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Preliminary Evaluation of the Toxicity and Some Pharmacological Properties of the Aqueous Crude Extract of *Solanum Melongena*

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Abstract: The toxicity and folkloric claim of use of *Solanum melongena* L (SM) for long term control of asthma and as a prokinetic and weight reducing agent was evaluated in whole animal and isolated tissues. The aqueous crude extract of SM was not toxic in Swiss albino mice (LD50>3000mg/kg/oral) but relatively toxic in Hartley guinea pigs [LD50: 1098 (95% CI: 550-2000)], caused loss of weight with anemia, unconjugated hyperbilirubinemia and elevated alkaline phosphatase on repeat dose studies in New Zealand rabbits. It also revealed significant ($P<0.05$) dose dependent anti-inflammatory activity in rat albumin and cotton pellet granuloma models of inflammation but dose-dependently produced an Atropine and Mepyramine inhibitable constriction of isolated guinea pig tracheal ring and isolated guinea pig ileum segments with EC50 of 46.8µg/ml and 20µg/ml respectively. This study supports the folkloric use of SM for weight loss, long term control of asthma and as a prokinetic agent but raises some doubt about its use for the control of acute attacks of asthma.
Key words: Solanum melongena L fruits, toxicity, anti-inflammatory activity, effect on isolated ileum and trachea.

INTRODUCTION

Solanum melongena L. (Solanaceae) is a widely distributed tender plant. Its fruit is widely consumed and exists in various colors which include bright green, brown, brown and green, black, white, purple pink, and white (1). The green and white fruit is called "Dauta' by the Hausa tribe of northwestern Nigeria, who uses it mainly as a dietary delicacy. In an exploratory pilot community survey of the association between disease and diet our attention was first drawn to *Solanum* melongena (SM) by an apparent negative correlation between quantity of intake of the fruit and prevalence or severity of asthma or dyspeptic symptoms. On focused region wide interview of randomly selected traditional healers, preliminary evidence of its medicinal use, especially for asthma and allergic rhinitis, became apparent to us. In the same pilot study, we also found the medicinal uses of SM to be particularly popular among the *Zuru* tribe and *Kambalawa* tribes of Birnin-Kebbi and Niger states (of northwestern Nigeria) respectively where asthma also appears to be common (about 16% in our pilot study). Also, the *Ebira* tribes of Kogi state (of middle belt Niger-Benue area of Nigeria) use the same fruit for weight loss, treatment of constipation, Gastro esophageal reflux disease (GERD), dyspepsia and as an expectorant. The context of the folkloric use of SM in various diseases appears to vary but the requirement of uncooked and dried fruit is almost always emphasized. In this regard, we found that the usual 'dose' for asthma or allergic rhinitis was one uncooked and dried fruit per day, with or without dipping into honey. In a pilot interview of randomly

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selected patients at a herbal home, self-reported asthmatic patients, who claimed they had poor response to orthodox medication prescribed in tertiary hospitals and who subsequently visited herbal homes and were placed on SM claim improvement in symptoms, increased sputum expectoration and reduced frequency and severity of acute attack of asthma-a few even claimed they had been cured! Current asthma drugs include bronchodilators, anti-inflammatory agents or modulators of cells of the immune system (2**)**. If effective, SM may be anti-asthmatic by one or all of these mechanisms or by modifying a yet undefined pathway. This study was therefore undertaken as a preliminary assessment of the acute and repeat oral dose toxicity of SM, its effect on isolated tracheal ring preparations, isolated ileum preparations and its anti-inflammatory activities. The phytochemistry of aqueous extract of SM has been well defined (3,4) and was evaluated in our pilot study to ensure that there was no significant difference.

MATERIALS AND METHODS

All experiments were conducted under a carefully designed good laboratory practice protocol supervised by external auditors (not part of the study group). The recommendations for quality standards in basic biomedical research (5**)** were noted and implemented.

Collection, identification and aqueous extraction: *Solanum melongena* fruits having a mixture of green and creamy white coloration were purchase randomly from five market shops in Salka, Niger state, Nigeria. The fruit was identified and authenticated by Dr. L. Garba, of the Department of Crop Science, Usmanu Danfodiyo University, Sokoto, Nigeria and Ibrahim Muazzam, a plant taxonomist in the Department of Medicinal Plant Research and Traditional Medicine, National Institute for Pharmaceutical Research and development (NIPRD), Abuja. A voucher specimen (number B011T) was deposited at Karaye herbarium, Sokoto, Nigeria. The fruits were pooled together, washed clean with water and dried to constant weight at room temperature for 14 days. Fruits with changes suggestive of microbe attack were selected out and discarded and those that looked neat were collected, pooled together, weighed and then reduced to fine powder in a new Philip Hr 1701 blender & mill (Philips, Sao Paulo, Brazil). Grinding was done in batches of 20 fruits, at default blender speed, in 4 blender runs (per pack of fruits), each run of one minute grinding and one minute resting interval (to avoid heating the sample). 500g of the powdered fruit were extracted in distilled water (5g to 150mls) for 24 hours, filtered and then evaporated to dryness at 60 ^{0}C in an incubator. The yield was 4.3 % W/W. All doses are based on this dried powder. All desired concentrations were freshly prepared in normal saline prior to use.

Animals: Animals used in this experiment include Hartley guinea pigs, Swiss albino mice, Adult Wister Rats and New Zealand rabbits of either sex. All animals were kept in a controlled environment of 12 hours light and 12 hours darkness cycle, and room temperature of 25-27 °C at the animal house of the National institute for Pharmaceutical research and development, Abuja, Nigeria, and were fed on standard laboratory food and water *ad labium*. All animals were handled humanely according to standard institutional animal care committee's protocol. This protocol is consistent with, and constantly updated to meet current European Community guidelines.

Drug: The drugs used in this experiment include Carbachol (Sigma, St. Louis, MO), Atropine sulphate, (Sigma, St. Louis, MO), Mepyramine (Rhone-Poulenc Rorer, Antony Cedex, France), Acetylsalicylic acid (Bayer, Leverkusen, Germany) and Prednisolone (N.V Organon, Oss, The Netherlands).

Acute toxicity studies: LD50: Oral acute studies were carried out by the revised Up and Down (UPD) procedure according to recommendation (6). Briefly, because SM is dietary and most extracts from dietary plants tend to have high LD50 and because herbal extracts with LD50 above 3000mg/kg/oral may be considered safe, we used this dose as our limit dose. The limit test procedure was then performed as follows: 5 healthy female albino mice, aged 10 weeks and weighing, 20 to 25g were obtained from the animal house of the National Institute of Pharmaceutical Research and Development (NIPRD) . All animals were fasted overnight before dosing. The limit dose of 3000mg/kg of the aqueous crude extract of SM (E) was given to the first mice orally via Ryle's tube and the animal was observed for mortality and clinical signs, once before, during and every 15 minutes for the first hour, then hourly for three hours, and then periodically for 72 hours and then daily for 14 days. The mice were dosed in sequence at 48 hours interval. The LD50 was predicted to be above 3000mg/kg if three or more mice survived. Using the same procedure on female Hartley guinea pigs weighing 250-300g, similarly obtained, the first two guinea pigs dosed 3000mg/kg/oral died within 10 minutes and the limit test procedure was therefore abandoned for the main UPD procedure using the *AOT425StatPgm* program (7**)** as the guide to determine dose sequence and stopping point. Because of the unexpected short time between dosing and

death in the limit test in guinea pigs, a good estimate of the LD50 as a guide to deciding starting dose for the main test was considered untenable. The starting dose of 175mg/kg and dose progression of 3.2 (default sigma of 0.5) was used as recommended in such circumstances. Because 3000mg/kg/oral was obviously lethal to guinea pigs, a limit dose of 2000mg was chosen for the UPD and this was the input into the *AOT425StatpPgm* program. Observations and dosing sequence was as discussed for the limit test above. The experiment was stopped when prompted to do so by the *AOT425StatPgm* program indicating that an UPD stopping criteria had been reached.

Repeat dose toxicity studies: Although, the result of acute toxicity studies suggests guinea pig as the animal likely to highlight potential toxicities of SM, we could not obtain sufficient guinea pigs of experimental status. Instead, 18 New Zealand rabbits (1200 to 1420g) were obtained and randomized as previously described into 3 equal groups: Untreated control-which were not treated and not sham handled (n=6), Vehicle treated control-normal saline and handling (n=6), and E group-E treatment and handling (n=6). Post randomization, the animals were weighed using a Mettler high capacity programmable meter (Mettler-toledo, Greifensee, Switzerland). Having checked that the weight were not significantly different between groups at an alpha of 0.05, the animals were then acclimatized for 21 days during which they were fed *ad libitum* and exposed to 12 hours light and 12 hours darkness. From day 21 and always after an overnight fast, either 5 mls of pyrogen free NS or 750mg/kg of freshly prepared E in 5ml of pyrogen free NS was given daily for 28 days orally with Ryle's tube to the rabbits .

All animals were observed immediately after dosing, then 1 hour and 8 hours later and subsequently three times daily from day 21 (day of 1st dosing) to day 27, then daily from day 28 to day 38. All animals were weighed on day 0, 5, 10, and on days 21, 23 and 25, and 27, then days 33 and 38. Blood samples were collected on days 21, and 38 for full blood counts and laboratory evaluation of biochemical parameters of liver and renal function using standard methods. Animals were then killed by cervical decapitation and exsanguinations. The heart, lungs, liver and Kidneys were removed, examined grossly and prepared for histological studies using standard procedures. An experienced consultant histopathologist (Dr. Pindiga) examined all the slides.

Isolated tracheal ring experiment: In a separate experiment, male Hartley guinea pigs (300-380g) were stunned by a blow at the back of the head and the tracheae were immediately excised and preserved in Krebs-Henseleit solution (KHS; in mM: 118NaCl, 4.7KCl, 1.10NaH_2PO_4, 11.1glucose, 25.0$NaHCO_3$, 1.38$MgSO_4$, and 2.32$CaCl_2$, pH 7.40,at 4°C) at 37 +-0.2 °C and bubbled with 95% O_2 balanced with CO_2 to maintain PH at 7.40 +-0.05. Surrounding connective tissues were then carefully dissected off the trachea, which was then cut into ~3mm rings. Rings from the lower end of the trachea were selected, mounted on stainless steel wires and suspended in thermostatically controlled 20mls organ bath connected to an isometric transducer 7004 (Ugo Basile, Comerio VA-Italy) that was in turn connected to an Ugo Basile one Channel Recorder Unirecord 7050 (Ugo Basile, Comerio VA-Italy) under 1g of passive tension. After equilibration for 60 minutes, the rings were rinsed twice, observed to return to baseline tension, three test doses of the carbamoylcholine were added to the bath non-cumulatively to test the presence and reproducibility of contractile responses. After 30 minutes washing and 30 minutes incubation with KHS, rings were then exposed to increasing concentrations of E(16,32,64,128, and 256µg/ml final bath concentrations) that had been preincubated in KHS for 30min at 37°C. The experiments were then repeated in the presence of atropine (10 µM) or Mepyramine ((10 µM). All experiments were repeated in triplicates. As a rule, rings from one animal were tested with both carbamoylcholine and E but a ring set up was tested with only one of either. Mean values were then calculated for each treatment using matched tracheal ring (from the same animal). Responses were expressed as percentage of the maximum contraction.

Isolated ileal segment experiment In a separate experiment, adult guinea pigs (300 to 400 g) of either sex were fasted overnight, then stunned and bled. 3cm segments of the ileum were excised rostrary, starting 7cm caudal to the ceacum, and each flushed of luminal contents and then placed in Tyrode solution [in mM: NaCl 136.9, KCl 2.7, CaCl2 1.8, MgCl2 1.0, NaHCO3 11.9, NaH2PO4 0.4, glucose 5.6.] kept at 37 °C and oxygenated with a mixture of 95% O2 and 5% CO2. After dissection, ileal segments were mounted vertically in organ baths that contained oxygenated Tyrode solution thermostatically maintained at 37°C and connected to an isometric transducer 7004 (Ugo Basile, Comerio VA-Italy) that was in turn connected to an Ugo Basile one Channel Recorder Unirecord 7050 (Ugo Basile, Comerio VA-Italy) under 0.5g of passive tension. The set up was equilibrated for 60 minutes and resting tension was adjusted to a load of 1.0g before isometric contractions were measured. Three test doses of the Acetycholine were added to the bath non-cumulatively to test the presence and reproducibility of

contractile responses. The ileal segments were then exposed to increasing concentrations of E (5,10,20,40,80,160,320 µg/ml final bath concentration) with 5 washing and 15 minutes rest between each dose. From the first 3 ileal segments from 3 different guinea pigs of either sex, the mean dose eliciting nil response and maximum response were determined and six doubling doses in this interval was chosen for dose response determination. All subsequent ileal segments were tested in triplicate runs (all dose ranges=1 run) with 30 minutes rest between runs. The experiments were then repeated in the presence of atropine (10 µM) or Mepyramine (10 µM). Responses were expressed as percentage of the maximum contraction.

Egg albumin induced paw edema in Wister rats In a separate experiment adult Wister rats (150-180g) of either sex were labeled and randomized into four groups, of 7 per group, by blindly drawing from a box containing labeled cards matched to the animals. The groups were tested for significant difference in weight and finding none, the groups were allocated to experimental arms by a different investigator blinded to the animals. There were four experimental arms; Vehicle (Normal saline), Acetyl salicylic acid 150mg/ kg, E 2mg/kg and E 4mg/kg all in constant volume. Anti-inflammatory test was performed using the method of Winter *et al*.(8) as modified by Akah and Nwambie(9). In this procedure, animal were fasted overnight, then dosed orally and 60 minutes later, 0.1mls of egg albumin was injected under the sub plantar aponeurosis of the right hind foot of each rat. The paw volume was determined using a Letica digital plethysmometer LE 7500 connected to an Ugobasile unirecorder 7050. Readings were taken before (time zero) and at intervals of 20 minutes after egg albumin treatment for 2 hours.

Cotton pellet granuloma in Wister rats: In another experiment, adult Wister rats (150-200g) were similarly randomized into 5 groups (of 7 animals each) namely Vehicle (Normal saline), Prednisolone 100mg/kg , E 2mg/kg, 4mg/kg, and 8mg/kg. Cotton pellet granuloma was induced as described by Swingle and Shideman (10)**.** Briefly, sterilized cotton pellets each weighing 30mg was introduced (1 pellet per animal) into the subcutaneous space of the groin region of each rat under light ether anesthesia. The rats were fasted overnight and then given the appropriate test agent orally, daily for 7 days (day 1 being day of insertion of pellets). Animals were humanely killed on day 8 and the pellets were carefully removed, freed of extraneous tissue, dried overnight at 60 °C in an incubator and weighed. The increase in the dry weight of pellets was taken as measure of granuloma formation and the percent inhibition was expressed by comparison with untreated control group.

Statistical analysis: The UPD procedure was analyzed using the *AOT425StatPgm* program. Other data was analyzed by *Systat 10.2* statistical software. Because variability in vitro data is probably from experimental imprecision, such data are presented as mean± SEM and because variability from whole animal studies are probably from biologic variability , such data are presented as mean±SD. The distribution of data was determined using Microsoft excel add-in resampling software. Matched parametrically distributed means were compared by paired t test and multiple means were compared with the use of ANOVA. Nonparametrically distributed means were compared with the Mann-Whitney rank sum test. Cumulative concentration-response curves were generated for the responses using standard curve fitting techniques. $P<0.05$ was considered significant.

RESULT AND DISCUSSIONS

Acute toxicity studies: None of the 5 mice died nor showed any sign of toxicity at the limit dose of 3000mg/kg/oral in the first 48 hours and no evidence of toxicity was noted during 14 days of observation. LD50 in mice was therefore taken as above 3000mg/kg/oral. On the other hand, the first and second Hartley guinea pigs given the limit dose of 2000mg/kg/oral died within 30 minutes and the main UPD procedure was therefore performed. No guinea pig died at 175mg/kg/oral and 550mg /kg /oral but all guinea pigs given 2000mg/kg/oral died (Table 1). Dosing stopped because five reversals were obtained in 6 tests. The estimated LD50 / guinea pig/ oral was 1098 (95% CI: 550-2000). At 175mg/k/oral and 550mg/kg/oral, all the guinea pigs became weak and dull within 15 minutes with loss of righting reflex but with full recovery within 120 to 150 minutes. 2 out of the 3 guinea pigs dosed 550mg/kg/oral developed watery stools but these stopped 4 days after dosing. All (3/3) of the guinea pigs that received 2000mg/kg/oral developed tonic clonic convulsion within 6-7 hours of dosing, loss consciousness, then died within 10 minutes of the convulsion without interim recovery.

Repeat dose toxicity studies: The extract treated rabbits lost weight (Table 2) and this weight loss was significant from the 3rd day of dosing (1588.1 ± 200.1 control versus 1482.5 ± 182.5 treated) and continued to the end of the experiment (1607.2 ± 200.3 control versus 1398.6 ± 66.7 treated) . The extract treated rabbits had significantly

Table 1: Experimental sequence and outcome of Up and down procedure in guinea pigs.

Guinea pigs sequence	Dose (mg/kg)	Short-term result (48 hours)	Long-term result (14 days)
1	175	O	O
2	550	O	O
3	2000	X	X
4	550	O	O
5	2000	X	X
6	550	O	O
7	2000	X	X

(X = Died, O = Survived)

Table 2: Effect of repeat dose of E on the weight of New Zealand Rabbits

	Weight (grams)								
	Acclimatization days			Treatment days					
Group	0	5	10	21	23	25	27	32	38
	1233.3	1282.0	1292.6	1400.0	1605.2	1588.1	1606.1	1606.1	1607.2
NS	±	±	±	±	±	±	±	±	±
	35.1	20.9	28.1	185.2	218.5	200.1	200.7	156.1	200.3
	1209.8	1284.5	1297.9	1398.2	1598.5	1462.5*	1450.0*	1404.8*	1398.6*
E	±	±	±	±	±	±	±	±	±
	89	71.2	55.8	172.4	187.4	182.4	172.3	88.2	66.7

*Significant difference in weight compared to control (P<0.05). All values are expressed as mean ± SD of n=6 observations. E= Aqueous extract of Solanum melongena. NS=0.9% saline.

Table 3: Effect of repeat dose of E on some blood cells parameters of New Zealand Rabbits

Group		PCV	Hb	TL
	Pretreatment	36.0±1.2	11.9±0.6	6.4±1.3
NS	Postreatment	35.0±4.8	10.4±0.3	7.3±1.3
	Pretreatment	39.0±0.1	12.4±0.8	7.5±0.1
E	Postreatment	34.0±1.6*	9.7±0.4*	3.1±0.8*

*Significant difference compared to pretreatment level (p<0.05). All values are expressed as mean ± SD of n=6 observations. E= Aqueous extract of Solanum melongena. NS=0.9% saline.

Table 4: Effect of repeat dose of E on some liver function parameters of New Zealand Rabbits

		Test parameters (serum)						
Group		Total protein	Albumin	Total Bilirubin	Conjugated Bilirubin	SGOT	SGPT	Alkaline Phospatase
	Pretreatment	6.0	3.3	0.36	0.22	12.4	14.1	21.4
		±	±	±	±	±	±	±
NS		0.2	0.2	0.1	0.1	2.7	3.4	2.3
	Postreatment	6.1	3.0	0.33	0.20	12.5	13.0	19.9
		±	±	±	±	±2	±	±
		0.4	0.1	0.1	0.1	0.9	1.9	4.9
	Pretreatment	5.8	3.1	0.29	0.19	10.5	12.0	19.3
E		±	±	±	±	±	±	±
		0.1	0.1	0.1	0.1	3.1	3.3	6.1
	Postreatment	5.8	3.1	0.39*	0.19	16.7*	11.2	28.8*
		±	±	±	±	±	±	±
		0.6	0.3	0.1	0.1	4.5*	4.6	2.8

*Significant difference compared to pretreatment level (p<0.05). All values are expressed as mean ± SD of n=6 observations. E= Aqueous extract of Solanum melongena. NS=0.9% saline.

Table 5: Effect of repeat dose of E on some renal function parameters of New Zealand Rabbits

	Test parameters (serum)				
	Sodium	Potassium	Bicarbonate	Urea	Creatine
NS	137.0±1.0	5.2±0.1	24.0±0.4	4.4±0.2	1.0±0.1
E	136.0±1.0	5.2±0.7	24.5±0.5	5.3±0.9	1.0±0.1

All values are expressed as mean ± SD of n=6 observations.. E= Aqueous extract of Solanum melongena. NS=0.9% saline.

Table 6: Effect of E on cotton pellet granuloma in Wister rats

Group	Dose (mg/kg/oral)	Gain in weight of pellet (mg)	Percentage inhibition
Control	Nil	66.3 ± 1.1	Nil
Prednisolone	100	20.1 ± 1.1	69.7
	2	30.0 ± 0.8	54.8
	4	15.3 ± 0.6	76.9
E	8	5.0 ± 0.3	92.5

Values are expressed as mean ± SD of n =7 observations. All vales are significantly (p<0.05) different from control and from one another. E= Aqueous extract of Solanum melongena.

lower post treatment PCV (39.0±0.1 versus 33.0±1.6),Hb(12.4±0.8 versus 9.7±0.4) and leucocytes (7.5±0.1 versus 3.1±0.8) (Table 3) and significantly higher total serum bilirubin (0.29±0.1 versus 0.39±0.1), SGOPT (10.5±3.1 versus 16.7±4.5) and Alkaline phosphatase (19.3±6.1 versus 28.8±2.8) (Table 4). However total serum protein, albumin and conjugated bilirubin and SGPT showed nil significant difference between pretreatment and postreatment levels (Table 4). Serum sodium, potassium, urea and creatinine were also not significantly different between control and treated rabbits (Table 5). The gross and histological appearance of the lungs, liver and kidneys were normal in both control and extract treated rabbits.

Effect on isolated tracheal ring: The isolated trachea responded satisfactorily to carbamoylcholine. The extract caused dose-depended contraction of guinea pigs tracheal ring preparations (Fig.1 and 2) with EC50 / EC99 of 46.8µg/ml / 137 µg/ml respectively. The contractions induced by both carbachol and E were both inhibited by pretreatment with 10micromolar of Atropine or Mepyramine.

Effect on isolated guinea pig ileum: The isolated ileum responded satisfactorily to acetylcholine. The extract caused dose-depended contraction of guinea pigs ileal segments (Fig. 3 and 4) with EC50 / EC99 of 20µg/ml / 121 µg/ml respectively. The contractions induced by both acetylcholine and E were both inhibited by pretreatment with 10micromolar of Atropine or Mepyramine.

Effect on egg albumin induced paw edema in Wister rats: E caused a dose dependent inhibition of egg albumin induced rat paw edema. This anti-inflammatory effect of E at 8mg/kg/oral is significantly ($P<0.05$) greater than that at 4mg/kg/oral, while that of E at 8mg/kg/oral is significantly ($p<0.05$) greater than of 150mg/kg/oral acetylsalicylic acid (fig. 5).

Effect on cotton pellet granuloma in Wister rats: E caused a dose dependent inhibition of cotton pellet induced granuloma in rats (Table 6). This anti-granuloma effect of E at 8mg/kg/oral is significantly ($P<0.05$) greater than that at 4mg/kg/oral, while that of E at 8mg/kg/oral is significantly ($p<0.05$) greater than that of 100mg/kg of oral prednisolone.

Conclusions: This study provides preliminary evidence that the crude aqueous extract (E) of SMF has acceptable acute toxicity profile in Swiss albino mice but that the acute toxicity in Hartley guinea pig's and repeat doses toxicity in New Zealand rabbits suggest some caution . The higher acute toxicity in guinea pigs may be

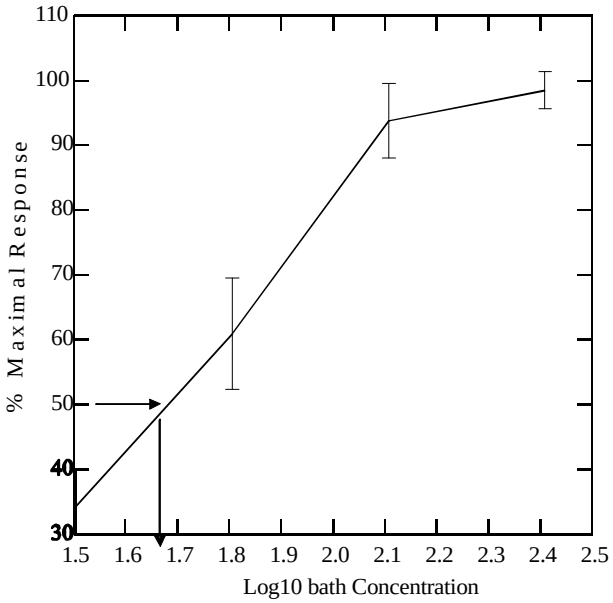

Fig 1: Concentration response plot of the effect of the aqueous crude extract of *Solanum melongena* on the isolated guinea pig tracheal ring preparation. Values are expressed as mean ± SEM of n=6 observations. (Arrows=EC50)

constitutive. Hartley guinea pigs and human trachea have been found to contain higher numbers of histaminergic receptors than Swiss albino mice or rats (11) and this may explain the higher toxicities of SMF in guinea pigs than mice. This is supported by the findings that the extract caused an Atropine or Mepyramine inhabitable dose dependent contraction of isolated guinea pig's tracheal rings and ileum. Bronchospasm and direct muscarinic receptor mediated alteration in neural activities may explain the drowsiness and convulsion noted in the toxicity experiments. SMF extract probably induced a hemolytic anemia in New Zealand rabbits and this probably explains the low PCV, low Hb and unconjugated hyperbilirubinemia. Elevated Serum Aspartate Aminotransferase (AST, SGOT) but normal Serum Alanine Aminotransferase (ALT, SGPT) support non hepatic (e.g. cardiac or skeletal) source (12). It may be important that severe hemolysis is a known source of elevated SGOT but not of elevated SGPT(12). However, the significant elevation of Serum Alkaline Phosphatase maintains some concern about hepatic toxicities but also suggest evaluation of the effect of SMF extract on skeletal bone. Considering the above, the findings of normal liver, lungs and kidneys histology in SM treated rabbits are reassuring. Also SMF extract caused, hypophagia and weight loss in New Zealand rabbits and these may justify its medicinal use for weight control. However, these effects may be related to the anemia and

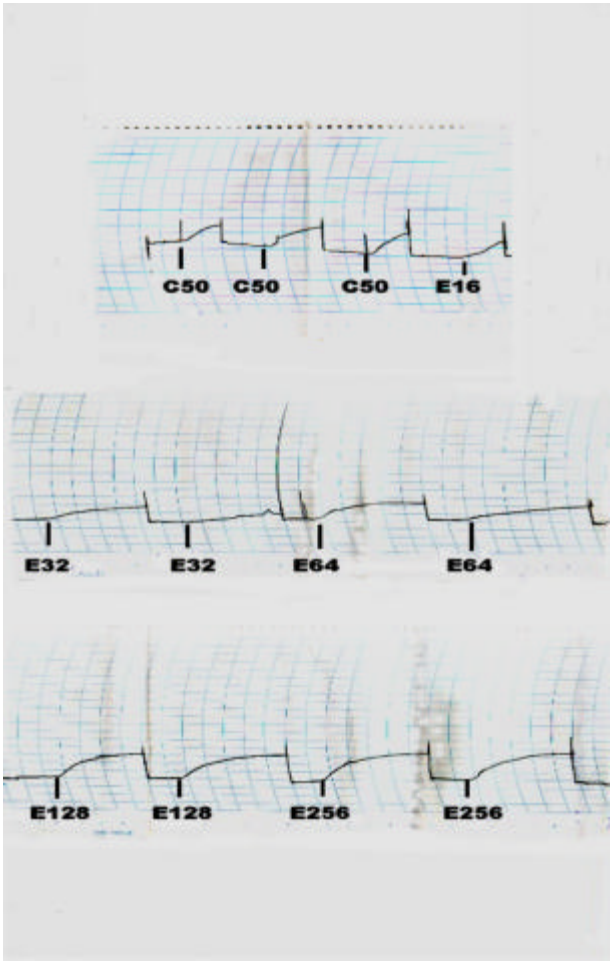

Fig 2: Tracing of the dose dependent contraction of guinea pigs tracheal ring by non cumulative doubling concentrations of the aqueous crude extract (*E*) of *Solanum melongena* , compared to that caused by EC50 of carbachol on the same set up.

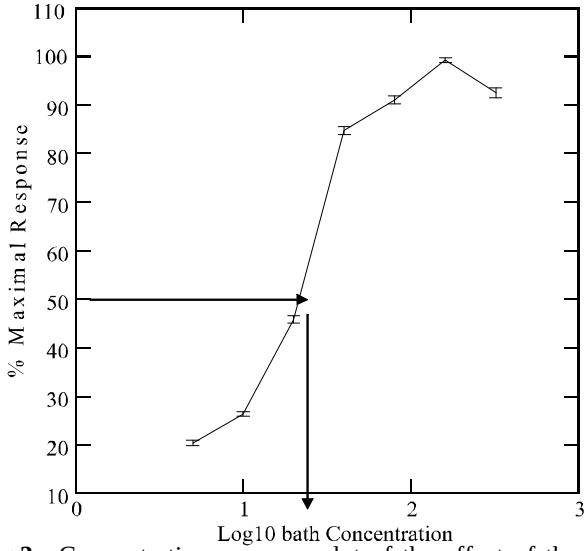

Fig 3: Concentration response plot of the effect of the aqueous crude extract of *Solanum melongena* on the isolated guinea pig ileum. Values are expressed as mean ± SEM of n=6 observations. (Arrows=EC50)

hyperbilirubinemia previously discussed. SM also induced leucopoenia in NZR. This may have some utility in hematological malignancies.

It may be difficult to explain the medicinal use of a bronchoconstrictive, probably muscarinic and histaminergic receptor agonist, like SMF as an antiasthmatic agent. However, this study has shown that SMF is also strongly and dose dependently anti inflammatory in both models of acute and chronic inflammation and that it compares favorably with aspirin and prednisolone respectively. Considering that the gold standard for long-term control of asthma is based on inhibition of inflammation, the anti inflammatory effect of SMF may explain its medicinal use for asthma. That the folkloric use of SMF is for *long-term* control of asthma may be related to similar observation in what may be described as the crude phase 3 clinical trail of herbal medicine by native. Also, the predicted response in vivo in human will depend on whether SMF is a partial or full agonist at the muscarinic and /or histaminergic receptor. An interaction study should clarify these. Meanwhile, it may be important to note the work of Eiser and Guz(13) , who reported a reduction in the broncho-constrictive response to histamine after anticholinergic medications. Furthermore Histamine-induced bronchoconstriction has been reported to shows desensitization in some species, such as guinea pigs, (14), normal human subjects and in patients with mild asthma (15). In these setting SM may be paradoxically helpful in the long term on the severity of acute attack by reason of its broncho-constrictive effect.

The constrictive effect of SMF on ileal segments may justify its medicinal use in Gastro esophageal reflux disease (GERD), dyspepsia and constipation. In these illnesses SM may effectively act as a prokinetic agent.

SMF, a widely consumed fruit has been demonstrated by this study to have potent pharmacological effects. The potential to modulate the cholinergic and histaminergic receptors may be important focus for further research. This study suggests that SM may have a place in the drug discovery efforts for intestinal dysmotility diseases and asthma. The apparent pharmacological effect of a widely consumed fruit, in 'small dose', and especially when uncooked may suggest further attempts at profiling the effects of other food items for potential drug leads.

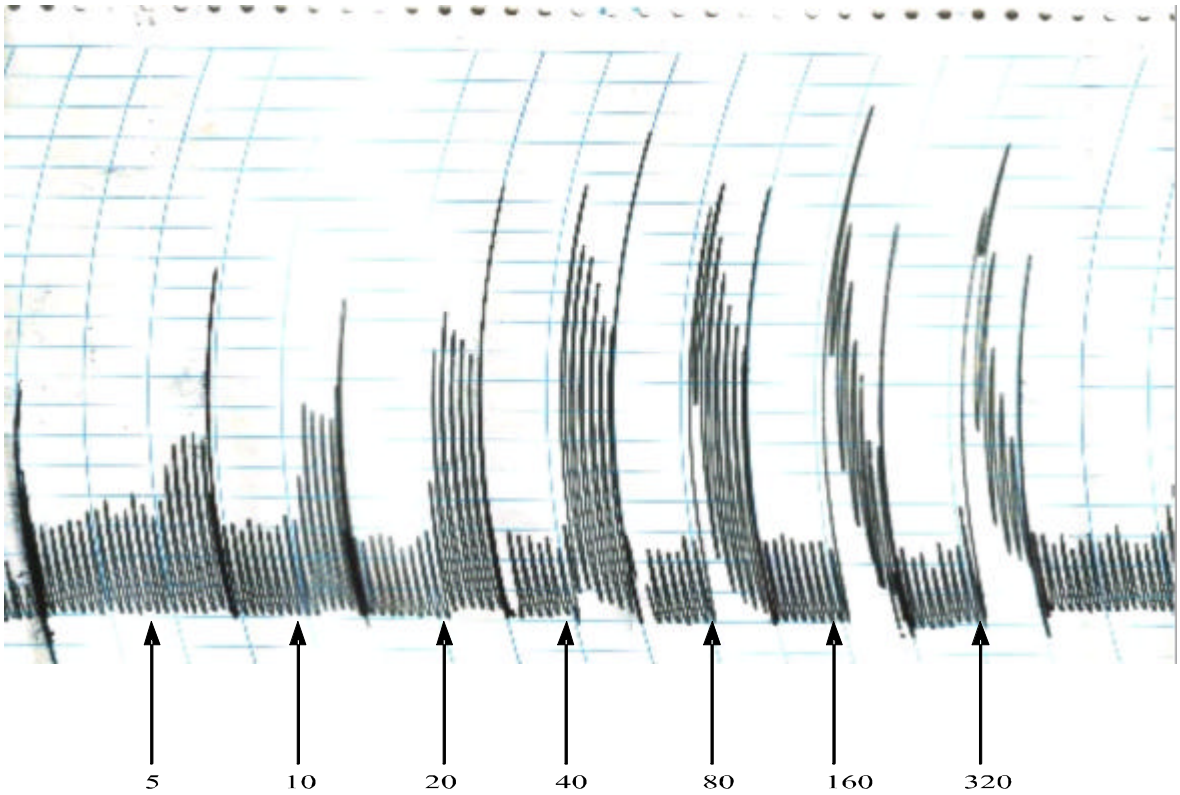

Fig 4: Tracing of the response of the isolated guinea pig ileum to non-cumulative dose of the aqueous crude extract of *Solanum melongena*. Bath concentrations are in µg/ml.

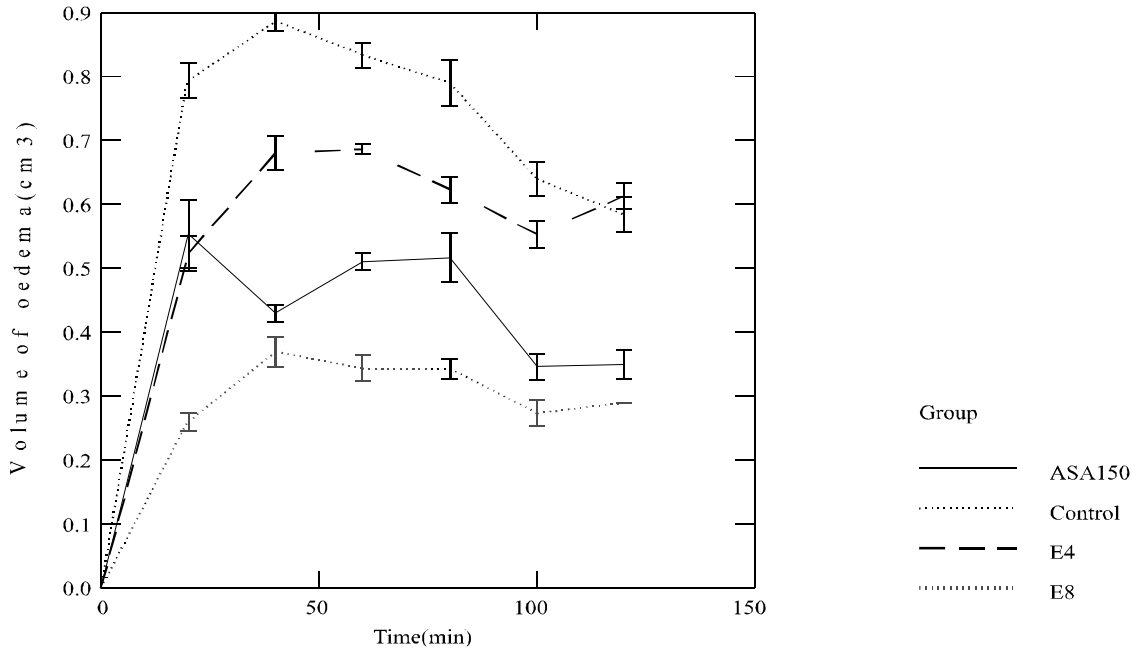

Fig 5: Effect of oral administration of the aqueous crude extract (*E*) of *Solanum melongena* fruit on albumin-induced paw oedema in Wister rats. Control : Acetylsalicylic Acid (ASA) .E4= 4mg/kg/oral of *E*, E8= 8mg/kg/oral of *E*, ASA150= 150mg/kg/oral of Acetylsalicylic acid. Control= vehicle treated. Values are means of 7 observations $P< 0.05$ for all treatment groups compared with control.

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