INHIBITION OF MICROLAX* - INDUCED EXPERIMENTAL DIARRHOEA WITH NARCOTIC-LIKE EXTRACTS OF PSIDIUM GUAJAVA LEAF IN RATS

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Summary

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 (Linn.), 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 per centage 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

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

morphine or aqueous extracts, 1 h before the challenge with
Microlax, the per centage inhibition to the hyperpropulsive
rate (antidiarrhoeal activity) was calculated. Both
morphine and the extracts produced a dose-response relation-
ship 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.

Introduction

The drinking of potions of decoctions of the leaf or of the
leaf and root bark/stem of the guava plant, Psidium guajava
Linn. (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 diarrhoes), 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 constitency is due to disturbance in the transport
of water and electrolytes in the intestines. Despite the
multiplicity of aetiologies, four major mechanisms responsi-
ble 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, H. and Hersh, T., 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, 1987). It is now widely accepted that, even though disorders in intestinal motility constitute part of the pathophysiological basis of diarrhoea, abnormalities in the intestinal transport of electrolytes and water play an important role in the genesis and maintenance 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 polyhdrolate 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 extra-cellular 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 1,000 million episodes of illness and some 4.5 million deaths in children under 5, excluding China (Synder and Merson, 1982; Baltazar, J. 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, A.H.P. 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, head-shakes, 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 days 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 $\pm$ 2^{O}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 in 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 $\pm$ 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 $20^{\circ}C$ 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

i) 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 sobic 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 8x the human microenema dose, equivalent to 1 ml/100 g body weight of a 1:9 (v/v) solution of Microlax in water.

ii) Morphine Sulphate Injection B.P. (10 mg/ml), 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.

iii) Phenol red was used as a dye marker of 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.

iv) Liquid paraffin was obtained by courtesy of the
Hospital Pharmacy Department, University 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 $\pm$ 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 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 to the ileo-caecal
junction, and was taken from the time of gavaging the rat up
to 60 minutes. At this cut-off time, the rat was sacrified
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 (Grcup 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 per centages of this value. The per cent 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 $75.4 \pm 6.0\%$ 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 1b animals and a mean value of $98.8 \pm 1.8\%$ 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 per cent in each group, based on the value for control rats in group 1b (Microlax gavage without previous protection with either morphine or extract).

Fig. 1 shows the log dose-response 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 water, E_c, a 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 - ½ (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 8x 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 on 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 acetylcholine release in the Auerbach's pelxus (Lutterodt, 1988). But 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. (Lutterodt,
1991, unpublished). 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,
C.A. et al., 1988), which so 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 Third-World poor 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 treat-
ment, 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

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

+ Animals were gavaged 1 h before challenge with Microlax or liquid paraffin (Treatment)

* 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.

TABLE 2

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

Group	N			$\dfrac{\text{Meal distance}**}{\text{Intestine length}}$ %	Hyperpropulsion Inhibition %
1a	8	Water	(1.0 ml/100 g)	75.4 ± 6.0	-
1b	18	Water	(1.0 ml/100 g)	98.8 ± 1.8	0**
2a	5	Morphine	(0.3 mg/100 g)	96.3 ± 1.8	2.5
2b	5	Morphine	(1.0 mg/100 g)	78.0 ± 7.6	21.1
2c	4	Morphine	(2.0 mg/100 g)	34.0 ± 8.2	65.6
3a	5	Extract E_D	(1.0 ml/100 g)	43.3 ± 5.2	56.2
3b	6	Extract E_F	(1.0 ml/100 g)	63.5 ± 8.8	35.7
3c	5	Extract E_C	(1.0 ml/100 g)	66.0 ± 15.3	33.2
3d	5	Extract E_C	(2.0 ml/100 g)	36.3 ± 5.4	63.6

+   Same groups and rats in Table 1

*   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.

**   'Meal distance' is the measured length (from the pyloric sphincter)
     of intestine traversed by the meal-dye solution.
     % Values are the mean ± SD

**   The value 98.8% was taken as the reference for hyperpropulsion.