



Pharmacological Study

Analgesic and hypnotic activities of *Laghupanchamula*: A preclinical study

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Abstract

Background: In Ayurvedic classics, two types of *Laghupanchamula* -five plant roots (LP) have been mentioned containing four common plants viz. *Kantakari*, *Brihati*, *Shalaparni*, and *Prinshniparni* and the fifth plant is either *Gokshura* (LPG) or *Eranda* (LPE). LP has been documented to have *Shothahara* (anti-inflammatory), *Shulanashka* (analgesic), *Jvarahara* (antipyretic), and *Rasayana* (rejuvenator) activities. **Aim:** To evaluate the acute toxicity (in mice), analgesic and hypnotic activity (in rats) of 50% ethanolic extract of LPG (LPGE) and LPE (LPEE). **Materials and Methods:** LPEG and LPEE were prepared separately by using 50% ethanol following the standard procedures. A graded dose (250, 500 and 1000 mg/kg) response study for both LPEE and LPGE was carried out for analgesic activity against rat tail flick response which indicated 500 mg/kg as the optimal effective analgesic dose. Hence, 500 mg/kg dose of LPEE and LPGE was used for hot plate test and acetic acid induced writhing model in analgesic activity and for evaluation of hypnotic activity. **Results:** Both the extracts did not produce any acute toxicity in mice at single oral dose of 2.0 g/kg. Both LPGE and LPEE (250, 500, and 1000 mg/kg) showed dose-dependent elevation in pain threshold and peak analgesic effect at 60 min as evidenced by increased latency period in tail-flick method by 25.1-62.4% and 38.2-79.0% respectively. LPGE and LPEE (500 mg/kg) increased reaction time in hot-plate test at peak 60 min analgesic effect by 63.2 and 85.8% and reduction in the number of acetic acid-induced writhes by 55.9 and 65.8% respectively. Both potentiated pentobarbitone-induced hypnosis as indicated by increased duration of sleep in treated rats. **Conclusion:** The analgesic and hypnotic effects of LP formulations authenticate their uses in Ayurvedic system of Medicine for painful conditions.

Key words: Analgesic, hypnotic potentiation, *Laghupanchamula*

Introduction

Ayurvedic classics treasures a rich repertory of medicinal plants used for the treatment, management and/or control of different types of *Shula* and this knowledge is passed from generation to generation.^[1] Both the formulations of LP, have been documented in various Ayurvedic classics for *Shothahara* (anti-inflammatory),^[2] *Shulanashka* (analgesic),^[3] *Rasayana* (antioxidant and rejuvenator),^[4] *Jvarahara* (antipyretic),^[5] *Kushtha Nashaka* (blood purifier activities and useful in skin disorders),^[6] and *Vranaropaka* (wound healing)^[7] properties. Two different classical formulations of *Laghupanchamula* (LP)

came into existence with the passage of time containing four common plants viz. *Kantakari* (*Solanum surratense* Burm f.), *Brihati* (*Solanum indicum* Linn.), *Shalaparni* (*Desmodium gangeticum* DC.), and *Prinshniparni* (*Uria picta* Desv.) with either *Gokshura* (*Tribulus terrestris* Linn.), advocated in *Charaka Samhita*,^[8] and *Chikitsa Granthas* like “*Chakradatta*”,^[9] *Shargadhara Samhita*, *Vangasena Samhita*, *Yogaratanakara*, and *Bhaisajyasatnavali* or roots of *Eranda* (*Ricinus communis* Linn.), advocated in *Sushruta Samhita*,^[10] *Kashyapa Samhita*,^[11] and *Siddhasara Samhita*^[12] as the fifth plant.

The plants included under LP have been explored individually for various phytochemicals and pharmacological properties. *D. gangeticum* DC. (DG) has great therapeutic value in treating typhoid, piles, inflammation, asthma, bronchitis, and dysentery.^[13] The aqueous extracts have strong anti-writhing and moderate central nervous system depressant activities. The phytochemical analysis of DG showed the presence of flavonoids, glycosides, pterocarpanoides, lipids, glycolipids, and alkaloids.^[14] Isolate obtained from the leaves of *U. picta* Desv. (UP) exhibited

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marked bacteriostatic or bacteriosidal and fungistatic or fungicidal activities. Isoflavonones, triterpenes and steroids were isolated from the roots of UP.^[15] β -sitosterol, β -sitosterol glucoside, dioscin, methyl protodioscin and protodioscin were isolated from *Solanum indicum* having many pharmacological activities. *Solanum surratense* (SS) has high concentration of solasodine, a starting material for the manufacture of cortisone and sex hormone and scientifically reported as antifungal, anti-nociceptive and hypoglycemic.^[16] *Tribulus terrestris* Linn. (TT) have been used in folk medicine as tonic, aphrodisiac, analgesic, astringent, stomachic, anti-hypertensive, diuretic, and urinary anti-infective.^[17] TT contained steroidal saponins, and reported to act as a natural testosterone enhancer.^[18] *Ricinus communis* seeds, seed oil, leaves and root have been used for the treatment of inflammation and liver disorder.^[19] Pain is centrally modulated via a number of complex processes including opiate, dopaminergic, descending noradrenergic and serotonergic systems. The hot-plate and tail-flick tests are useful in elucidating centrally mediated anti-nociceptive responses, which focuses mainly on changes above the spinal cord level. It is generally accepted that the sedative effects of drugs can be evaluated by measurement of pentobarbital sleeping time in laboratory animals. The prolongation of pentobarbital hypnosis is thus, a good index of Central Nervous System (CNS) depressant activity.^[20] Therefore, the present study was undertaken to evaluate analgesic and hypnotic activity of the two classical types of LP, *Laghupanchamula* with the fifth plant *Gokshura* (LPG), and *Laghupanchamula* with the fifth plant *Eranda* (LPE) using their 50% ethanolic extract, LPG Extract (LPGE) and LPE Extract (LPEE). Tail-flick, hot-plate and acetic acid-induced writhing tests were selected for evaluating analgesic activity and pentobarbitone-induced hypnosis was used for studying their hypnotic potentiating effect in rats. Acute toxicity study was done in mice to see the safety profile of LPEE and LPGE.

Materials and Methods

Animals

Charls-Foster strain albino rats (150-200 g) and Swiss albino mice (20-30 g) of either sex were obtained from the Central Animal House of the Institute. They were kept in the departmental animal house at $24 \pm 2^\circ\text{C}$ and relative humidity 44-56%, light and dark cycles of 10 and 14 h respectively for 1 week before and during the experiments. Animals were provided with standard rodent pellet diet. Principles of laboratory animal care (NIH publication no. 82-23, revised 1985) guidelines will be followed. The ethical permission for the investigation of animals used in experiments was taken from the Institutional Animal Ethics Committee (Notification No. Dean/2006-07/810 dated 25.11. 2006).

Collection of plant materials

Roots of *Kantakari*, *Brihati*, *Shalaparni*, *Prinshniparni*, *Eranda*, or *Gokshura* were collected in months of November-December 2006, authenticated in Department of Dravyaguna, Faculty of Ayurveda, IMS, BHU, Varanasi and a sample specimen, of each plant was preserved in the Department (No.-COG/LP-06), for future reference.

Preparation of plant extracts

The collected roots of the above mentioned plants were shade

dried and reduced to coarse powder (Sieve no. 8) using a mechanical grinder and stored in air dried containers. 200 g each of dried powder of roots of *Kantakari*, *Brihati*, *Shalaparni*, *Prinshniparni* plus either *Gokshura*, i.e. LPG (first combination) or *Eranda*, i.e., LPE (second combination) were taken. 50% ethanol extracts of 1 kg powder of each LPG and LPE were prepared separately by soxhlation. The percentage yield of LPGE and LPEE was 10.92% and 10.78% respectively.

Drugs and Chemicals

Pentazocin (Fortwin, Ranbaxy Pharmaceuticals, New Delhi, India), diclofenac sodium (Jagsonpal Pharmaceuticals, New Delhi, India), acetic acid (Merck, Mumbai, India), pentobarbitone (Loba Chemie, Mumbai, India) were used.

Dose selection and treatment protocol

In the classical texts, for an adult dose of *Kvatha* (decoction) mentioned is 60 ml/day prepared from ~50 g of the powdered drug.^[21] The percentage yield of LPGE and LPEE was $\geq 10\%$ and considering this, the rat/mouse dose would approximately be 0.5 g/kg body surface area.^[22] The test extracts/standard drug was suspended in 0.5% Carboxy-Methyl Cellulose (CMC). The suspension was administered in a volume of 1 ml/100 g body weight, orally, single dose per day with the help of an orogastric tube either just before or 30 min before experiment. A graded dose (250, 500, and 1000 mg/kg) response study for both LPEE and LPGE was carried out for analgesic activity against rat tail-flick response which indicated 500 mg/kg as the optimal effective analgesic dose ($>50\%$ response at 120 min peak response). Hence, 500 mg/kg dose of LPEE and LPGE was used for further studies.

Acute toxicity study

Adult Swiss albino mice of either sex, weighing between 20 and 25 g fasted overnight, were used for toxicity study. Suspension of LPGE and LPEE were orally administered at 2 g/kg stat dose (four times of the optimal effective dose of 500 mg/kg) to mice. Subsequent to extracts administration, animals were observed closely for first three hours, for any toxicity manifestation like increased motor activity, salivation, convulsion, coma, and death. Subsequently observations were made at regular intervals for 24 h. The animals were under further investigation up to a period of 2 weeks.^[23]

Analgesic activity

Tail-flick test

Control group received 0.5% CMC (1st group) and the treated groups (2nd-7th groups) received 250, 500, and 1000 mg/kg doses of LPGE and LPEE while the 8th group received pentazocine (PTZ, 10 mg/kg). The extracts/drug was administered orally just before experiment. The tail-flick latencies were recorded by analgesiometer (Elite) in sec at pre-drug (basal, 0 min reading) and at 30, 60, 120, 180, and 300 min after administration of CMC/LPGE/LPEE/Pentazocin (PTZ) following the standard procedure. Percent increase in latency period was calculated by following the formula:

$$[T_T/T_C - 1] \times 100,$$

where, T_C and T_T were mean analgesic time at basal (0 min) and post-treatment time of 30, 60, 120, 180, and 300 min respectively.^[24]

Hot-plate test

Rats were placed on hot-plate kept at $55 \pm 0.5^\circ\text{C}$ for a maximum time of 10 s to avoid any thermal injury in the paws. Reaction time was recorded using Eddy's hot-plate apparatus, when the animals licked their fore and hind paws and jumped; at before (basal/0 min) and after 30, 60, 120, 180, and 300 min following administration of CMC (control), LPGE/LPEE (Test drugs, 500 mg/kg) and PTZ (positive control, 10 mg/kg). Reaction time in sec was recorded and percent increase in reaction time was calculated following the formula:

$$[T_T/T_C-1] \times 100,$$

where, T_C and T_T were mean analgesic time at basal (0 min) and post-treatment time of 30, 60, 120, 180, and 300 min respectively.^[25]

Acetic acid-induced writhing

Control group received CMC and treated groups received diclofenac (10 mg/kg), or LPGE or LPEE (500 mg/kg). Thirty minutes later, 0.7% acetic acid (10 ml/kg) solution was injected intraperitoneal to all the rats in the different groups. The number of writhes (abdominal constrictions) occurring between 5 and 20 min after acetic acid injection was counted. A significant reduction of writhes in tested animals compared to those in the control group was considered as an anti-nociceptive response.^[26]

Hypnotic activity

Control group received CMC and treated groups received LPGE or LPEE (500 mg/kg). Thirty minutes later, sub-hypnotic dose of pentobarbitone (20 mg/kg, intraperitoneal) was administered to each rat of all the groups for observing the potentiation of pentobarbitone-induced hypnosis in rats. Each rat was observed for the time of onset of sleep (time between the administration

of pentobarbitone to loss of righting reflex) and duration of sleep (time between the onset of sleep to regaining of righting reflex).^[27]

Statistical analysis

Results were presented as mean \pm Standard Error of Mean (SEM) statistical comparison was performed using one way analysis of variance (ANOVA) and for multiple comparisons versus control group was done by Dunnett's *t* test.

Results

Acute toxicity study

LPGE and LPEE did not produce any mortality during 72 h period at single, 2 g/kg oral dose. Animals showed no stereotypical symptoms associated with toxicity, such as convulsion, ataxia or increased diuresis.

Analgesic activity

Both, LPGE and LPEE dose-dependently (250, 500, and 1000 mg/kg) increased the latency time in tail-flick test during 180 min of study duration showing peak analgesic effect at 60 min. Therefore for further studies on hot-plate, acetic acid-induced writhing and potentiation of pentobarbitone hypnosis, 500 mg/kg dose of both LPGE and LPEE were selected [Table 1]. LPGE and LPEE (test extracts) at 500 mg/kg dose showed significant analgesic effect from 30 min onwards till the 180 min duration of study period both in tail-flick and hot-plate studies which was comparable with PTZ, positive control [Tables 1 and 2; Figure 1a and b]. Further, both LPGE and LPEE (500 mg/kg) significantly reduced the number of writhing induced by acetic acid in rat [Table 3]. Both LPGE and LPEE showed good analgesic effect that was comparable with the standard drug, PTZ.

Table 1: Analgesic activity of LPEE and LPGE by tail-flick method in rats

Oral treatment (mg/kg)	Latent period (s)				
	Basal (0 min) (T_C)	30 min (T_T)	60 min (T_T)	120 min (T_T)	180 min (T_T)
Control (CMC)	4.18 \pm 0.128 (0.0)	4.25 \pm 0.174 (1.7)	4.30 \pm 0.191 (2.9)	4.35 \pm 0.178 (4.1)	4.22 \pm 0.158 (1.0)
LPGE (250)	4.11 \pm 0.131 (0.0)	4.80 \pm 0.213 (16.8)	5.14 \pm 0.293 ^a (25.1)	4.98 \pm 0.211 ^a (21.2)	4.34 \pm 0.183 (5.6)
LPGE (500)	4.09 \pm 0.143 (0.0)	5.80 \pm 0.367 ^b (41.8)	6.18 \pm 0.451 ^b (51.1)	5.87 \pm 0.411 ^b (43.5)	5.03 \pm 0.313 ^a (23.0)
LPGE (1000)	4.25 \pm 0.190 (0.0)	6.39 \pm 0.248 ^c (50.4)	6.90 \pm 0.212 ^c (62.4)	6.72 \pm 0.267 ^c (58.1)	5.62 \pm 0.319 ^b (32.2)
LPEE (250)	4.21 \pm 0.197 (0.0)	5.27 \pm 0.253 ^b (25.2)	5.82 \pm 0.274 ^b (38.2)	5.52 \pm 0.293 ^b (31.1)	4.82 \pm 0.224 ^a (14.5)
LPEE (500)	4.31 \pm 0.172 (0.0)	6.48 \pm 0.371 ^c (50.3)	7.15 \pm 0.363 ^c (65.9)	6.56 \pm 0.298 ^c (52.2)	5.53 \pm 0.313 ^b (28.3)
LPEE (1000)	4.28 \pm 0.220 (0.0)	7.13 \pm 0.258 ^c (66.6)	7.66 \pm 0.281 ^c (79.0)	7.40 \pm 0.324 ^c (72.9)	5.97 \pm 0.324 ^c (39.5)
PTZ (10)	4.18 \pm 0.148 (0.0)	9.23 \pm 0.188 ^c (120.8)	8.80 \pm 0.347 ^c (110.5)	8.27 \pm 0.269 ^c (97.8)	7.20 \pm 0.214 ^c (72.2)

Values expressed as mean \pm SE (n=6). Percentage increase in analgesic time= $[T_T/T_C-1] \times 100$. Results in parenthesis indicate percentage increase in analgesic time from respective basal value. ^aP<0.05, ^bP<0.01, and ^cP<0.001 compared to respective min control group. CMC: Carboxymethyl cellulose, PTZ: Pentazocine

Table 2: Analgesic activity of LPEE and LPGE by hot-plate method in rats

Oral treatment (mg/kg)	Latent period (s)				
	Basal (T_C)	30 min (T_T)	60 min (T_T)	120 min (T_T)	180 min (T_T)
Control (CMC)	3.95 \pm 0.148 (0.0)	4.02 \pm 0.180 (1.8)	3.97 \pm 0.185 (0.5)	3.95 \pm 0.185 (0.0)	3.99 \pm 0.263 (1.0)
LPGE (500)	3.97 \pm 0.176 (0.0)	5.97 \pm 0.363 ^c (50.4)	6.48 \pm 0.345 ^c (63.2)	5.79 \pm 0.395 ^b (45.8)	5.12 \pm 0.316 ^a (29.0)
LPEE (500)	4.02 \pm 0.154 (0.0)	6.65 \pm 0.319 ^c (65.4)	7.47 \pm 0.396 ^c (85.8)	6.88 \pm 0.424 ^c (71.1)	5.93 \pm 0.417 ^b (47.5)
PTZ (10)	3.95 \pm 0.172 (0.0)	9.25 \pm 0.315 ^c (134.2)	8.47 \pm 0.376 ^c (114.4)	8.02 \pm 0.431 ^c (103.0)	7.43 \pm 0.306 ^c (88.1)

Values expressed as mean \pm SE (n=6). Percentage increase in analgesic time= $[T_T/T_C-1] \times 100$. Results in parenthesis indicate percentage increase in latency time from respective basal value. ^aP<0.05, ^bP<0.01, and ^cP<0.001 compared to respective min control group. CMC: Carboxymethyl cellulose, PTZ: Pentazocine

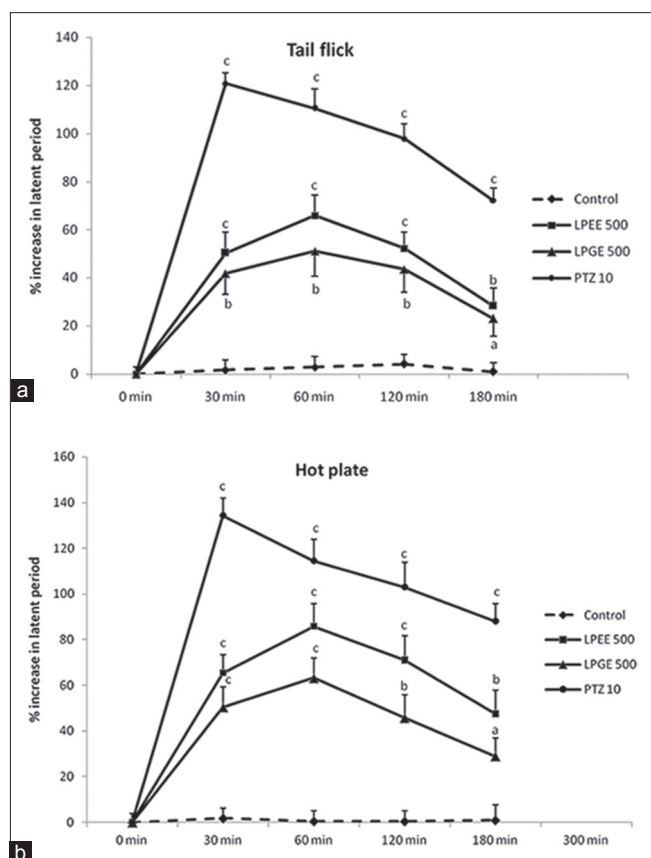


Figure 1: (a and b) Analgesic activity of LPEE, LPGE, and pentazocine at 0 min (basal) to 180 min of study duration in tail-flick and hot-plate study methods in terms of % increase in latency period from respective group basal (0 min) value. *P < 0.05, ^bP < 0.01, and ^cP < 0.001 compared to respective min control carboxymethyl cellulose value

Hypnotic activity

Effects of oral pre-treatment with LPGE and LPEE (500 mg/kg) on the sleep latency and duration induced by sub-hypnotic dose of pentobarbitone (20 mg/kg) are shown in Table 3. LPEE showed early onset of sleep while, both LPGE and LPEE prolonged the sleeping time induced by pentobarbitone [Table 4].

Discussion

The 50% ethanolic extracts of both the formulations of LP - LPG, and LPE, at the dose of 500 mg/kg protected rat against both thermal and chemical-induced noxious stimuli, which were evidenced from their effects on tail-flick hot-plate tests and acetic acid-induced writhing indicating both the central and peripheral components of pain perception [Tables 1-3]. Peripherally acting analgesics act by blocking the generation of impulses at chemoreceptor site of pain, while centrally acting analgesics not only raise the threshold for pain, but also alter the physiological response to pain and suppress the patient's anxiety and apprehension.^[28] Analgesic effect mediated through central mechanism indicates the involvement of endogenous opioids peptides and biogenic amines like 5HT.^[29] In tail-flick and hot-plate study, pre-treatments with LPGE and

Table 3: Effects of LPEE and LPGE on acetic acid induced writhing in rats

Treatment	Number of writhing	% inhibition*
Control (CMC)	62.6±2.29	-
LPGE (500)	27.6±1.50 ^c	55.9
LPEE (500)	21.4±1.94 ^c	65.8
DCF (10)	15.8±2.27 ^c	74.8

Results are mean±SEM (n=6). *Percentage inhibition=[1-W_T/W_C]×100. **Male rats only ^cP<0.001 as compared to respective control group. CMC: Carboxymethyl cellulose, DCF: Diclofenac sodium

Table 4: Effects of LPEE and LPGE on pentobarbitone-induced sleeping time in rats

Treatment**	Sleep latency (min)	Sleeping time (min)
Control (CMC+PENTO)	6.67±0.49	32.0±2.26
LPGE (500)+PENTO	6.67±0.88	58.5±4.65 ^c
LPEE (500)+PENTO	4.33±0.95 ^a	77.8±8.85 ^c

Results are mean±SEM (n=6). **Male rats only ^aP<0.05, ^cP<0.001 as compared to respective control group. PENTO: Pentobarbitone, CMC: Carboxymethyl cellulose

LPEE significantly increased the reaction time indicating central mechanism in analgesic action. Acetic acid-induced abdominal writhing is a sensitive visceral pain model which detects anti-nociceptive effects of compounds at dose levels that may appear inactive in tail-flick test.^[30] Acetic acid-induced writhing syndromes causes algia by releasing endogenous substances, prostaglandins (PGs) and bradykinin, which then excite the pain nerve endings to other pain provoking stimuli^[31] and the abdominal constriction is related to the sensitization of nociceptive receptors to PGs.^[32] Increased level of eicosanoids (Prostaglandin E₂, Prostaglandin F₂α and Leukotrienes) has been found in the peritoneal fluid after intraperitoneal injection of acetic acid.^[33] The analgesic effect of the extract may therefore be due either to its action on visceral receptors sensitive to acetic acid or to the inhibition of the production of algogenic substances or the inhibition at the central level of the transmission of painful messages.

Phytochemical analysis of plants used in LPGE and LPEE reported the presence of flavonoids, tannins, alkaloids, essential oils, and saponins.^[13-20] Tannins are important compounds known to be potent cyclooxygenase-1 inhibitors and have anti-inflammatory actions.^[34] Analgesic and anti-inflammatory effects have been observed in flavonoids as well as tannins.^[35] Flavonoids have also been reported to possess anti-oxidant and anti-radical properties.^[36] As, in the visceral pain model, there is release of arachidonic acid byproducts via cyclooxygenase and lipooxygenase pathways which plays a role in the nociceptive mechanism.^[37] So, LPEE and LPGE might be suppressing the formation of eicosanoids or antagonize their action and thus, exert their peripheral analgesic activity in acetic acid-induced writhing test as was observed with diclofenac sodium, a potent cyclooxygenase inhibitor. Analgesics effects of alkaloids, essential oils, and saponins have been observed by various workers.^[38,39]

Both the extracts potentiated pentobarbitone-induced sleep in rats. It may be assumed that the bioactivity elicited by these extracts may be due partly to its flavonoid and tannin contents, since these have been shown to have analgesic and hypnotic activity. The analgesic and hypnotic effects of the extracts may therefore, be due to the presence of flavonoids, tannins, alkaloid, or saponins. Acute toxicity study in mouse with both the extracts proved them to be safe.

Conclusions

50% ethanolic extract of LP types containing either *Gokshura* (LPGE) or *Eranda* (LPEE) at 500 mg/kg oral dose, possessed similar anti-nociceptive and hypnotic activities at both central and peripheral levels which authenticate their use for the treatment of painful conditions as advocated in traditional Ayurvedic system.

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हिन्दी सारांश

लघुपंचमूल का शूलहर प्रभाव-चिकित्सा पूर्व अध्ययन

शिवानी घिल्डीयाल, मनीष के. गौतम, विनोद के. जोशी, राज के. गोयल

लघुपंचमूल पांच द्रव्यो का समूह है, जिसके अंतर्गत शालिपर्णी, पृश्निपर्णी, बृहती, कण्टकारी, गोक्षुर या एरण्ड आते हैं। लघुपंचमूल में वर्णित चार द्रव्य सभी आयुर्वेदिक ग्रंथों में एक समान हैं परंतु पंचम द्रव्य एरण्ड या गोक्षुर भिन्न हैं। इस प्रकार लघुपंचमूल के दो भिन्न समूह गोक्षुर या एरण्ड के कारण मिलते हैं। यह बृहत पंचमूल के साथ या अकेले चिकित्सा हेतु प्रयोग किया जाता है। अतः प्रस्तुत लेख में लघुपंचमूल के दो भिन्न समूह के शूलहर कर्म का अध्ययन किया गया। जिससे कि लघुपंचमूल के अंतर्गत गोक्षुर या एरण्ड का युक्तिसंगत प्रयोग किया जा सके।