**Artocarpus heterophyllus** seeds inhibits sexual competence but not fertility of male rats

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According to Ayurvedic literature of Sri Lanka, roasted seeds of *Artocarpus heterophyllus* Lam. (Family: Moraceae) has aphrodisiac activity. However, some reproductively active young men in rural areas of Sri Lanka claim that consumption of these seeds few hours prior to coitus disrupts sexual function. Because of these two conflicting claims, it was thought useful to scientifically investigate the effects of *A. heterophyllus* seeds on male sexual function and fertility. This was done using a seed suspension in 1% methylcellulose (SS) in rats. In a sexual behaviour study using receptive female rats, an oral administration of 500mg/kg dose of SS markedly inhibited libido, sexual arousal, sexual vigour and sexual performance within 2hr. Further, the treatment induced a mild erectile dysfunction. These antimasculine effects on sexual function was not evident 6hr post treatment indicating rapid onset and offset of action. Further, these actions on the sexual behaviour was not due to general toxicity, liver toxicity, stress or reduction in blood testosterone level but due to marked sedative activity. In a mating study, SS failed to alter ejaculating competence and fertility. These results suggest that *A. heterophyllus* seeds do not have aphrodisiac action, at least, in rats.

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**Artocarpus heterophyllus** Lam. (Family: Moraceae, Kos in Sinhala and Pagol in Tamil) is a large evergreen tree widely cultivated throughout Sri Lanka. The fruit of this plant is large and is one of the most massive fruiting structures in the plant kingdom. The fruit and its seeds (which is about 5% of the fruit) are commonly eaten in various forms by many Sri Lankans. In the Ayurvedic system of medicine in Sri Lanka, the roasted seeds are claimed to be an aphrodisiac. However, the practicing Ayurvedic physicians in Sri Lanka generally do not prescribe these seeds in the treatment of male sexual dysfunctions. Further, to our knowledge there is no experimental support in favour of aphrodisiac actions of *A. heterophyllus* seeds. On the other hand, some married reproductively active male village folks in Sri Lanka indicate that consumption of roasted seeds few hours prior to coitus deteriorates sexual performance rather than improve it.

Because of these two paradoxical claims regarding the effects of *A. heterophyllus* on masculine sexual activity, it was thought apt to scientifically investigate the validity of these claims using male rats which form the main objective of the current study. In addition, we also investigated the immediate effects of these seeds on male fertility as this has not been examined previously.

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**Materials and Methods**

Ripe fruit of *A. heterophyllus* were plucked (between October and December, 1999) from a home garden at Ganemulla, Sri Lanka. The seeds were removed and shade dried for 2-3 days. The seeds and the pericarp were cut into small pieces (1.0-1.5cm length) and dried in an rotary (Thermal Equipment Ltd., Greenfield, UK) at 60°C until a constant weight was reached (usually about 3 days). The dried pieces were finely powdered using an electric grinder (Restch, Gmbh and Co. Ltd., Haan, Germany). The powdered seeds were stored at 4°C until suspended in 1% methyl cellulose (vehicle) (Griffin and George Ltd., Wembley, UK) to obtain desired concentrations (125, 250 or 500mg/kg) in 2mL. These seed suspensions (SS) were freshly made on the day of administration.

The seed powder was subjected to standard chemical tests as described by Farnsworth to determine the presence (qualitatively) of alkaloids, flavanoids, phe-nols, steroids, oils, saponins, carbohydrates, starch, glucose, amino acids and peptides.

Healthy adult cross bred Albino rats (males weighing 225-250g and females weighing 175-200g) were used as experimental animals. All rats were kept in wire meshed cages under standardised animal house conditions (temperature; 28-31°C, photoperiod; approximately 12hr natural light per day, relative...
humidity; 50 -55%) with free access to pelleted food (Vet House Ltd., Colombo Sri Lanka) and tap water.

Thirty-six rats were randomly assigned into 2 groups and were orally treated either with 500mg/kg of SS (n=24) or 2mL of vehicle (n=12) and were observed throughout the study period for non sexual behaviour (such as cleaning of face, self grooming, climbing), any overt signs of toxicity (salivation, rhinorrhea, lachrymation, ptosis, squinted eyes, wilting, convulsions, tremors, yellowing of fur or loss of hair) or stress (erection of fur and exophthalmia).

These rats were placed individually in cages at 2hr [SS (n=12) and vehicle (n=6)] and 6hr [SS (n=6) and vehicle (n=6)] following the administration of SS or vehicle. Following a 10-15min adaptation period, a female that had been brought into oestrus (determined by vaginal smearing) by im administration of 12 μg oestradiol benzoate (Sigma Chemical Co., St. Louis, MO, USA) in olive oil 5hr prior to pairing, and 0.5 mg progesterone (Sigma Chemical Co., St.Louis, MO, USA) in olive oil 8hr prior to pairing was placed in the cage. The pre coital sexual behaviour of these rats was observed and the following masculine sexual behavioural parameters were monitored until ejaculation or for 15min after pairing if ejaculation failed to occur: mount frequency, intromission frequency, mount latency (the time from the introduction of the receptive female to the first mount); intromission latency (the time from the introduction of the receptive female to the first intromission) and ejaculation latency (the time from the introduction of the receptive female to ejaculation). Using these parameters the following parameters were computed: % mounted; % intromitted; % ejaculated; copulatory efficiency [(number of intromissions/number of mounts) × 100]; intercopulatory interval (average time between intromisions); and intromission ratio [number of intromissions/(number of mounts + number of intromissions)].

The effect of the SS on ejaculatory competence and fertility was investigated in 12 rats. These rats were randomly divided into 2 groups (n=6 per group) and orally treated either with 500mg/kg of SS or 2mL of vehicle. 2hr later, each male was paired with a pro-oestrous female (16.00-16.30hrs). Vaginal smears of the paired females were taken the following morning (8.00-8.30hrs) and examined microscopically (× 100). If spermatozoa were present, their numbers were estimated and gross morphology were noted, and this was taken as the onset of pregnancy. At 14 days after mating, the females were subjected to uterotomy under ether anaesthesia using aseptic precautions to determine the number, viability and size of foetuses, the number of resorption sites, and the gross appearance and number of corpora lutea. The following reproductive indices were computed: quanatal pregnancy =number pregnant/number mated, fertility index =number pregnant/number paired, implantation index =total number of implantations/number mated, pre-implantation loss =[(total number of corpora lutea - total number of implantations)/total number of corpora lutea]×100, post-implantation loss =[(total number of implantations-total number of viable implantations)/total number of implantations] ×100.

A third group of male rats (n=24) was used to determine the sedative activity of the SS using the rat hole board technique. The rats were randomly divided into four groups and treated orally either with 125 (n=6), 250 (n=12) or 500 (n=6)mg/kg of SS or 2mL of vehicle (n=18). 2hr later, these rats were individually placed on the centre of rat hole-board apparatus and given a 7.5min trial period. During this time, the number of head dips, rears and locomotory activity, and the number of faecal boluses produced were recorded. The time per head dip was then computed.

In a forth set of experiments, randomly selected male rats were either orally treated with 250 (n=6) or 500 (n=6) mg/kg of SS or 2mL of vehicle (n=12). 2h post-treatment each of these rats were subjected to bar holding test to evaluate muscle strength and the time taken (in sec) for the rats to fall from the bar was determined. Immediately following this test, these rats were individually subjected to the Bridge test to evaluate muscle co-ordination and the latency to slide off (in sec) was recorded.

A fifth group of male rats was used to determine the effects of SS on wet weight of selected number of organs. Randomly selected male rats were orally treated with either 500mg/kg of SS (n=6) or 2mL of vehicle daily for 7 consecutive days (between 13.00 and 14.00hrs). On day 1 post-treatment, these rats were killed with an overdose of ether and the animals were weighed and necropsied. The gross external morphology of liver, kidney, testes, excurrent ducts and sexual accessory glands was noted. Weights were recorded for the paired seminal vesicles with coagulatory glands (glandular secretions were not removed), lateral prostates, testes, epididymis and vasa deferentia, liver or kidney and were expressed as percentage body weight.
The liver toxicity of SS was tested in another set of male rats. Randomly selected male rats were orally treated with either 500mg/kg of SS or 2mL of vehicle (n=6 per group) for 7 consecutive days (between 13.00-14.00hrs). On day 1, post-treatment 2mL of blood was collected from the tail using aseptic precautions under mild ether anaesthesia. The blood was allowed to clot (25-30min) at room temperature (28-30°C) and subjected to 15min centrifugation using a Wifug Lab Centrifuge (Eltex of Sweden Ltd., Bradford, UK) at 3200rpm. Serum was collected and activities of serum glutamic oxaloacetic transaminase (EC 2.6.1.1, SGOT) and glutamic pyruvate transaminase (EC 2.6.1.2, SGPT) were determined (within 1-2h) using a Randox enzyme assay kit (Randox Laboratories Ltd., Co, Antrim, UK) and a spectrophotometer (Jasco V500, Jasco Corporation, Tokyo, Japan). All readings were taken within 10min after incubation.

Data are presented as means ± SE. Statistical analyses were made using Mann-Whitney U-test and G-test (in the case of proportional data). Significance was inferred when \( P < 0.05 \).

### Results

Chemical testing showed the presence of proteins, amino acids, carbohydrates, starch and reducing sugars in the seeds.

The SS was well tolerated by all the treated animals. No overt clinical signs of toxicity, stress or changes in behaviour, alertness and appearance were evident.

Data obtained in the sexual behaviour study are summarised in Table 1. As shown, at 2hr post-treatment the high dose significantly (\( P < 0.05 \)) and drastically altered all the parameters of masculine sexual behaviour investigated. In contrast, at 6hr post-treatment with the highest dose none of these parameters of sexual behaviour was significantly changed.

In the fertility study, all the rats treated with SS mated and none of the fertility parameters investigated and/or computed was markedly and significantly altered (data not shown).

As depicted in Table 2, in the rat hole-board experiment, the lower dose of SS (125 mg/kg) did not significantly alter any of the parameters monitored. On the other hand, the mid and higher doses of SS significantly (\( P < 0.05 \)) impaired the number of rears

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### Table 1 — Effects of an acute oral dose of 500 mg/kg of powdered seed suspension (SS) of *A. heterophyllus* on masculine sexual behaviour of rats measured at 2 hr and 6 hr post-treatment

[Values are mean ± SE of 12 rats in each group. Range is given in parentheses]

<table>
<thead>
<tr>
<th></th>
<th>2 hr post-treatment</th>
<th>6 hr post-treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vehicle (1% methyl</td>
<td>500 mg kg(^{-1}) SS</td>
</tr>
<tr>
<td></td>
<td>cellulose)</td>
<td></td>
</tr>
<tr>
<td>% mounted</td>
<td>100</td>
<td>58.3****</td>
</tr>
<tr>
<td>% intromitted</td>
<td>100</td>
<td>50.0****</td>
</tr>
<tr>
<td>% ejaculated</td>
<td>100</td>
<td>8.3**</td>
</tr>
<tr>
<td>Number of mounts</td>
<td>19.8±2.2 (15-30)</td>
<td>9.3±2.5* (0-35)</td>
</tr>
<tr>
<td>Number of</td>
<td>19.8±2.2 (15-30)</td>
<td>5.9±2.6** (0-28)</td>
</tr>
<tr>
<td>Intromissions</td>
<td>31.3±23.8 (5-150)</td>
<td>481.0±110*** (33-900)</td>
</tr>
<tr>
<td>Mount latency (s)</td>
<td>31.3±23.8 (5-150)</td>
<td>481.0±110*** (33-900)</td>
</tr>
<tr>
<td>Intromission latency (s)</td>
<td>615.0±70.9 (624-900)</td>
<td>822±23.0*** (646-900)</td>
</tr>
<tr>
<td>Ejaculation latency (s)</td>
<td>0.5±0.0 (0-95)</td>
<td>0.46±0.01** (0-95)</td>
</tr>
<tr>
<td>Intromission ratio</td>
<td>100</td>
<td>48.6±13.4** (0-95)</td>
</tr>
<tr>
<td>Copulatory efficiency</td>
<td>33.07±5.1 (22-900)</td>
<td>229±13.6* (22-900)</td>
</tr>
<tr>
<td>Intercopulatory interval (s)</td>
<td>33.07±5.1</td>
<td>229±13.6* (22-900)</td>
</tr>
</tbody>
</table>

\( P \) values: *<0.05, **<0.01, ***<0.001, ****<0.0001, as compared with control (Mann-Whitney U-test and G-test).
Table 2 — Effects of oral administration of 500 mg kg⁻¹ different concentrations of seed kernel suspension (SS) of *Artocarpus heterophyllus* on the parameters of rat hole-board technique

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Site</th>
<th>Number of Head Dips</th>
<th>Time/Head Dip (s)</th>
<th>Locomotory Activity</th>
<th>Number of Faecal Boluses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vehicle (1% methyl cellulose)</td>
<td>19.7±3.4 (4-37)</td>
<td>5.7±0.95 (1-11)</td>
<td>5.00±1.20 (3-28)</td>
<td>14.2±2.32 (2-9)</td>
<td>3.2±0.80 (1-7)</td>
</tr>
<tr>
<td>500 mg kg⁻¹ SS</td>
<td>7.6±1.9 (3-16)</td>
<td>3.6±1.1 (1-7)</td>
<td>7.1±2.18 (3-11)</td>
<td>6.2±1.42 (1-7)</td>
<td>2.3±1.20 (1-7)</td>
</tr>
<tr>
<td>250 mg kg⁻¹ SS</td>
<td>7.6±1.7** (0-20)</td>
<td>4.2±0.82 (0-9)</td>
<td>4.3±1.27 (0-16)</td>
<td>7.3±1.64* (1-5)</td>
<td>2.7±0.44 (1-5)</td>
</tr>
<tr>
<td>125 mg kg⁻¹ SS</td>
<td>17.5±3.3 (4-26)</td>
<td>5.3±1.62 (2-9)</td>
<td>3.6±1.49 (0-17)</td>
<td>13.0±3.02 (4-9)</td>
<td>2.6±1.26 (4-9)</td>
</tr>
</tbody>
</table>

*P* values: *<0.05, **<0.01, as compared with control (Mann-Whitney U-test).*

(by 61%) and locomotory activity (mid by 48% and high by 57%). EC₅₀ values for inhibition of locomotory activity was 219.18 mg/kg. Further, there was a significant relationship between the doses and locomotory activity (*r² = 0.84, *P* < 0.05).

The latency to fall in the bar holding test was not significantly changed by the mid and high doses of the SS (data not shown). However, in the Bridge test the highest dose of SS markedly (by 49%) and significantly (*P* < 0.01) reduced the latency to slide off (control vs treatment: 12.08±3.78 vs 6.18±2.44 sec).

Sub-chronic treatment of high dose of SS did not induce marked changes in the gross appearance in any of the organs investigated. Further, their wet weights were not significantly altered (data not shown).

The sub chronic treatment of high dose of SS had no significant change in the serum SGPT and SGOT activities (data not shown).

### Discussion

This study examined the effects of orally administered single high dose of SS of *Artocarpus heterophyllus* on male sexual function and fertility in rats. A suspension form was selected as the powdered seed was insoluble in water and the dose used was the maximum possible with this mode of preparation. The results show that the SS had caused a marked deterioration in sexual arousal, vigour and performance supporting the folklore claims. On the other hand, the SS had no effect whatsoever on ejaculatory competence (in terms of vaginal sperm counts), libido (in terms of indices of libido and fertility) and immediate fertility (in terms of quantal pregnancy, number of uterine implants, implantation index and pre- and post-implantation loss). Almost similar effects on male sexual behaviour and fertility of rats are reported with a seed suspension (high dose) of *Terminalia catappa* (Ratnasooriya and Dharmasiri, 2000) and water extract of small unripe nuts of *Areca catechu*.

The onset of the reduction in sexual activity was very rapid (within 2 hr) and so was its offset (disappeared by 6 hr). Further, the impaired sexual behaviour was not accompanied with signs of overt clinical toxicity, general lethargy, behavioural abnormalities, motor deficits, liver toxicity or stress. Collectively, these observations suggest that the impairments in sexual behaviour is not due to a generalized toxic effect of the SS but due to a selective inhibitory action possibly at the central nervous system: mating is a complex phenomenon integrated in spinal and brain centres. The short duration of action may be due to rapid metabolic clearance of the active component/s.

At 2 hr post-treatment, the SS drastically reduced the number of rats mounting, intromitting or ejaculating. This implies an inhibition of libido. Libido is testosterone dependant. However, the onset of this inhibitory effect on libido was rapid, therefore cannot be attributed to impaired testosterone secretion: usually a longer time period is required to reduce blood testosterone level via such a mechanism. Further, the wet weight of the sexual accessory glands remained undiminished even after 7 day subchronic treatment of the SS: the structural and functional integrity of male sexual accessory organs are androgen dependant and their weights are used as an index of androgen status of animals. On the other hand, loss of libido may have resulted from androgen receptor blockade at the nervous centres controlling libido as is
claimed for *Mucuna prurita* seeds. In complete contrast, a reduction in libido can result from a sedative action of SS: indeed, SS showed a dose dependent sedative activity in the rat hole board technique. Sedatives are known to inhibit libido and several plants products with sedative potential have inhibited libido in rats. Amino acids were present in the seed and some amino acid derivatives such as 5-hydroxytryptamine possesses sedative potential. Tryptophan, precursor of this amino acid is reported to be present in *A. heterophyllus* seeds. Thus, there is a possibility that sedation of SS may have been mediated through amino acid derivative.

At 2 hr post treatment, the SS caused a marked prolongation of latencies of mounting, intromission or ejaculation. Taken together, prolongation of these latencies suggest an impairment in sexual arousability/motivation: an inverse relationship exists between latencies of these three parameters and sexual arousability/motivation. Prolongation of ejaculatory latency without any effect on the latencies of the other two parameters indicates an efficient aphrodisiac action. As such, the seeds of *A. heterophyllus* is neither a powerful nor a useful aphrodisiac as is claimed in Sri Lankan Ayurvedic medicine.

The administration of SS also caused a rapid and a marked inhibition of mounting, intromission or ejaculation. Taken together, prolongation of these latencies suggest a disruption in sexual vigour and the later observation indicates a deterioration of sexual performance. The SS possessed muscle incoordination activity when evaluated through the Bridge test. Thus, this action could have played a substantial role in inhibiting the sexual performance: skeletal muscles play an critical role in the act of coitus. A slight but significant impairment in intromission ratio was also evident with SS treatment. This is indicative of mild erectile dysfunction. Obviously, these effects would override any aphrodisiac potential of *A. heterophyllus* seeds: there is high matching of rat and human data, particularly involving effects on libido, erection or ejaculation.

In conclusion, this study shows that the seeds of *A. heterophyllus* has short lasting depressive effects on male rat sexual function. This supports the claim of some rural reproductively active men of Sri Lanka who claim a deterioration in sexual activity with consumption of these seeds. This is against what has been claimed in Ayurvedic medicine that *A. heterophyllus* seeds possess aphrodisiac action.

References