Journal of Ethnopharmacology, 37 (1992) 151–157
Elsevier Scientific Publishers Ireland Ltd.

Inhibition of Microlax*-induced experimental diarrhoea with narcotic-like extracts of *Psidium guajava* leaf in rats

George D. Lutterodt

Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan (Malaysia)

(Received May 11, 1991; accepted June 28, 1992)

Measurement of rates of propulsion in the small intestine in control and experimental groups of male Sprague–Dawley rats (200–250 g) were carried out as a means of assessing antidiarrhoeal activity of aqueous extracts of the leaf of *Psidium guajava* (L.), using morphine as the standard drug of reference. Hyperpropulsion (diarrhoea) was induced by gavaging rats in a control group with Microlax, using phenol red mixed into it as a marker in the intestine, and the mean rate of the hyperpropulsion was determined. The normal rate of propulsion, defined as the percentage of the length of the ileum traversed by the front of the dye in 1 h after gavaging animals with a liquid paraffin-phenol red meal, was also determined in another control group. In experimental groups pretreated with enteral administration of either morphine or aqueous extracts, 1 h before the challenge with Microlax, the percentage inhibition to the hyperpropulsive rate (antidiarrhoeal activity) was calculated. Both morphine and the extracts produced a dose-response relationship in their antidiarrhoeal effects. A dose of 0.2 ml/kg fresh leaf extract produced 65% inhibition of propulsion. This dose is equiactive with 0.2 mg/kg of morphine sulphate. The antidiarrhoeal action of the extract may be due, in part, to the inhibition of the increased watery secretions that occur commonly in all acute diarrhoeal diseases and cholera.

Key words: hyperpropulsion; ileum; experimental diarrhoea; morphine sulphate; *Psidium guajava;* flavonoids; rat

Introduction

The drinking of potions of decoctions of the leaf or of the leaf and root bark/stem of the guava plant, *Psidium guajava* L. (Myrtaceae), as well as chewing of the fresh leaf, have been employed in the treatment of acute diarrhoeal diseases for many centuries in folk medicine, especially in tropical areas of the globe where the plant grows naturally. In a previous report by this author, the antidiarrhoeal action of an alcoholic extract of the leaf was shown to be due, in part, to the presence of a flavonoid compound identified as quercetin. Both the extract and the isolated compound elicited a concentration-response relationship in the inhibition of gastrointestinal release of acetylcholine in the electrically stimulated guinea-pig isolated ileum preparation, as well as a spasmolytic effect on the spontaneously contracting isolated ileum, by acting directly on the smooth muscle fibres (Lutterodt, 1988).

More than twenty identified compounds from the guava leaf have been reported in the literature (Seshadri and Vasishta, 1965; Osman et al., 1974; Lutterodt, 1988). The medicinal uses of the leaf as an analgesic, antidiarrhoeal (including cholera and related diarrhoeas) and as a neuroleptic have also been reported (Singh, 1986; Lutterodt and Maleque, 1988). Antibiotic and anti-inflammatory effects have been reported by Watt and Breyer-Brandwijk (1962) and Middleton et al. (1981), respectively.

In diarrhoea, the abnormally frequent expulsion of faeces of low consistency is due to a disturbance in the transport of water and electrolytes in the intestines. Despite the multiplicity of aetiologies, the four major mechanisms responsible for the pathophysiology in water and electrolyte transport are (i) increased luminal osmolarity (osmotic diarrhoea), (ii) increased electrolyte secretion (secretory diarrhoea), (iii) decreased electrolyte absorption, and (iv) deranged intestinal motility, causing decreased transit time (Jinich and Hersh, 1982). The actions of morphine, the prototypical antidiarrhoeal drug, on the gastrointestinal tract are mediated both centrally and locally (Galligan and Burks, 1983; Megens, 1990), the most important component being the stimulation of the net absorption of water and electrolytes in the small and large intestine in several species of animals, including man (Awouters et al., 1983; Coupar,

Correspondence to: George D. Lutterodt, Department of Pharmacology, School of Medical Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, Malaysia.

*Microlax is a registered trade name of a microenema produced by Pharmacia AB, S-751 82 Uppsala, Sweden.

0378-8741/92/$05.00

1987). It is now widely accepted that abnormalities in the intestinal transport of electrolytes and water play an important role in the genesis and maintenance of diarrhoea, even though disorders in intestinal motility constitute part of the pathophysiological basis of diarrhoea (Dobbins and Binder, 1981). Indeed, it is now recognised that normalization of the deranged water and electrolyte transport across the mucosal cells is a more useful therapeutic effect than any action on intestinal motility and propulsion.

The objective of this work was, therefore, to verify whether the increased amount of intestinal watery secretions and loss of electrolytes, as occurs in diarrhoea, are diminished by the antidiarrhoeal principle(s) present in the leaf of *Psidium guajava*, as this effect, if shown to occur, would be a third possible mode of action.

The choice of Microlax for the induction of experimental diarrhoea was based on the fact that its action is physiological and it does not stimulate the gut wall nor does it produce any systemic reactions. The main ingredients of Microlax are sorbitol, sodium citrate and sodium lauryl sulphoacetate. Sorbitol is a polyhydrolate compound and, like glycerol or lactulose, its emollient action producing mild catharsis is due to the osmotic effects that draw large amounts of water from the extracellular space of intestinal tissues into the lumen. Sodium citrate similarly draws water into the lumen, reinforcing the action of sorbitol, whereas sodium lauryl acetate, a non-toxic, non-irritant wetting agent, facilitates the penetration of the sodium citrate into faecal matter and thus enhances the cathartic effect.

Although the annual global figures for mortality and morbidity due to diarrhoeal diseases in infants and young children, especially in developing countries, remain very high, with an estimated 1000 million episodes of illness and some 4.5 million deaths in children under 5, excluding China (Synder and Merson, 1982; Baltazar et al., 1988), there appears to be a diminution in the knowledge of the use of traditional remedies for treating diarrhoeal diseases. A survey by questionnaire carried out in villages around the Kota Bahru area of Kelantan State, East Malaysia, showed that acute diarrhoeal disease is one of the major cause of morbidity in infants and young children of below 6 years. The unpublished report also showed that, even though the guava plant grows wildly and abundantly in all these villages, 46.8% of householders interviewed were unaware of the antidiarrhoeal activity of the leaf of the plant (size of population in survey = 205). However, 91.9% of those with this knowledge of the use of the leaf testified to the promptness and the efficacy of the antidiarrhoeal effect (Lutterodt, 1991, unpublished report).

Megens et al. (1990) studied gastrointestinal propulsion and the presence of diarrhoea in rats pretreated with various opioids and challenged orally with either castor or paraffin oil, both of which contained phenol red as a marker of gastrointestinal propulsion. The method employed in the present study is a modification of that of Megens and co-workers.

Although polar fractions of extracts of the leaf show narcotic-like effects in rats and mice (Lutterodt and Maleque, 1988; Lutterodt, 1988), its effects, especially the inhibition of acetylcholine release in the electrically driven guinea-pig isolated ileum, are not reversed by naloxone. In experiments using the polar extract to produce a mouse narcotic-dependent model, there were no withdrawal symptoms (repeated vertical jumps, headshakes, rearing, etc.) as occurs with opioids. Also when the aqueous extract, in various concentrations, was made the only source of watering in cages holding these narcotic-dependent model mice, there was only a slight initial increase in daily water consumption but this returned to normal levels and stayed so, after about day 3 to day 5 of the 12-day period of observation (Lutterodt, 1991, unpublished report). Chemical analysis of the extract failed to show the presence of cannabinoid or opioid compounds (Lutterodt and Maleque, 1988). Extracts of the leaf as used in the treatment of diarrhoea are unlikely to produce dependence.

Methods

Animals

Male Sprague–Dawley rats (200–250 g) obtained from the Animal Holding Unit, National University of Singapore, were housed in the Animal House of the School of Medical Sciences, Universiti Sains Malaysia, Kelantan subcampus, at a controlled temperature of 22° ± 2°C. Experimental animals were fasted overnight (16 h) but ordinary water was made freely available as usual in the cages.

Collection and drying of leaves

The leaves were collected in the afternoon from kampungs (villages) surrounding the Kubang Kerian campus of the School of Medical Sciences,

Universiti Sains Malaysia. After washing in tap water and air-drying at room temperature, the leaves were dried in a Memmert drier for 3 days at 60°C. The dried leaves were then machine-ground into a coarse powder and stored at laboratory temperature (19° ± 3°C).

Preparation of extracts

(i) Aqueous extract of dried leaves. The powdered dry leaf (50 g) was soaked in 200 ml of water and heated to boiling which was then maintained for 1 h. After cooling to room temperature, the extract was seived and then centrifuged for 15 min at 2000 rev./min. The supernatant was tested for possible antidiarrhoeal activity.

(ii) Aqueous extract of fresh leaves. The leaves were cut into very tiny pieces by hand and treated similarly to method (i) above.

(iii) Cold aqueous extract of fresh leaves. The leaves (50 g) were cut into tiny pieces by hand and placed in 200 ml of cold water inside a Moulinette Chopper Blender (Model 647) and blended for 20 min at 20°C into a thin paste. The paste was pressed through a seive and the extract obtained was centrifuged for 15 min at 2000 rev./min to obtain a clear straw-coloured solution. This was tested for antidiarrhoeal activity.

Drugs, chemicals and doses

Microlax is the trade name of a mild microenema produced by Pharmacia AB of Sweden. The composition/ml solution is 90 mg sodium citrate, 9 mg sodium lauryl sulphoacetate, 1 mg sorbic acid, glycerol, sorbitol and purified water q.s. It was purchased from a local agent.

The oral dose that induced diarrhoea in rats was approximately 8 × the human microenema dose, equivalent to 1 ml/100 g body weight of a 1:9 (v/v) solution of Microlax in water.

Morphine sulphate injection B.P. (10 mg/ml), was from Makmal Ubat, Petaling Jaya, Malaysia, by courtesy of the Hospital Pharmacy Department, Universiti Sains Malaysia. The dose used was 0.4 ml/100 g body weight of 1:12.3 (v/v) of morphine injection in dist. H_2O, equivalent to 0.3 mg/100 g body weight.

Phenol red was used as a dye marker of the proximal phase of propulsion of both liquid paraffin (control animals) and Microlax (test animals) by mixing it thoroughly into each liquid at 5 mg/ml concentration.

Liquid paraffin was obtained by courtesy of the Hospital Pharmacy Department, Universiti Sains Malaysia Hospital, Kubang Kerian, Kelantan, Malaysia. The dose used was 1 ml/100 g body weight.

Measurement of gastrointestinal rate of propulsion and antidiarrhoeal activity

The rats (200–250 g) were caged and kept in a temperature-regulated laboratory (19° ± 3° C) without food overnight (16 h) but they were supplied with freely available water as usual in the cages. On the morning of and 1 h before the experiment, control animals were gavaged with 1 ml water, whereas experimental animals received pretreatment with either morphine or a dose of aqueous extract. One hour after this pretreatment, half the control rats were gavaged with the liquid paraffin-dye meal and the other half received the

TABLE 1

GROUP OF RATS (200–250 g) AND GAVAGES GIVEN IN THE DETERMINATION OF INTESTINAL PROPULSION RATE AND ITS INHIBITION BY MORPHINE AND EXTRACTS FROM *PSIDIUM GUAJAVA* LEAF

Group	*n*	Pretreatment[a]	(/100 g)	Treatment	(/100 g)
1a	8	Water	(1.0 ml)	Liquid paraffin	(1.0 ml)
1b	11	Water	(1.0 ml)	Microlax	(1.0 ml)
2a	5	Morphine	(0.3 ml)	Microlax	(1.0 ml)
2b	5	Morphine	(1.0 ml)	Microlax	(1.0 ml)
2c	4	Morphine	(2.0 ml)	Microlax	(1.0 ml)
3a	5	Extract E_D	(1.0 ml)[b]	Microlax	(1.0 ml)
3b	5	Extract E_F	(1.0 ml)[b]	Microlax	(1.0 ml)
3c	6	Extract E_C	(1.0 ml)[b]	Microlax	(1.0 ml)
3d	5	Extract E_C	(2.0 ml)[b]	Microlax	(1.0 ml)

[a]Animals were gavaged 1 h before challenge with Microlax or liquid paraffin (Treatment).

[b]E_D, E_F are aqueous extracts (by boiling) of the dried (D) and fresh (F) leaves. E_C is aqueous extract of fresh leaves ground into a paste extracted cold (C) at laboratory temperature.

Microlax-dye meal in similar fashion (Table 1). Three dose levels of morphine, 0.3, 1.0 and 2 mg/100 g, were administered in three experimental groups (2a, 2b, 2c, respectively) 1 h before challenging with Microlax. Three types of aqueous extract, namely from dried powdered leaf (E_D), fresh leaf (E_F) and freshly ground leaf paste extracted cold (E_C), were administered in groups 3a–3d (Table 1).

Measurement of gastrointestinal propulsion rate was limited to events in the small intestine, down to the ileo-caecal junction and was taken from the time of gavaging the rat up to 60 min. At this cut-off time, the rat was killed immediately by cervical dislocation, followed by opening of the abdominal cavity and removal of the small intestine. The total length of the intestine (pyloric sphincter to ileo-caecal junction) and the length traversed by the dye were measured. It was necessary to mark the front of the dye with Indian ink immediately after exposure.

In control animals gavaged with the paraffin oil-dye meal, the distance travelled by the meal in 60 min was taken as the normal rate of propulsion.

Antisecretory, antipropulsive activity was expressed as the percentage of inhibition to propulsion of the dye front, taking into account the length of intestine with meal-dye to the total length of the isolated intestine (Table 2). The mean hyperpropulsive rate (Group 1b) in control animals (pretreated with solvent, H_2O) was taken as the reference rate and the values obtained for protected animals (pretreated with morphine or extract 1 h before challenge with Microlax) were expressed as percentages of this value. The percentage inhibition was thus calculable for the various groups (Table 2).

Results

The normal rate of propulsion in the small intestine in male Sprague–Dawley rats (200–250 g), using the liquid paraffin-phenol red meal, was 75.4 ± 6.0% h^{-1}. Microlax at a dose of 1.0 ml/100 g (commercial sample diluted 1:9 in water) produced 100% h^{-1} propulsion in 61.1% of group lb animals and a mean value of 98.8 ± 1.8% h–1 (n = 18), which was used as the reference value for hyperpropulsion. The mean time for diarrhoea in whole rats was 95.1 min (n = 11). Table 2 shows propulsion rates for the various experimental groups and the calculated inhibition percentage in each group, based on the value for control rats in group lb (Microlax gavage without previous protection with either morphine or extract).

Figure 1 shows the log dose-response curve for morphine on which are superimposed the inhibition activities of the various extracts for ease of reference to equiactivity to morphine.

Comparing the extract prepared from oven-dried powdered leaves with that from fresh leaves, each of which was a 1:4 (w/v) extraction in boiling water for 1 h, the former showed greater activity of about 1.6 times the latter. The extraction in cold

TABLE 2

ANTIDIARRHOEAL ACTION OF EXTRACTS OF *PSIDIUM GUAVA* LEAF AND MORPHINE IN GROUPS OF RATS[a] CHALLENGED WITH MICROLAX[b] (1.0 ml/100 g) FOR 60 MIN

Group	n	Treatment	(/100 g)	Meal distance[c] / Intestine length %	Hyperpropulsion inhibition %
1a	8	Water	(1.0 ml)	75.4 ± 6.0	—
1b	18	Water	(1.0 ml)	98.8 ± 1.8	0[d]
2a	5	Morphine	(0.3 mg)	96.3 ± 1.8	2.5
2b	5	Morphine	(1.0 mg)	78.0 ± 7.6	21.1
2c	4	Morphine	(2.0 mg)	34.0 ± 8.2	65.6
3a	5	Extract E_D	(1.0 ml)	43.3 ± 5.2	56.2
3b	6	Extract E_F	(1.0 ml)	63.5 ± 8.8	35.7
3c	5	Extract E_C	(1.0 ml)	66.0 ± 15.3	33.2
3d	5	Extract E_C	(2.0 ml)	36.3 ± 5.4	63.6

[a]Same groups and rats in Table 1.
[b]A microenema (diluted 1:9 in water) as the cathartic agent. Group 1a received liquid paraffin as control for the determination of normal rate of propulsion.
[c]Meal distance is the measured length (from the pyloric sphincter) of intestine traversed by the meal-dye solution. % values are the mean ± S.D.
[d]The value 98.8% was taken as the reference for hyperpropulsion.

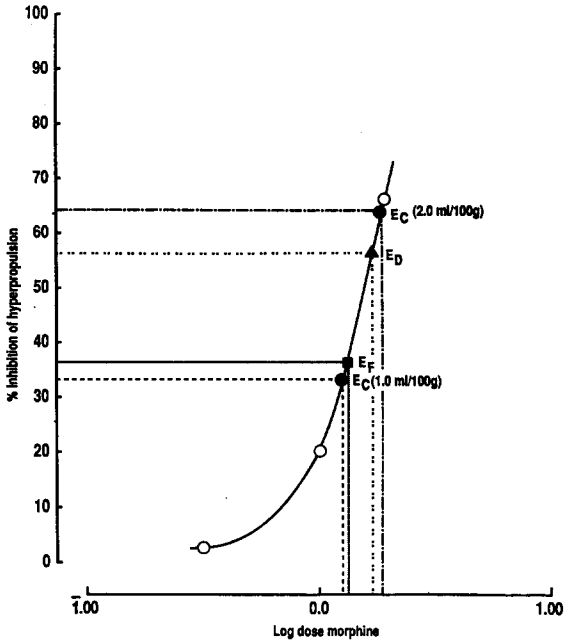

Fig. 1. Dose-response curve of morphine on which are superimposed the levels of inhibition produced by various aqueous extracts to show equivalent activities (E_D, dry leaf; E_F, fresh leaf; E_C, cold fresh leaf extract). Each dose was given at 1 ml/100 g, except E_C in two doses. ▲ E_D 1:4 (w/v) extraction for 1 h by boiling; ■ E_F 1:4 (w/v) extraction for 1 h by boiling; ● E_C 1:2 (w/v) extraction in the cold; O morphine.

water, E_C, 1:2 (w/v), showed a dose-response related activity, 2.0 ml/100 g of it producing an equiactive inhibition with 2 mg/kg morphine. From Table 2, 1.0 ml/100 g dose of either E_F or E_C are very close to the expected dose for normalizing propulsion rate (75.4 ± 6.0% h^{-1}). The calculated dose for normalization of propulsion should be (75.4 − 0.5(63.5 + 66.0) ml/100 g), roughly 0.86 ml/100 g of either extract. This calculated dose should prevent the induced diarrhoea in the rats.

A few minutes (< 10 min) after gavaging the animals in groups 3a and 3d with the aqueous extracts (relatively high doses), the animals became cataleptic and locomotion was reduced significantly.

On examining the excised small intestine, a dose of ≤ 1 mg/100 g morphine, as well as the highest dose of extract used (E_C), caused a strong spasm in the whole intestine with almost occlusion of the lumen of the tract beyond the front of the dye marker.

Discussion

Even though Microlax is used clinically as a microenema, in the diluted form (1:9, v/v in H_2O) and at a dose which is 8 × the human enema dose, it was effective in producing experimental diarrhoea in Sprague–Dawley rats. The mode of action of Microlax, according to the manufacturers, Pharmacia AB of Sweden, is an osmotic effect that draws large amounts of water from the extra-cellular space of intestinal tissues into the lumen, without any stimulant action on the intestinal smooth muscle and without any systemic effects. Thus, it would appear that this type of experimental diarrhoea would be more appropriate for investigatory work on antidiarrhoeal activity, since the increased secretion and decreased reabsorption of water and electrolytes in diarrhoeal states of the intestine are currently the targets of therapeutics, rather than effects on motility changes as could be induced by the administration of castor oil in experimental animals. It would appear that the effect of the aqueous extract, at least at doses that normalize propulsion, was due to a large extent to the inhibition of the action of Microlax on the transport of intestinal extracellular fluid. This may be due either to stimulation of the reabsorption process or to an antisecretory activity, the latter being more plausible because of the known antimuscarinic effect due to inhibition of acetyl choline release in the Auerbach's plexus (Lutterodt, 1988). However, to this effect must be added the spasmolytic activity of the extract (Lutterodt, 1988).

Because of the ubiquitous abundance of the guava tree, with nearly every tropical village or hamlet having from a few to many trees growing in or around dwelling places, there is virtually no limit to the supply of the leaves. Unfortunately, knowledge of the antidiarrhoeal usefulness of the leaf is surprisingly low. In a survey carried out in villages around Kota Bharu, the capital of Kelantan State in Malaysia, almost half (46.8% of a random sample of 205) of the population interviewed were ignorant of this use of the leaf, although in some villages all interviewed had knowledge of its antidiarrhoeal efficacy in acute diarrhoeal diseases. A few volunteered the information that the guava leaf is their trusted remedy for acute diarrhoea for years. The plant is propagated in the wild mainly by animal dispersal of the indigestible stony seeds of the fleshy fruit, but it is also cultivated in house gardens and in orchards, especially the exotic and improved cultivars, for manufacturing guava jams.

The World Health Organization (WHO), since 1947, has collaborated closely in several multiple projects of many research bodies and government

organizations and by the 1970s there were new possibilities for a better understanding of the pathogenesis of the acute diarrhoeas and for the development of improved methods of diagnosis, treatment and prevention, including oral vaccines, which were later to prove ineffective, contributing to the abolition of the requirement of cholera vaccination for international travel in the International Health Regulations in 1973 by the World Health Assembly. Most important was the demonstration by WHO field studies of the effectiveness of a single oral rehydration salts (ORS) formulation in the treatment of all diarrhoeas, including cholera, in all age groups (Martinez et al., 1988). This convinced public health administrators around the world that diarrhoeal diseases control should become an essential component of national primary health programmes. In 1978, the 31st World Health Assembly launched the global diarrhoeal diseases control programme (CDD) and between 1980 and 1987, the total number of multidisciplinary research programmes supported by the WHO through the CDD was 452.

Research in oral rehydration therapy (ORT) has shown that a more stable formulation of ORS containing trisodium citrate dihydrate is effective as ORS containing sodium bicarbonate and may result in less stool output in high-purging patients. It has also been shown that ORS containing cooked rice powder in place of glucose results in a 13–42% reduction in daily diarrhoeal output, a 17–30% reduction in the duration of diarrhoea and a 15–49% reduction in total stool volume (Martinez et al., 1988).

The efficacy of ORT in acute diarrhoeas is now firmly established. Be that as it may, the availability of ORT in many countries, especially in poor Third World countries, is very disappointingly low, even in some urban and sub-urban clinical facilities. By 1989, the WHO targeted number of countries that should be in production of ORS was 60 (only 55 in 1987). Poorer countries, for whom, ironically, diarrhoeal diseases form the major cause of morbidity and mortality, may not be in a position either to start or maintain production, or may have problems with the logistics of making ORS available nationwide.

The guava leaf has been used very successfully for many centuries against diarrhoeal diseases. In South-East Asia and especially in China, the leaf is first fed to the giant thorny stick insect, *Hepteropteryx dilata* or other insects such as the walking stick insect or the praying mantis, and the droppings of the insect in dry pellet forms are collected and stored. A few of these pellets are used when necessary by extraction in hot water, giving a pleasantly flavoured wine-coloured drink, which is claimed to be efficacious in the treatment of acute diarrhoeas (Lutterodt, 1988). This knowledge, like the use of the leaves, is slowly disappearing because of over-reliance on treatment in the Western medical system with drugs. Many poor villagers simply do not go to hospitals because they cannot pay for the simplest of treatment, including diarrhoeal cases.

If knowledge of the use of this traditional medicine is rekindled, many lives could be saved in poor Third World countries, since early treatment, in most cases of diarrhoea, prevents the development of the more serious and life-threatening event of dehydration, especially in babies and very young children.

Acknowledgements

This work is an offshoot of a project on *Psidium guava* funded by a short-term grant from the Universiti Sains Malaysia. I am very grateful for this financial support. For their very able technical assistance, Miss Christina G. Yap and Miss Khor Lee Kean deserve mention with my sincere thanks. I am also indebted to Cik Halimah Mohd Noor for typing the report from the manuscript into the present format.

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