activity due to its inhibitory effect both on gastrointestinal propulsion and fluid secretion. Dry latex significantly inhibited the castor oil induced intestinal fluid accumulation (enteropooling) and the volume of intestinal content was equivalent to that of normal rats. Dry latex of *C. procera* produced a statistically significant reduction in the frequency and severity of diarrhoea produced by castor oil. Dry latex delayed the onset of diarrhoea and a larger number of rats (80%) were protected against the castor oil induced diarrhoea. Like atropine and phenylbutazone (PBZ), a single oral dose of dry latex (500 mg/kg) produced a significant decrease in frequency of defecation, severity of

diarrhoea and afforded protection from diarrhoea in 80% rats treated with castor oil. Unlike atropine, Dry latex significantly inhibited castor oil induced enteropooling.[32]

Cinnamomum tamala

Cinnamomum tamala extract (25, 50 and 100 mg/kg, orally) produced a dose-dependent reduction in the total amount of faecal matter in castor oil-induced diarrhoea. The mean distance travelled by charcoal meal at 50 and 100 mg/kg of extract showed a significant reduction in the secretion of gastrointestinal fluid accumulation by 32.5-65.0%. [35]

Cleome viscosa

Methanol extract of the entire plant *Cleome viscose* extract at doses of 200, 400 and 600 mg/kg body wt. significantly inhibited frequency of defecation and wetness of fecal droppings, like the standard antidiarrhoeal agent (Diphenoxylate) as compared to untreated control rats. The antimuscarinic drug atropine and methanol extract of the entire plant *C. viscose* at different dose levels (200, 400 and 600 mg/kg body wt.) decreased the intestinal propulsive movement in the charcoal-meal-treated model. Methanol extract of the entire plant *C.viscose* in graded doses (200, 400 and 600 mg/kg body wt.) reduced diarrhoea by inhibiting motility and PGE_2 enteropooling. The tannin present in the methanol extract of the entire plant *C.viscose* may be responsible for the antidiarrhoeal activity.[33]

Clerodendrum phlomidis

Methanolic extract of leaves of *Clerodendrum phlomidis* showed significant inhibitory activity against castor oil induced diarrhoea and PGE_2 induced enteropooling in rats. The extract also showed a significant reduction in gastrointestinal motility in charcoal meal test in rats. The extract at the doses 600 and 800 mg/kg p.o., like the standard anti-diarrhoeal agent diphenoxylate, significantly inhibited the frequency of defecation and the wetness of the faecal droppings compared to untreated control rats. The anti-muscarinic drug atropine and extract at different dose levels (200, 400, 600 mg/kg p.o.) decreased the intestinal propulsive movement in the charcoal meal treated model, methanolic extract of leaves of *C. phlomidis*, 800 mg/kg showed activity similar to that of atropine. The methanolic extract at a dose of 600 mg/kg p.o. reduced diarrhoea by inhibiting gastrointestinal motility and PGE_2-induced enteropooling. The underlying mechanism appears to be spasmolytic and an anti-enteropooling property by which the plant extract produced relief in diarrhoea. The tannins present in the plant extract may be responsible for the anti-diarrhoeal activity.[34]

Commelina coelestis

The methanolic extracts of *Commelina coelestis* showed dose related antidiarrhoeic activity at doses of 12.5-50 mg/kg on diarrhoea induced by castor oil or magnesium sulphate. Methanol extract of *C. coelestis* is more effective at dose of 50 mg/kg (71.4% of inhibition) in record time, whereas 100 mg/kg dose showed diminished effect (39.6% inhibition).[20]

Costus lucanusianus

Costus lucanusianus at doses of 100 mg/kg, 200 mg/kg and 400 mg/kg caused a marked inhibition of the diarrhoea response following castor oil administration ($P < 0.0001$). It also significantly ($p < 0.0001$) inhibited the small intestinal transit in mice. 200 and 100 mg/kg of *C. lucanusianus* gave the highest effect in the castor oil-induced diarrhoea and small intestinal transit respectively. In comparism with Atropine, its antidiarrhoeal effect at 100mg/kg was found to be 179% and 165% respectively on castor oil induced diarrhoea and on small intestinal transit.[2]

Combretum sericeum

The aqueous extract of *Combretum sericeum* (*Combretacae*) on castor oil induced diarrhoea decreased the number of faecal matter pass by the animals. At 25 and 50 mg/kg extract, a significant ($P < 0.05$) reduction in diarrhoea was observed representing 58.54 and 94.91% inhibition, respectively. The extract significantly protects the rats against diarrhoea evoked by castor oil in a dose dependent manner.[36]

Conyza dioscoridis

Oral administration of methanol extract from *Conyza dioscoridis* in a 200 mg/kg dose exhibits a significant antidiarrhoeal effect against castor oil-induced diarrhoea. In a dose of 400 mg/kg, *C. dioscoridis* produced a significant ($P < 0.01$) effect; Methanol extract of *C. dioscoridis* induced a dose-dependent (0.4- 2.8 mg/ml) relaxation of rabbit's duodenal smooth muscle.[19]

Cylicodiscus gabunensis

Like loperamide (3 mg/Kg body weight), a single oral dose of *Cylicodiscus gabunensis* (Mimosaceae) ethyl acetate extract (375, 750 mg/Kg body weight) produced a significant decrease in the severity of diarrhoea. *C. gabunensis* ethyl acetate extract produced a decrease in intestinal transit (10.26-30.75%), and unlike atropine, it significantly inhibited castor oil induced enteropooling. The extract also led to a marked reduction in the weight and the volume of the intestinal contents.[4]

Dalbergia lanceolaria

Ethanol extract of *Dalbergia lanceolaria* (Fabaceae) bark exhibited significant activity against castor oil, magnesium sulphate and barium chloride induced changes in gastrointestinal tract. Extract reduced significantly intraluminal fluid accumulation and intestinal motility. The extract is also showing inhibition of peristalsis activity in normal as well as in barium chloride induced increase peristalsis as evident from distance traveled by charcoal meal. This significant reduction in peristaltic activity is one of the important factor contributing to antidiarrhoeal activity of extract.[37]

Dalbergia sissoo

Dalbergia sissoo (Fabaceae), known as Indian Rosewood. The decoction reduced the production and the binding of CT and bacterial adherence and invasion. *D. sissoo* is antidiarrhoeal as it affects bacterial virulence.[38]

Emilia coccinea

Antidiarrhoeal effect of both methanol and aqueous *Emilia coccinea* (Asteraceae) extracts may be due to the inhibition of prostaglandin biosynthesis. The methanol extracts, and to a lesser extent the aqueous extract, significantly prolonged the time for diarrhoeal induction; it reduced the frequency of diarrhoea episodes and decreased the propulsion of charcoal meal through the gastrointestinal tract in a dose dependent manner. These extracts significantly inhibited the castor oil-induced intestinal fluid accumulation (enteropooling) and weight of intestinal content. Extracts of *Emilia coccinea* reduced diarrhoea by increasing reabsorption of electrolytes and water or by inhibiting induced intestinal accumulation of fluid just as loperamide. These extracts suppressed the propulsion of charcoal meal (probably in the same way as atropine sulphate) which thereby increases the time for absorption of water and electrolytes.[39]

Eremomastax speciosa

The aqueous extract of *Eremomastax speciosa* leaves showed significant antidiarrhoeal activity ($P < 0.01$) against castor oil induced diarrhoea in mice. It reduced the number of wet faeces

produced by castor oil administration from 20.50 ± 3.69 to 12.00 ± 1.40 (42.50%) and 10.50 ± 1.84 (48.75%) when experimental animals were respectively administered 400 and 800 mg/kg plant extract. The plant extract thus stimulates the reabsorption of water from the intestinal lumen, resulting to the normalisation of the deranged water transport across the mucosal cells which are seen in the type of faeces produced.[40]

Ficus hispida

The *Ficus hispidus* leaf methanolic extract when administered orally to rats, showed a significant and dose-dependent anti-diarrhoeal activity. The dose of 600 mg/kg seems to show an equivalent effect of that of 5 mg/kg of diphenoxylate. Moreover, it decreased significantly the propulsion of charcoal meal through the gastrointestinal tract and the PGE_2-induced enteropooling rats.[42]

Galla Chinensis

Galla Chinensis extract exhibited anti- heat-labile enterotoxin -induced diarrheal effect in the patent mouse gut assay, with IC_{50} value of 4.7 ± 1.3 mg/ml. Ethyl acetate (EA) soluble fraction was the most active fraction of Galla Chinensis that inhibiting the binding of B subunit of heat-labile enterotoxin to G_{M1} with an IC_{50} value of 153.6 ± 3.4 µg/ml. The major components of the EA fraction should be phenolic derivatives according to a thin-layer chromatography analysis. Gallic acid, the major component of EA fraction, blocked the binding of B subunit of heat-labile enterotoxin to G_{M1}, resulting in the suppression of heat-labile enterotoxin -induced diarrhoea. Galla Chinensis and gallic acid might be potent drugs for the treatment of heat-labile enterotoxin -induced diarrhoea. [40]

Gentianopsis paludosa

The 75% ethanol extract (100-400 mg/kg) of *Gentianopsis paludosa* inhibited castor oil-induced diarrhoea and also reduced gastrointestinal motility in the charcoal meal test in mice. In the rabbit-isolated ileum, the extract showed inhibitory effects not only on its spontaneous contraction, but also on acetylcholine (Ach, 0.1 mM)- and KCl (60 mM)-induced contractions. Anti-diarrhoeal activity may be attributed to its inhibition of intestinal motility through interference with Ca^{2+} movement.[43]

Geranium incanum

The leaf aqueous extract of *Geranium incanum* significantly reduced faecal output in castor oil -induced diarrhoea and also significantly reduced the number of diarrhoeal episodes. *G. incanum* significantly delayed the onset of diarrhoea induced by castor oil and significantly reduced thenumber of animals exhibiting diarrhoea. Both *Geranium incanum* and loperamide significantly reduced the intestinal propulsion of charcoal meal in mice. Leaf aqueous extract of *G. incanum* has both antidiarrhoeal and antipropulsive activities.[45]

Guiera senegalensis

The *Guiera senegalensis* extract produced 100% inhibition of castor oil-induced diarrhoea in mice. The frequency of defecation as well as the wetness of the faecal droppings was significantly reduced. The oral LD_{50} values obtained were >5000 mg/kg in both mice and rats. The extract of *G. senegalensis* produced relief in diarrhoea by spasmolytic activity *in vivo* and anti-enteropooling effects. *Guiera senegalensis* also exerted significant anti-enteropooling effects causing a dose-related inhibitory effect on castor oil-induced enteropooling in rats.[44]

Jatropha curcus

The methanol extract of *Jatropha curcus* (Euphorbiaceae) showed activity against castor oil induced diarrhoea and intraluminal accumulation of fluid. It also reduced gastrointestinal

motility after charcoal meal administration in albino mice. Methanol extract of *J. curcus* roots has shown dose dependent antidiarrhoeal activity in a castor oil induced model in albino mice. This activity is significant at a dose of more than 100 mg/kg. Methanol extract of *J. curcus* root could be through a combination of inhibition of elevated prostaglandin biosynthesis and reduced propulsive movement of the small intestine.[46]

Juniperus Phoenicia

The aqueous extract of *Juniperus Phoenicia* (Cupressaceae) caused a dose dependent protection of rats against castor oil induced diarrhoea and reduced castor oil induced enteropooling. The extract also caused a dose dependent decrease in intestinal transient and showed a significant dose dependent relaxant effect (EC_{50} = 65.1 ± 8.4 mg /mL) on rat ileal smooth muscle. The antidiarrhoeal activity of *J. Phoenicia* extract could be due to several mechanisms. These mechanisms include: (A) the extract may increase the reabsorption of water and NaCl by decreasing intestinal motility as observed by the reduction in intestinal motility by charcoal meal. (B) The presence of tannates in the aqueous leaves extract of *juniperus Phoenicia* may make the intestinal mucosa more resistant and reduces secretion. Tannic acid and tannins are water soluble polyphenols that are present in many plants. (C) The extract may reduce prostaglandins secretion from intestinal mucosa.[47]

Litsea polyantha

Approximately 90% of the untreated animals developed diarrhoea by the end of 4 h and 100% by the end of 5 h after castor oil administration, whereas only 25% of treated animals (methanol extract of dried bark and aerial parts of *L. polyantha* 100 mg/kg) developed diarrhoea by the end of 5 hr. Methanol extract of dried bark and aerial parts of *L. polyantha* inhibits significantly the onset of diarrhoea and intestinal transit like the standard anti-diarrheal agent, loperamide.[48]

Ludwigia hyssopifolia

The methanol extract of *Ludwigia hyssopifolia* (Onagraceae) showed significant antidiarrhoeal property by reducing diarrheal episodes in castor oil and serotonin induced diarrhoea in laboratory mice at a dose of higher than 100 mg/kg body weight as compared to standard drug loperamide given at a dose of 66.67 µg/kg body weight. The percent reduction in diarrheal episode by 56.32 and 89.66 after castor oil challenge and 59.09 and 86.36 in serotonin induced diarrhoea was observed at doses of 200 mg/kg and 400 mg/kg body weight of the extract respectively. The methanol extract of *L. hyssopifolia* was also found to reduce the gastrointestinal motility by 53.8% at a dose of 100mg/kg body weight as compared to control. Mechanism of antidiarrhoeal activity of the test methanol extract of *L. hyssopifolia* may be its ability to enhance fluid and electrolyte absorption through the gastrointestinal tract. As cholinergic stimulation often cause diarrhoea by increasing GI motility, the significant inhibition of GI motility by methanol extract of *L. hyssopifolia* suggested its probable mode of action to be the prevention of cholinergic transmission or its anticholinergic effect on gastric mucosa. [49]

Mangifera indica

Both methanolic and aqueous extracts were given orally in the dose of 250 mg/kg, showed significant anti-diarrhoeal activity comparable with that of the standard drug loperamide. Methanolic extract significantly reduced intestinal transit in charcoal meal test as compared with atropine sulphate (5 mg/kg; im).[52]

Mezoneuron benthamianum

The effect of the *Mezoneuron benthamianum* extract at the highest dose was significantly ($p < 0.05$) lower than that of the standard drug. In a dose-dependent manner, the extract delayed the

onset of diarrhoea, produced a significant decrease in the frequency of defecation, severity of diarrhoea and protected the mice treated with castor oil. Total diarrhoea scores were 12.0 ± 0.63, 10.3 ± 2.06, 8.5 ± 2.15, 7.1 ± 0.91 and 5.8 ± 0.79 for control, extract (400, 800 and 1600 mg/kg) and morphine, respectively. The extract significantly decreased the volume (ml) of intestinal fluid secretion induced by castor oil (1.75 ± 0.02 to 0.93 ± 0.04) compared with 1.90±0.05 for control. The inhibitory effect on fluid accumulation by the extract was also attenuated by yohimbine (1.0 mg/kg). The extract (400, 800 and 1600 mg/kg, orally) produced a significant ($p < 0.05$) and dose-dependent reduction in propulsion in the castor oil-induced intestinal transit in mice. *M. benthamianum* possesses anti-diarrhoeal activity due to its inhibitory effects on gastrointestinal propulsion and intestinal fluid accumulation.[50]

Momordica cymbalaria

The *Momordica cymbalaria* fruit extract showed significant ($p<0.05$) inhibitory activity against castor oil induced diarrhoea and PGE_2 induced enteropooling in rats when tested at 200 mg/kg. The extract also showed significant ($p<0.001$) reduction in gastrointestinal motility in charcoal meal test in rats.[51]

Nelumbo nucifera

Methanolic extract of rhizomes of *Nelumbo nucifera* treated animals showed significant inhibitory activity against castor oil induced diarrhoea and inhibited significantly PGE_2 enteropooling in rats. It also showed significant reduction in gastrointestinal motility following charcoal meal in rats.[53]

Ocimum gratissimum

The aqueous leaf extract of *Ocimum gratissimum* (Labiatae) offered a dose -related protection against castor oil -induced diarrhoea within the dose-range (25 to 100 mg/kg body wt.) tested. This was evidenced by the significant reduction in the frequency of defecation and wetness of faeces.[54]

Ocimum selloi

Ocimum selloi essential oil produced a significant reduction in the severity and frequency of diarrhoea produced by castor oil in mice. At 200 mg/kg; p.o., the *O. selloi* essential oil significantly reduced the charcoal meal intestinal transit in mice.[55]

Pongamia glabra

The aqueous and methanolic extract of *Pongamia glabra* at lower doses were less effective, but at higher doses the extracts were more effective. The methanol extract of the plants had greater anti-diarrhoeal effect than aqueous extract against castor-oil induced diarrhoea. For gastro-intestinal disorders or in diarrhoeal diseases the lower dose of 7.5 mg and below of *P. glabra* is useful.[16]

Parkia biglobosa

The anti-diarrhoeal action may be linked partly to direct inhibitory effect of the *Parkia biglobosa* extract on the propulsive movement of the gastrointestinal tract smooth muscle. The hot water extract of stem bark of *P. biglobosa* contains active principle with remarkable anti-diarrhoeal properties.[56]

Paullina Pinnata

Paullinia pinnata (Sapindaceae) at a dose of 50 mg/kg significantly ($p < 0.01$) decreased the total number of stools passed (6.50 ± 0.866) as compared to the castor oil treated control groups

(14.25 ± 0.479), while the 200 mg/kg caused a near blockade of diarrhoea induced by castor oil with only 2.25 ± 0.75 stools passed. It also inhibited the castor oil induced diarrhoea by delaying the onset of diarrhoea, with the 200 mg/kg dose giving the highest effect (153.75 ± 27.207 minutes). While the 50 mg/kg and 100 mg/kg doses delayed the onset of diarrhoea by 82.0 ± 20.01 and 92.25 ± 19.76 minutes respectively. The extract at 50mg/kg, 100 mg/kg and 200 mg/kg, significantly ($p > 0.05$, $p < 0.01$ and $p < 0.001$) inhibited the transit of charcoal meal along the intestine by 37.06%, 59.81% and 79.34% respectively (compared to the control group, and standard (Atropine 0.2 mg/kg) group which caused 56.91% inhibition). [47]

Pentaclethra macrophylla

Antidiarrhoeal potential of *Pentaclethra macrophylla* extracts was evidenced by a significant reduction in faecal output and protection from castor oil-induced diarrhoea in rats treated with the extracts. The i.p. LD_{50} values were established to be 770 mg/kg and 280 mg/kg for the aqueous and ethanol extracts, respectively. Extracts significantly ($p < 0.05$) decreased propulsive movement of gastrointestinal contents in mice.[57]

Phoenix dactylifera

The date palm (*Phoenix dactylifera*) extract significantly ($P<0.01$) inhibited the mean number of defecation when compared to saline group, and produced a dose-dependent (19-42%) inhibition of the severity of diarrhoea induced by castor oil. Aqueous extract significantly reduced both castor-oil induced intestinal transit and frequency of diarrhoea effects.[58]

Psidium guajava

Psidium guajava (Myrtaceae) leaf aqueous extract (50–400 mg/kg *p.o.*) produced dose-dependent and significant ($P<0.05$–0.01) protection of rats and mice against castor oil-induced diarrhoea, inhibited intestinal transit, and delayed gastric emptying. Compared with control animals, *P. guajava* leaf aqueous extract dose-dependently and significantly ($P<0.05$–0.01) decreased the volume of castor oil-induced intestinal fluid secretion, and reduced the number, weight and wetness of faecal droppings. *P. guajava* leaf aqueous extract also produced concentration-related and significant ($P<0.05$–0.01) inhibitions of the spontaneous, rhythmic, pendular contractions of the rabbit isolated duodenum.[13]

Punica granatum

Punica granatum seed extract (100, 200, 400, and 600 mg/kg orally), like standard antidiarrhoeal agent, diphenoxylate, significantly inhibited the frequency of defecation and the liquid content of the faecal droppings compared to control rats. The antimuscarinic drug atropine and *Punica* seed extract decreased intestinal propulsive movement in the charcoal meal treated model. The *P. granatum* extract (in graded doses) reduced diarrhoea by inhibiting gastrointestinal motility and PGE_2-induced enteropooling. Tannins are responsible for protein denaturation producing protein tannate, which reduces secretion from intestinal mucosa. *P. granatum* seed extract also contains tannin which may produce antisecretory activity. Mechanisms for treatment of diarrhoea appear to be spasmolytic and anti-enteropooling.[59]

Rhus javanica

The methanolic extract of *Rhus javanica* treated mice, showed significant reduction in the faecal output and protected them from castor oil-induced diarrhoea. The extract also reduced the intestinal fluid secretion induced by $MgSO_4$ and gastrointestinal motility after charcoal meal administration in the albino mice. The methanolic extract of ripen fruits of *R. javanica* inhibited significantly the frequency of defecation and reduced greatly the wetness of the faecal excretion like the standard antidiarrhoeal agent, loperamide.[60]

Rumex maritimus

The methanol extract of *Rumex maritimus* at 50, 100 and 200 mg/kg body weight doses, significantly lowered several typical parameters of diarrhoea. The methanol extract also showed significant anti-motility activity like the standard drug atropine. Hexane and ethylacetate extract showed mild to moderate antidiarrhoeal and antimotility activity. The methanol extract most significantly prolonged the time for induction of diarrhoea, reduced the frequency of diarrhoeal episodes and also decreased the propulsion of charcoal meal through the gastrointestinal tract.[60]

Saccharum spontaneum

The antidiarrhoeal activity of the *Saccharum spontaneum* extract (200 and 400 mg/kg) was obsereved in castor oil induced diarrhoea in mice and a dose dependent decrease in the total number of faecal dropping.[62]

Sanseviera liberica

Sanseviera liberica (25-400 mg/kg, p.o.) produced significant ($P < 0.05$) dose dependent reduction in propulsive movement in both the normal and castor oil induced intestinal transit tests in mice. In the castor oil induced diarrhoea test, *S. liberica* significantly delayed the onset and decreased the frequency and severity of diarrhoea. *S. liberica* at the dose of 200 mg/kg significantly reduced the volume of intestinal secretion induced by castor oil. The aqueous root extract of *S. liberica* possesses antidiarrhoeal activity due to inhibition of gastrointestinal propulsion and fluid secretion, possibly mediated through inhibition of the nitric oxide pathway.[63]

Securinega virosa

The methanolic root bark extract of *Securinega virosa* (Euphorbiaceae) produced a dose-dependent protection against the castor oil- induced diarrhoea with the highest protection (100%), obtained at 100 mg/kg comparable to that of loperamide (5 mg/kg), the standard agent. The leaves extract also protected the mice but was not dose-dependent. The highest protection (60%) was obtained at the lowest dose (50 mg/kg). Anti-diarrhoeal effects of methanolic leaves and root bark extracts may be due to the inhibition of prostaglandin biosynthesis.[64]

Sphaeranthus senegalensis

Sphaeranthus senegalensis (Asteraceae) inhibited the onset time and severity of diarrhoea induced by castor oil. The activity of the extract against the experimentally induced diarrhoea by castor oil may thus be attributed to an anti-electrolyte permeability action. The extract also inhibited the intestinal propulsion as shown by its inhibitory action against charcoal meal motility.[65]

Spondias mangifera

A significant decrease in the number of wetness and frequency of defecation was observed in castor-oil induced diarrhoea by *Spondias mangifera* (Anacardiaceae) bark extract (100-200 mg/kg, p.o). The extracts also showed significant ($p < 0.01$) reduction in intestinal propulsion in charcoal meal test in rats.[66]

Stereospermum kunthianum

Aqueous extract of *Stereospermum kunthianum* stem bark possessed antidiarrhoeal activity in castor oil treated animals. The extract dose-dependently inhibited castor oil-induced transit in mice. There was delay in onset of diarrhoea and the total number of stools, number of wet stools, and weight of wet stools were all dose dependently decreased, with the highest effect observed

with the 200 mg/kg body weight of the extract. The extract produced a significant antidiarrhoeal index reinforces its protective action in diarrhoea.[68]

Strychnos nuxvomica

Methanol extract of the plants had greater anti-diarrhoeal effect than aqueous extract against castor-oil induced diarrhoea. *Strychnos nux*vomica extract at higher doses are very effective but was toxic to the animals.[16]

Strychnos potatorum

Methanol extract of the dried seeds of *Strychnos potatorum* (100, 200 and 400 mg/kg, p.o.. significantly (P<0.001) inhibited the frequency of defecation and reduced the wetness of faecal droppings in castor oil-induced diarrhoea, decreased the propulsion of charcoal meal through the gastrointestinal tract, and also reduced the PGE_2-induced enteropooling.[67]

Swietenia macrophylla

At various doses (25, 50 & 100 mg/kg body weight) of *Swietenia macrophylla* (Meliaceae) extract showed a remarkable antidiarrhoeal activity evidenced by the reduction in the rate of defecation and consistency of faeces. A single oral dose of *S. macrophylla* extract of 100mg/kg body weight produced a significant decrease in the severity of diarrhoea. Extract produced profound decrease in intestinal transit (4.45 - 34.60%) also significantly inhibited castor oil induced enteropooling comparable to that of intraperitoneal injection of standard drug atropine sulphate at doses of 0.1 mg/kg body weight and 3 mg/kg body weight respectively.[1]

Thespesia populnea

Alcoholic and aqueous extracts of *Thespesia populnea* (Malvaceae) exhibited significant antidiarheal activity against castor oil induced diarrhoea in rats. Alcoholic extracts (100, 200 & 400 mg/kg) and aqueous extracts (50,100 & 200 mg/kg) reduced diarrhoea by inhibiting PGE_2 induced intestinal accumulation of fluid. Alcoholic extracts (100, 200 and 400 mg/kg) and aqueous extracts (50, 100 and 200 mg/kg) suppressed the propulsion of charcoal meal there by increased the absorption of water and electrolytes. The inhibition of peristaltic movement with alcoholic and aqueous extracts of stem bark of *T. populnea* may be due to the anti histaminic and anticholinergic actions Alcoholic extracts and aqueous extracts possess significant antidiarrhoeal activity due to their inhibitory effect both on gastrointestinal propulsion and fluid secretion.[69]

Vitex doniana

The extract *Vitex doniana* (Verbenaceae) possesses a concentration-dependent inhibition of both acetylcholine and histamine-induced contractions. The extract (at doses of 150-650 mg/kg) also inhibited gastric peristalsis in mice fed charcoal meal and significantly protected mice against castor oil–induced diarrhoea. Inhibition of gastrointestinal tract motility is one mechanism of action of antidiarrhoeal drugs. The antagonistic effect of plant extracts on muscarinic receptors is another possible mechanism of action of the aqueous extract of *V. doniana*.[3]

Xanthium Indicum

The methanol extract of *X. indicum* successfully inhibited the castor oil-induced diarrhoea; the extract might have exerted its antidiarrhoeal action via antisecretory mechanism which was also evident from the reduction of total number of wet faeces. The extract may have increased the absorption of water and electrolyte from the gastrointestinal tract, since it delayed the gastrointestinal transit in mice as compared to the control. The delay in the gastrointestinal transit prompted by the extract might have contributed, at least to some extent, to their antidiarrhoeal activity by allowing a greater time for absorption.[70]

Xylocarpus moluccensis
At the doses of 250 and 500 mg/kg, the MeOH extract of *Xylocarpus moluccensis* showed significant antidiarrhoeal activity. Antidiarrhoeal action *Xylocarpus moluccensis* was exerted by antisecretory mechanism.[71]

Zingiber officinale
Zingiber officinale (Zingiberaceae) decoction probably modifies bacterial as well as host cell metabolism to exhibit its antidiarrhoeal action.[75]

Zizyphus spinachristi
The methanol extract of *Zizyphus spinachristi* caused a dose dependent protection of rats against castor oil induced diarrhoea, decreased the intraluminal fluid accumulation and gastrointestinal transit. The methanol extract of *Z. spinachristi* stem bark administered orally caused significant inhibition of the severity and prolong the onset time of diarrhoea induced experimentally in rats by castor oil. The extract might achieve this activity through the inhibition of electrolyte permeability and/or inhibition of prostaglandin release. The antidiarrhoeal effect of the extract may be attributable to its inhibitory action against gastrointestinal motility and the inhibition of enteropooling property.[73]

Ziziphus mauritiana
The Antidiarrhoeal effect of the methanolic extract of *Ziziphus mauritiana* (*Rhamnaceae*) exhibited a concentration dependent inhibition of the spontaneous pendular movement of the isolated rabbit jejunum and inhibited acetylcholine induced contraction of rat ileum. A dose dependent decrease of gastrointestinal transit was observed with extracts (25 and 50 mg/kg) which also protected mice against castor oil induced dirrhoea and castor oil induced fluid accumulation, respectively. The extract was able to inhibit electrolyte permeability in the intestine due to castor oil and or through the inhibition of prostaglandins release.[74]

Triphala *Mashi*, an *Ayurvedic* Formulation
Aqueous and alcoholic extracts, at various doses 200, 400 and 800 mg/kg displayed remarkable anti-diarrhoeal activity as evidenced by a significant increase in first defecation time, cumulative fecal weight and intestinal transit time. The remarkable anti-diarrhoeal effect of Triphala and Triphala *Mashi* extracts against castor oil-induced diarrhoea suggest its potential for application in a wide range of diarrhoeal states.[79]

Wei-Chang-An-Wan, an *Ayurvedic* Formulation
Wei-Chang-An-Wan (WCAW), a traditional pharmaceutical preparation. At the doses of 400 and 800 mg/kg, Methanol extract significantly protected mice against castor oil-induced diarrhoea as well as the number of faeces and wet faeces. Methanol extract also dose-dependently attenuated spontaneous contractions of the isolated rabbit jejunum, and those induced by acetylcholine (Ach) and neostigmine. [80]

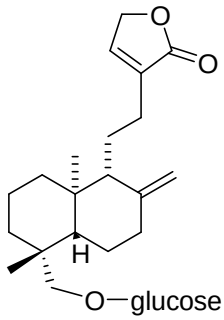
Natural lead compounds
Ethnopharmacological research on natural products can contribute to the discovery of new active compounds with novel structures which may serve as leads to development of new antidiarrhoel drugs. Phytochemical screening of plants extracts (made in organic solvents or water) has revealed the presence of numerous chemicals including alkaloids, tannins, flavonoids, sterols, terpenes, carbohydrates, lactones, proteins, amino acids, glycosides, and saponins etc. Different phytochemicals display various mechanism of action (given in table-3).

Table 3: Different natural lead compounds with mechanism of action

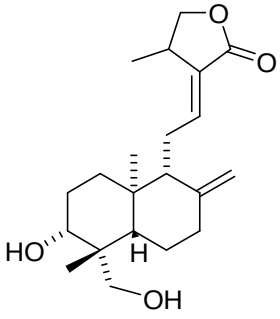
Natural lead compounds	**Plants name**	**Mechanism of action**	**Ref.**
Quercetin	*P. guajava*	Inhibit spasmogenic effects of various agonists (acetylcholine, carbachol, potassium chloride) on guinea-pig isolated ileum, Inhibit gastrointestinal release of acetylcholine	13
Steroids	*S. macrophylla*	Enhance intestinal absorption of Na^+ and water	1
Flavonoids	*A.marmelos, Z. officinale. A. racemosus, E. coccinea, G. paludosa*	Inhibition of intestinal motility, antimicrobial action and antisecretory effects	26,39,43,40,17
	J. phoenicia, X. indicum, C. gigantea, V. doniana	Release of autocoids and prostaglandins.	22,3, 70
	E. speciosa	Stimulating the normalization of the deranged water transport across the mucosal cells and the reduction of the intestinal transit,	40
	Z. mauritiana	Inhibitory activity of on intestinal motility in a dose related manner.	74
	C. sericeum	Inhibit contraction caused by spasmogenes, inhibit intestinal secretion and small intestinal transit.	36,22
Alkaloids	*J. phoenicia*	Release of autocoids and prostaglandins.	47
Tannins	*A.marmelos, Z. officinale. C. gigantea*	Inhibition of intestinal motility, antimicrobial action and antisecretory effects.	22,82,17
	E. speciosa, C. gabunensis	Stimulating the normalization of the deranged water transport across the mucosal cells and the reduction of the intestinal transit	4,40
	C. gabunensis, Z. spinachristi, X. Indicum, E. coccinea, S. senegalensis, F. hispidus, C. viscosa,	Reduce secretion and make the intestinal mucus resistant through the formation of protein tannate.	4,39,65,73,42,33,34, 70
Gallic acid (tannins)	Galla Chinensis,	Blocked the binding of B subunit of heat-labile enterotoxin to G_{M1}, resulting in the suppression of heat-labile enterotoxin -induced diarrhoea.	78
	A. catetu, G. incanum	Astringent action	15,45
Saponins	*Z. mauritiana*	Inhibit histamine release *in vitro*	74

Dehydroleucodine	*A. douglasiana*	Inhibitory action against gastrointestinal motility and the inhibition of enteropooling property	77
Andrographolide and neoandrographolide	*A. paniculata*	Antisecretory agents	8
Methyl chavicol	*O. selloi*	Analgesic and antidiarrhoeal properties	55

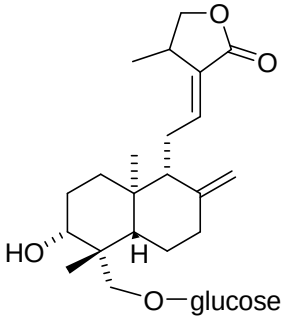
Structure of Natural Lead Compounds



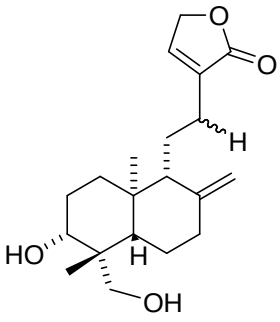
Neoandrographolide



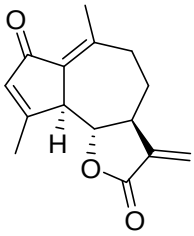
Andrographolide



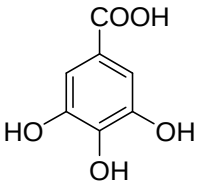
Andrographiside



Deoxyondrographolide



Dehydroleucodine



Gallic acid

CONCLUSION

There are several plants known for their antidiarrhoel activity, with different mode of action and phytoconstituents. This is an effort to streamline the phytoconstituents of specific family with specific mode of action to diarrhoea. The need for newer, more effective, and most importantly, cheaper antidiarrhoeal drugs has become a paramount issue to tackle this present situation.[23] The natural drugs are used as antidiarrhoeal drugs, which are not always free from adverse effects. [14] Therefore, the search for safe and more effective agents has continued to be an important area of active research.[1]

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