

1. INTRODUCTION:

Balacaturbhadra churna (BC)[1-3] is a well-known poly herbal formulation described in the management of bala roga (pediatric illnesses) like vomiting, diarrhea, fever and respiratory disorders in ayurveda. BC is a combination of three words namely bala (referring to children under the age of 16 years), chatuh (four in number) and bhadra (advantageous or auspicious). Thus, it is considered as one of the compound preparations consisting of four ingredients that are advantageous to treat common gastro intestinal and respiratory disorders illnesses in children. It is one among the most prescribed formulation by ayurveda pediatricians. However, less scientific documentation is available on this drug. Thus, this review aims to compile the recent research updates on this formulation.

Aim and objective: To systematically analyse recent research updates highlighting the therapeutic applications, safety, and efficacy of *Bala Chaturbhadra Churna*.

2. MATERIAL AND METHODS:

A systematic search on *bala chaturbadra churna* in Ayurveda classics and scientific publications were analysed. A total of nine full text articles retrieved (from PUBMED and Scholar google) using the key word "*Balachaturbadra churna*" and were reviewed for drafting this manuscript. Amongst them two review articles, one in silico study, two clinical trials and one experimental study were analysed to compile the information on recent updates on Balachaturbarda

churna. The researches on the individual components of BC were used as resources for further evidences to discuss the efficacy and therapeutic potentials of BC.

3. Results and pharmacodynamic profile:

Bala chaturbhadra churna is a powder dosage form prepared with equal quantity of *kanda* (rhizome) of *Cyperus rotundus* Linn. (Cyperaceae), *phala* (fruit) of *Piper longum* Linn. (Piperaceae), *moola* (root) of *Aconitum heterophyllum* Wall. ex. Royale. (Ranunculaceae) and *Shringi*, horn like out growth (gall) of *Pistacia integerrima* Stew. Ex. Brandis. (Anacardiaceae)[4] The rasa panchaka (ayurveda pharmacological profile) of the ingredients are given in table 1. To sum up, BC is predominantly seem to have *Katu-Tikta Rasa* (pungent -bitter taste), *katu vipaka* (Bio-transformed *Rasa*), *ushna veerya* (hot potency), *Guna* (properties) like *Laghu* (light for digestion), *ruksha* and properties like *Deepana* (digestant), *Pachana* (carminative) and *grahi* (absorptive). Thus, it can be therapeutically used to treat *Ama* (metabolic moiety), *jwara* (febrile illness), *trishna* (thirst), *atisara* (diarrhea), *kasa* (cough) and *shvasa* (Dyspnea). Considering the overall profile of the compound formulation its therapeutic applications can be extended to *aruchi* (distaste), *shula* (abdominal pain) and *krimi* (worm infestation). In other words, it can be a choice of drug in almost all common respiratory and gastro intestinal disorders in children including those of seasonal viral etiology.[5]

Table 1: Rasa panchaka (pharmacological properties) of ingredients in BC[6-10]

Ingredient	Rasa	Guna	Veerya	Vipaka	Doshaghnata (action on Dosh)	Karma (pharmacologic action)	Rogaghната (Therapeutic utility)
<i>Ghana (Cyperus rotundus Linn.)</i>	<i>Katu</i> (pungent), <i>Tikta</i> (bitter), <i>Kashaya</i> (astringent)	<i>Laghu</i> (light), <i>Ruksha</i> (dry)	<i>Sheeta</i> (cold)	<i>Katu</i>	<i>Kapha-Pitta-Rakta-hara</i> (alleviate <i>Kapha, Pitta</i> and <i>Rakta Dosh</i>)	<i>Grahi</i> (absorptive), <i>Pachana, Deepana, Swedajanaka</i> (diaphoretic), <i>Mutra-Janaka</i> (diuretic), <i>Stanyavardhana</i> (galactagogue), <i>Artava-Janaka</i> (emmenagogue) <i>Keshavardhana</i> (promotes hair growth), <i>Vrana-Ropana</i> (wound healing)	<i>Releives Trit</i> (thirst), <i>Jwara Aruchi</i> (distaste), <i>Krimihar</i> (wormicidal), <i>Atisara</i>
<i>Krishna (Piper longum Linn.)</i>	<i>Katu Tikta</i>	<i>Laghu, Snigdha</i> (unctuousness), <i>ushna</i> (hot)	<i>Anushna</i> (neither hot nor cold)	<i>Madhura</i> (sweet)	<i>Vata-Kaphahara</i> (alleviate <i>Vata</i> and <i>Kapha Dosh</i>)	<i>Deepana, Vrisya</i> (aphrodisiac), <i>Rasayana</i> (rejuvenating), <i>Rechaka</i> (laxative), <i>Pittala</i> (increases <i>Pitta</i>)	<i>Swasa, Kasa, Udarroga</i> (ascites), <i>Jwara, Kustha</i> (skin disease), <i>Prameha</i> (diabetes mellitus), <i>Gulma</i> (lump), <i>Arsha</i> (haemorrhoids), <i>Pliharoga</i> (splenic disorders), <i>Shula</i> (pain), <i>Aam Maruta</i> (rheumatism due to <i>Ama</i>), <i>Kshaya</i> (phtysis)
<i>Aruna (Aconitum heterophyllum)</i>	<i>Katu Tikta</i>	<i>Laghu Ruksha</i>	<i>Ushna</i>	<i>Katu</i>	<i>Kapha-Pittahara</i> (alleviates	<i>Pachana</i> (carminative), <i>Deepana</i> (digestive)	<i>Atisara</i> , <i>Ama, Visha</i> (metabolic moety), <i>Kasa, Krimiroga</i>

m Wall.)					Kapha and Pitta Dosha)		(worm infestation), Chardi (vomiting), Amatisara (diarrhea due to Ama)
Shringi (Pistacia integerrima stew. ex brandis)	Tikta Kashaya	Guru (heavy for digestion)	Ushna	Katu (pungent)	Kapha-Vatahara (pacifies Kapha and Vata Dosha)	Kasahara (cough reliving) Hikka nigrahana (cures hiccup)	Jwara, Shwasa (dyspnea) Urdhavata (reverse peristalsis), Trit (thirst), Kasa, Hikka (hiccup), Aruchi (anorexia), Chardhi, Atisara, Raktapitta (haemorrhage)

Balachaturbhadra Churna-in-silico study:

The *in-silico* study by Choudhary KR *et al*[11] demonstrates that present in BC such as, aconitine, lappaaconitine from *Aconitum heterophyllum*, 2'-hydroxyorientin from *Pistacia intergerrima* and guinesine, piperide and pipericoic acid from *Piper longum* have the potential to bind favorably with SARS-CoV-2 drug targets. Additionally, the study provides evidence of their drug-likeness and ADMET properties, suggesting that BC could be further explored as a potential therapeutic option for treating SARS-CoV-2 infection. It might also prevent post-infectious disease, characterized by MIS-C in rare cases and other viral infections in pediatrics.

Joshi *et al.* conducted pharmaceutical, pharmaceutical testing and high-performance thin-layer chromatographic standards for BC. Organoleptic characters of BC shows that this powder is fine consistency, astringent-bitter flavor, and light brown

color.[12] A quality control study was conducted on BC by Ajazuddin and Shailendra Saraf using physicochemical, phytochemical and spectrophotometric analysis. In which, moisture content was within the acceptable range indicating a good flow characteristics. Additionally higher alcoholic extractive value (39.294 ± 2.226) of BC was demonstrated the study on phytochemical prove that alcohol is the better solvent for BC.[13] In an another study the available market samples were comparable to the Standard formulation with respect to water soluble extractive, alcohol soluble extractive, total ash value, acid insoluble ash content, loss on drying at 105°C, as well as phytochemical analysis and microscopic analysis [14]. BC was effective in the management of kasa, mild persistent allergic bronchitis[15].

Toxicological evaluation of balachaturbadra churna: [5]

Nariya MB et al conducted toxicity study of *balachaturbadrika churna* on Wistar albino rats of either sexes each weighing between 150–200 g.

Acute toxicity

Oral administration of *Balacaturbhadrika Churna* in doses of 360, 720, 1440 and 2000 mg/kg respectively in four separated groups of rats against a control group which received 10 ml/kg of 1% aqueous suspension of carboxymethyl cellulose orally. Each group consisted of six animals. The rats were monitored for behavioural changes, signs of toxicity as well as mortality rate during first four hours and later periodic monitoring until 14 days. However, BC treated group did not show any changes in behaviour or acute toxicity study parameters. Neither, there were any signs of toxicity or mortality even at highest dose up to 2000mg/kg dose. This obviously proves that BC does not induce any toxic effect despite the presence of *ativisha* (*A. heterophyllum*), a cardio-toxic drug.

Long-term toxicity evaluation:

Long-term toxicity evaluation was conducted by administering doses of 450 and 900 mg/kg of BC orally for continuous 45 days. Even with a dose of 900 mg/kg, BC demonstrated any changes on hematological, biochemical and histological parameters. At this higher dose also there was no toxic effect BC was noted validating its safety profile.

Research updates on Pharmacological Properties of BC

Contents:

***Musta* (*Cyperus rotundus* Linn):**

C. rotundus have been extensively researched for phenolic acids, flavonoids, ascorbic acids and essential

oils in the tuber and rhizomes. *C. rotundus* is proven for its “antidiarrheal”, “anti-inflammatory”, “antibacterial”, “antimalarial”, “anticonvulsant”, “anti-obesity”, “antilipidemic”, “antidiabetic”, “antiandrogenic”, “antigenotoxic”, “anticancerous”, “antimutagenic”, “antioxidant”, “anti-uropathogenic”, “hepatoprotective”, “cardioprotective”, “neuroprotective”, and “nootropic activities”.[16]

Anti-diarrheal activity:

The methanol extract of *Cyperus rotundus* rhizomes, administered in doses of 250 and 500 mg/kg, demonstrated potent antidiarrheal activity against diarrhea induced by castor oil in mice. [17] *C. rotundus* tuber in aqueous extract demonstrated anti-diarrheal activity in cases of infectious diarrhea. In addition, it inhibits enteropathogenic *Escherichia coli* adhesion and entero invasive *E. coli* and *Shigella flexneri* invasion into Human epithelial type 2 cells by its antidiarrheal action.[18]

Anti-inflammatory activity:

Tuber extract from *C. rotundus* showed significant anti-inflammatory activity over paw edema in rats induced by carrageenan. Cyperalin A has a strong anti-inflammatory effect because it inhibits the inflammatory mediator’s prostaglandin E2 (PGE-2), cyclooxygenase-2 (COX-2), and arachidonate 5-lipoxygenase (LOX-5). Similar enzyme inhibitory effect were also seen with PGE-2, COX-2, as well as LOX-5 enzyme in mononuclear cell lines of peripheral blood after exposure to sugetriol triacetate, another biologically significant *C. rotundus* chemical.[19-20]

Anti-ulcer activity:

Greatest ulcer reduction activity comparable to ranitidine was shown by powder extract from the *C. rotundus* tuber in two animal models involving gastric mucosal injury brought on by aspirin in rats and histamine-induced ulcer guinea pig. [21] These therapeutic effects could be attributed to flavonoids, saponins, alkaloids, terpenoids and also glycosides in the drug. Flavonoids, in particular, are well-known for their cytoprotective properties with proven antiulcerogenic efficacy. Additionally chloroform extract of *C. rotundus* was also beneficial to treat gastric lesions.[22]

Anti-allergic activity:

Ethanol extract from *C. rotundus* rhizomes demonstrated anti-allergic properties. Sesquiterpenes were discovered to inhibit the 5-LOX-catalyzed producing leukotrienes. In addition, they inhibited β -hexosaminidase production and its degranulation.

Phytochemically *C. rotundus* is rich in essential oils, polyphenols, alkaloids, and saponin contents [23-24] Other active chemical constituents include “ α -cyperone”, “cyperene”, “cineole”, “ β -selinene”, “sugeonol”, “patchoulone”, “sesquiterpenes”, “oleanolic acid”, and “glycerol” [25-26]. *C. rotundus* has very high concentrations of α -cyperone that suppresses LPS-induced COX-2 expression in RAW264.7 cells that inhibits the production and mRNA expression of IL-6, and inflammatory cytokines. Furthermore, treatment with α -cyperone in LPS-induced RAW 264.7 cells effectively inhibits the transcription activity of NF- κ B and thus preventing nuclear translocation to p65 NF- κ B

subunit [27] which could be attributed to effects of *Musta*.

Anti-inflammatory Activity

C. rotundus extract (500 mg/kg) oral and α -cyperone (480 and 800 μ g/kg) through intra peritoneal route effectively prevents the onset of pain induced by cold and mechanical pressure. *C. rotundus* extract significantly down regulated the gene and protein expressions of tyrosine hydroxylase and noradrenergic receptors (α 1- and α 2-adrenergic), that are upregulated by paclitaxel. Additionally it reduced the paclitaxel induced elevation of tyrosine hydroxylase expression. These findings are suggestive of alleviation of neuropathic pain by *C. rotundus* possibly through inhibition of NE/pAkt signals at spinal cord. [28] Moreover a potent anti-inflammatory activity noted against carrageenin-induced edema and cotton pellet-induced inflammation in rats which was comparable to that of hydrocortisone. [29]

Ovicidal and Larvicidal Effect

Essential oil in *C. rotundus* possesses ovicidal and larvicidal property on eggs, and larvae of *Aedes albopictus* in a concentration ranges between 5 and 150 ppm. The ethanol extract from the drug had peak activity against bacteria. [30] Additionally a significant activity against helminthes was seen with 50 mg/ml concentration. This was equivalent to that of albendazole. [31] Similarly, anti-plasmodial activity was very good with *C. rotundus* extracted in Ethyl acetate medium (IC 50 < 10–10 μ g/mL). [32]

Neuroprotective effect:

The rhizome extract of *Cyperus rotundus* exerts oxidonitrosative and anti-apoptotic effects in human neuroblastoma SH-SY5Y cells, protecting against neuronal damage. This can be attributed to effective modulation of SIN-1-induced apoptotic biomarkers, including Bcl-2 and Caspase-3, thereby mitigating proteolytic cell injury.[33]

Pippali (*Piper longum*):

Various studies have explored and highlighted numerous properties of *Pippali* (*P. longum* L.) through “anti-arthritis”, “anti-asthmatic”, “anti-diabetic”, “anti-epileptic”, “anti-inflammatory”, “anti-microbial”, “anti-oxidant”, “anti-stress”, “anti-tumor”, “anti-ulcer”, as well as “immunomodulatory” properties [34-35]. It acts as hepato-protective by reducing lipid peroxidation levels and increasing the levels of glutathione (GSH). [36] Additionally it has cardio-protective effect against biochemical and histopathological damages of acute myocardial infarction in rat models. Furthermore, *P. longum* L. (50 mg/kg) shown anti-thrombogenic properties in the pulmonary thrombosis mice model [37].

Anti-diarrheal activity:

The ethanol extractives of *P. longum* fruit and its bio active compound piperine, were significantly effective in improving cecal amebiasis in rats, with a reduction of 90% and 40%, respectively[38]

Anti-pyretic and anti-inflammatory activity:

Decoction and alcohol soluble extract of *Amalakyadi Gana* (Amalaki, haritaki, pippali, and chitraka) shown moderate anti-pyretic activity in rats may be due to inhibition the enzyme cyclooxygenase and reducing the

levels of PGE-2 within the hypothalamus.[39] oral administration of *P. longum* root powder as aqueous suspension of in a dose of 200, 400, and 800 mg/kg in mice and rats, exhibited a mild opioid-like analgesic effect while indicating potent “non-steroidal anti-inflammatory drug” (NSAID)-type analgesia which was comparable to standard NSAIDs.[40] Moreover *P. longum* fruit decoction demonstrated marked anti-inflammatory activity on carrageenan induced rat edema [41-42].

Antiasthmatic activity:

P. longum fruits extractives either in petroleum ether or alcohol and decoction remarkably decreased the production of histamine from mast cells when given at 100 µg/kg dose in Guinea pigs.[43]

Anti-microbial activity:

The essential oil in *P. longum* shows “anti-bacterial activity” against multiple bacterial strains.[44] It also shows anti tubercular activity.[45]

Immunomodulatory effect:

A mixture of alcoholic extract *Piper longum* fruit and “piperine” shows immuno stimulative effect on hematopoietic system indicating stem cell proliferation.[46] *Pippali rasayana* containing *P. longum* shown immunostimulatory activity in *Giardia lamblia* infected mice infected by activating macrophages, as evidenced by increased macrophage migration index and phagocytic index[47].

Hepatoprotective activity:

Piperine was protective against hepatotoxicity induced by tertiary butyl hydroperoxide and carbon tetrachloride

through reduced lipid peroxidation in both in vitro and in vivo models[48-49].

Antihyperlipidemic activity:

“Piperlonguminine”, “piperine”, and “piperonaline” extractives from ethanol extract of the *P. longum* L. fruit demonstrated “anti-hyperlipidemic” activity *in vivo* which was comparable with that of the commercial anti-hyper lipidemic drug simvastatin[50].

Bioavailability enhancer

Piperine from *P. longum* known to enhance the bioavailability of various drugs may be through increased absorption may be through modulation of lipid dynamics and conformational change of enzymes in the intestine. It also enhances the oral bioavailability of phenytoin in humans[51-53].

Safety Profile of *P. longum*

Acute toxicity studies indicated no mortality and morbidity when *P. longum* fruit was administered at doses of 3 to 5 g/kg to animals in a pharmacological study. However, fruits of *P. longum* should be used cautiously in pregnancy and lactation, the because of contraceptive activity in experimental models and potential interactions.[54] Furthermore, the plant appears to be nontoxic and safe, as no deaths were reported even with high doses of the plant extracts.[55]

Ativisha (*Aconitum heterophyllum* Wall ex Royle):

A. heterophyllum Wall ex Royle. is an important medicinal herb whose tuberous roots are used in the management of dyspepsia, abdominal colic, diabetes and diarrhea. Roots are extensively used to correct

appetite, to treat fever, to prevent recurrent illness and also as tonic to boost vitality. Additionally it is used to treat gastro intestinal complaints like vomiting and diarrhoea in children. It also serves as a remedy for poisonous bites from snakes and rats and scorpion sting.[56]

Anti-pyretic activity:

The antipyretic activity of aqueous, chloroform and hexane extracts of roots of *Aconitum heterophyllum* on yeast induced pyrexia against standard drug aspirin have been evaluated. The results indicated that the extracts did not show any toxic effects up to 1.6 g/kg dose and also did not exhibit significant antipyretic activity [57].

Anti-diarrheal activity:

A. heterophyllum was investigated for antidiarrheal effect on castor oil-induced diarrhea in mice and found to have an inhibitory impact on ricinolic acid secretion.[58]

Anti-inflammatory activity:

A. heterophyllum demonstrated in cotton pellet-induced granuloma in mice similar to diclofenac sodium, a nonsteroidal anti-inflammatory drug.[59]

Hypolipidemic activity:

Methanol extractives of *A. heterophyllum* tubers showed a lipid lowering effect on obesity induced by diet in rats through inhibition of hydroxymethylglutarate Coenzyme A reductase and activation of lectin cholesterol acyl transferase enzymes.[60]

Antioxidant activity:

Ativisha also shown to have antioxidant activity that was comparable to Vitamin C.[61]

Karkatshringi (*Pistacia integerrima* Stew. Ex. Brandis.):

Pistacia integerrima is traditionally used for various ailments especially to treat cough, reduced appetite, dyspeptic vomiting, phthisis, asthma and dysentery. Galls of *P. integerrima* are bitter, aromatic, and known for their expectorant and tonic properties.[62-63] They in combination with other drugs are used to treat snake bite and scorpion sting as well.[64] Extract from bark decoction of *P. integerrima* is used to treat jaundice and hepatitis in few area of Pakistan.[65] Stem resin is wound healing.[66] Fruits are edible besides being remedy for liver disorders.[67, 63]

Anti-diarrheal activity:

Alcoholic and aqueous extracts of *Karkatshringi* suppressed *E. coli* and *Vibrio cholera* but *Enterococcus faecalis* was inhibited by the aqueous extract. [68] Further, methanolic extract of *P. integerrima* given orally to mice protected them from castor oil-induced diarrhea, comparable to the action of loperamide, and it was also shown to be safe with no signs of acute toxicity.[69]

Anti-oxidant activity:

Ethanol extract of leaf galls was studied for anti-oxidant activity and was linked to high total phenolic and flavonoid concentration than aqueous extract. [70] *P. integerrima* has expectorant properties and help in clearing mucus from the lungs, bronchi, and trachea. It is effective in treating childhood whooping cough. It controls hiccoughs as well. Anti-asthmatic activity of

pistacia is attributed to LOX-5, and histamine release inhibition properties.[71]

Discussion:

Balachaturbhadra Churna as the name suggests, is a safe and effective formulation, particularly beneficial for the pediatric population in managing common gastrointestinal and respiratory illnesses. The presence of *Musta* imparts *pachana*, *grahi*, *swedajanana*, and *mutrajanana* properties, contributing significantly to the *jwarahara* (antipyretic), *atisarahara* (anti-diarrheal), and *shothahara* (anti-inflammatory) actions of BC. *Avitisha*, with its *deepana* and *pachana* qualities, further enhances the *jwarahara*, *atisarahara* and *amaharana* (detoxifying) effects of the formulation. *Karkataka Shringi* plays a key role in addressing respiratory conditions, offering *kasahara* (anti-cough), *shwasahara* (anti-asthmatic), *hikkahara* (anti-hiccup), and *chardihara* (anti-emetic) benefits. *Pippali*, apart from its disease-alleviating properties, is well known for its *rasayana* (rejuvenating), *vrishtya* (aphrodisiac), and *pachana* (digestive stimulant) actions. It also improves the bioavailability of the formulation, thereby enhancing the overall therapeutic efficacy of *Balachaturbhadra Churna*. Recent researches provide evidence for immune-modulating, anti-inflammatory, anti-spasmodic, anti-asthmatic, anti-bacterial, anthelmintic, antioxidant, anti-fungal, hepatoprotective, cardioprotective and analgesic activity of BC. Thus it can be potentially used as both curative and preventive medicine safely in both acute and chronic conditions. This formulation is effective to relieve acute cough, congestion, loss of appetite and

loose stools. It also restores appetite and energy during and recovery phase of illnesses. Recurrent and chronic conditions that respond good to BC include loss of appetite, loose stools, vomiting, abdominal pain and milk intolerance etc. The therapeutic actions of BC can be attributed the chemical constituents of the respective component drugs present in it.

Conclusion:

Safety and efficacy of BC have been studied in in vitro and in-silico studies. Experimental studies on components of BC serve as evidence for proposed action of the formulation. Very few clinical trials are published on BC in spite being frequently prescribed in pediatric illnesses. Researches on drug Standardization and clinical efficacy are the need of the hour to generate further clinical evidence on the efficacy of BC. Various dosage forms of BC should be explored to enhance the palatability and acceptance in pediatric population along with its safety and efficacy.

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References:

1. Tripathi J. editor. Chakradatta of Shri Chakrapanidatta, Hindi commentary Ch. 64, Ver. 22. 5th edition. Varanasi: Chaukhamba Sanskrit Series; 1983:523.
2. Rajeshwar Dutta Shastri editor. Bhaishajyaratnavali of Shri Govinda Dasa Sen.chau Ch. 17, Ver. 39. 9th edition. Varanasi: Chaukhamba Sanskrit Sansthan; 1991:747.
3. SreeLaksmipati Shastri editor. Yogaratnakara oHindi Commentary. Balrogadhikara: Hikkayam Chardhyam. Reprint edition 2017. Varanasi: Chaukhamba Prakashan; 2017:443.
4. Anonymous. Ministry of Health and Family Welfare, Govt. of India. The Ayurvedic Formulary of India. Part 1. 2nd revised ed. New Delhi: Department of Indian Systems of Medicine and Homeopathy, Ministry of Health and Family Welfare Govt. of India; 2003:113.
5. Nariya MB, Parmar P, Shukla VJ, Ravishankar B. Toxicological study of Balacaturbhadraka churna. Journal of Ayurveda and Integrative medicine. 2011 Apr;2(2):79. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3131776/> [last accessed on April 1, 2025]
6. Chuneekar KC, Pandey GS, editor. Bhavprakash Nighantu of Sri Bhavamisra. Haritakyadi varga and Karpuradi Varga. Revised ed. Varanasi: Chaukhamba Bharati Academy; 2010:15,95-96,122-123, 232-233
7. Sharma P, Sharma GP, editor. Kaiyadeva Nighantu of Acharya Kaideva (Pathyapathya-Vibodhakah), Oushadhi Varga. Ver. 1120,1133,1166- 1169,1358. 1st ed. Varanasi: Chaukhamba Orientalia; 1979:207, 209, 215, 252.
8. Anonymous. Ministry of Health and Family Welfare, Govt. of India.The Ayurvedic Pharmacopoeia of India. Part 1. Vol. 3. 1st ed. New Delhi: Ministry of Health and Family Welfare, Govt. of India; 2001:129-130.
9. Anonymous. Ministry of Health and Family Welfare, Govt. of India. The Ayurvedic Pharmacopoeia of India. Part 1. Vol. 1. 1st ed. New Delhi: Ministry of Health and Family Welfare, Govt. of India; 1986:22-23.

10. Anonymous. Ministry of Health and Family Welfare, Govt. of India. The Ayurvedic Pharmacopoeia of India, Part 1. Vol. 4. 1st ed. New Delhi: Ministry of Health and Family Welfare, Govt. of India; 2004:91-92.
11. Choudhary KR, Thrigulla SR, Gundeti MS, Mantena P, Koulgi S, Jani V, et al. *Balchaturbhadra Churna* as a potential medicine for SARS-CoV2 infection in pediatric setting: An *in silico* study. *AYU* 2022;43:146-58. Available from: https://www.researchgate.net/publication/376398319_Balchaturbhadra_Churna_as_a_potential_medicine_for_SARS-CoV2_infection_in_pediatic_setting_An_in_silico_study.pdf. [last accessed on April 1, 2025]
12. Joshi A, Aparna K, Rajgopala S, Patel KS, Harisha CR, Shukla VJ. Pharmacognostical and pharmaceutical assay of Balachaturbhadra churna – A compound Ayurvedic formulation. *Int J Pharm Biol Arch* 2013;4:170-4. Available from: https://www.researchgate.net/profile/Abhishek-Joshi-16/publication/272159173_Pharmacognstical_and_pharmaceutical_assay_of_Balachaturbhadrachurna_-_a_compound_ayurvedic_formulation/links/54f93ae60cf2ccfe9e05d21/Pharmacognstical-and-pharmaceutical-assay-of-Balachaturbhadrachurna-a-compound-ayurvedic-formulation.pdf [Last accessed on April 1, 2025]
13. Saraf S. Development of Fingerprinting Methods of Balacaturbhadrika Churna: An Ayurvedic Formulation. *Pharmacognosy Journal*. 2012 Jan 1;4(27):20-4. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0975357512800162> [Last accessed on April 1, 2025]
14. Ghadiyali SN, Patel N, Trivedi N, Desai H. Development of evaluation parameters for Balchaturbhadra churna and comparison with market formulation. *Int J Pharm Res Allied Sci* 2012;1:75-84.
15. Simran, Minaj Dosani, Harish Kumar Singhal. Clinical study of *Balchaturbhadra Churna* in the management of Kasa Roga (allergic bronchitis) in children. *Int J Health Sci Res*. 2024; 14(12):206-211. Available from: https://www.ijhsr.org/IJHSR_Vol.14_Issue.12_Dec2024/IJHSR24.pdf [Last accessed on April1,2025]
16. Peerzada AM, Ali HH, Naeem M, Latif M, Bukhari AH, Tanveer A. *Cyperus rotundus* L.: Traditional uses, phytochemistry, and pharmacological activities. *Journal of ethnopharmacology*. 2015 Nov 4;174:540-60. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0378874115300799> [last accessed on April 1,2025].
17. Uddin S, Mondal K, Shilpi JA, Rahman MT. Antidiarrhoeal activity of *Cyperus rotundus*. *Fitoterapia* 2006;77:134-6. Available from: https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=17.%09+Uddin+S%2C+Mondal+K%2C+Shilpi+JA%2C+Rahman+MT.+Antidiarrhoeal+activity+of+Cyperus+rotundus.+Fitoterapia+2006%3B77%3A134+6.+&btnG= [Last accessed on April 12025].
18. Das B, Pal D, Halder A. A review on *Cyperus rotundus* as a tremendous source of pharmacologically active herbal medicine. *IJGP* 2015;9:198-203. Available from: <https://greenpharmacy.info/index.php/ijgp/article/view/564> [Last accessed on April1, 2025].
19. Ahmad M, Rehman AB, Mahummad R, Wazir A. Assessment of Anti-inflammatory, anti-ulcer and neuro pharmacological activities of *Cyperus rotundus* L. *PJPSC* 2014;27:2241-6. Available from <https://www.cabidigitalibrary.org/doi/full/10.5555/20153261853> [last accessed on April 1,2025].
20. Mohamed SR, Khayat GA, Zayed MT, El-Kholy MF. Anti-inflammatory terpenoids from *Cyperus rotundus* rhizomes. *Pak J Pharm Sci* 2018; 31:1449-56. Available from: https://www.researchgate.net/profile/Mohamed-Zayed-13/publication/326719700_Anti-inflammatory_terpenoids_from_Cyperus_rotundus_rhizomes/links/5ccd4b75a6fdccc9dd8b693b/Anti-inflammatory-terpenoids-from-Cyperus-rotundus-rhizomes.pdf [last accessed on April1,2025].
21. Arshad M, Nagarajaiah BH, Kudagi BL. Experimental evaluation of antiulcer activity of *Cyperus rotundus*. *Asian*

- J Biomed Pharm Res 2012;2:261-8. Available from: <https://www.cabidigitallibrary.org/doi/full/10.5555/20123230919> [last accessed on April1,2025].
22. Gangwar AK, Ghosh AK. Antiulcer activity of chloroform extract of *Cyperus rotundus*. International Journal of Pharmacognosy and Phytochemical Research. 2017;9(6):780-2. Available from: https://impactfactor.org/PDF/IJPPR/9/IJPPR_Vol9_Issue6_Article8.pdf [last accessed on April1,2025].
23. Nagulendran K., Velavan S., Mahesh R., Begum V.H. In vitro antioxidant activity and total polyphenolic content of *Cyperus rotundus* rhizomes. J. Chem. 2007;4:440–449. doi: <https://10.1155/2007/903496> [DOI] [Google Scholar]
24. 27.Scientific C.O., Publications I.R., Directorate I. Second Supplement to Glossary of Indian Medicinal Plants with Active Principles: A-K (1965-1981) Publications & Information Directorate, CSIR; New Delhi, India: 1992. [Google Scholar]
25. Siebert T.E., Wood C., Eley G.M., Pollnitz A.P. Determination of Rotundone, the pepper aroma impact compound, in grapes and wine. J. Agric. Food Chem. 2008;56:3745–3748. doi: <https://10.1021/jf800184t> [DOI] [PubMed] [Google Scholar]
26. Jung S.-H., Kim S.J., Jun B.-G., Lee K.-T., Hong S.-P., Oh M.S., Jang D.S., Choi J.-H. α -Cyperone, isolated from the rhizomes of *Cyperus rotundus*, inhibits LPS-induced COX-2 expression and PGE2 production through the negative regulation of NF κ B signalling in RAW 264.7 cells. J. Ethnopharmacol. 2013;147:208–214. doi: <https://10.1016/j.jep.2013.02.034> . [DOI] [PubMed] [Google Scholar]
27. Safety M. The Korean Pharmacopoeia. 12th ed. Ministry of Food and Drug Safety; O-song, Republic of Korea: 2014. [Google Scholar]
28. Park KT, Sim I, Lee JC, Jin YH, Kim W. *Cyperus rotundus* Extract and Its Active Metabolite α -Cyperone Alleviates Paclitaxel-Induced Neuropathic Pain via the Modulation of the Norepinephrine Pathway. Metabolites. 2024 Dec 20;14(12):719. <https://doi.org/10.3390/metabo14120719> [last accessed on April1, 2025]
29. Ahmad M, Rehman AB, Mahummad R, Wazir A. Assessment of anti-inflammatory, anti-ulcer and neuropharmacological activities of *Cyperus rotundus* Linn. Pak J Pharm Sci. 2014;27(6):2241-6. PMID: 26045387.
30. Sharma SK, Singh AP. Antimicrobial investigations on rhizomes of *Cyperus rotundus* Linn. Der Pharma Lett. 2011;3:427–431. Available from: https://www.researchgate.net/publication/279558303_Antimicrobial_investigations_on_rhizomes_of_Cyperus_rotundus_Linn [last accessed on April1,2025].
31. Kasala S, Ramanjaneyulu K, Himabindhu J, Alluri R, Babu RR. Preliminary phytochemical screening and in vitro anthelmintic activity of *Cyperus rotundus* (L) J Pharmacogn Phytochem. 2016;5:407–409. Available from: <https://www.phytojournal.com/archives/2016/vol5issue5/PartF/5-5-46-462.pdf> [last accessed on April1,2025]
32. Kaushik NK, Bagavan A, Rahuman AA, Mohanakrishnan D, Kamaraj C, Elango G, Zahir AA, Sahal D. Antiplasmodial potential of selected medicinal plants from eastern Ghats of South India. Exp Parasitol. 2013;134(1):26-32. doi: <https://10.1016/j.exppara.2013.01.021> Epub 2013 Feb 9. PMID: 23399920.
33. Kumar KH, Khanum F. Hydroalcoholic extract of *Cyperus rotundus* ameliorates H 2 O 2-induced human neuronal cell damage via its anti-oxidative and anti-apoptotic machinery. Cellular and molecular neurobiology. 2013;33:5-17. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC11497979/> [last accessed on April1,2025]
34. Bezerra DP, Pessoa C, Moraes MO, Alencar NM, Mesquita RO, Lima MW, et al. *In vivo* growth inhibition of sarcoma 180 by piperlonguminine, an alkaloid amide from the *Piper* species. J Appl Toxicol 2008;28:599–607.
35. Choudhary N, Singh V. A census of *P. longum*'s phytochemicals and their network pharmacological evaluation for identifying novel drug-like molecules against various diseases, with a special focus on neurological

- disorders. PLoS One. 2018 Jan 10;13(1):e0191006. Available from: <https://pubmed.ncbi.nlm.nih.gov/29320554/> [last accessed on April1,2025].
36. Gurumurthy P, Vijayalatha S, Sumathy A, Asokan M, Naseema M. Hepatoprotective effect of aqueous extract of Piper longum and piperine when administered with anti-tubercular drugs. Bioscan. 2012 Nov 29;7:661-3.
37. Lee SE, Park BS, Huh TL, Lee EW, Yum JH. Proteomic evaluation on antiplatelet activity of piperlongumine derived from Piper longum. Molecular & cellular toxicology. 2010 Sep;6:295-303. Available from: <https://link.springer.com/article/10.1007/s13273-010-0040-3> [last accessed on April1,2025].
38. S Ghoshal, V Lakshmi. Potential antiamebic property of the roots of *Piper longum* Linn. Phytother Res. 2002;16:689-691. Available from: https://scholar.google.com/scholar?hl=en&as_sdt=0%2C5&q=38.%09S+Ghoshal%2C+V+Lakshmi.+Potential+antiamebic+property+of+the+roots+of+Piper+longum+Linn.+Phytother+Res.+2002%3B16%3A689-691.++&btnG= [last accessed on April1,2025].
39. Timbadiya MJ, Nishteswar K, Acharya R, Nariya MB. Experimental evaluation of antipyretic and analgesic activities of Amalakyadi Gana: An Ayurvedic formulation. Ayu 2015;36:220-4. Available from: <https://pubmed.ncbi.nlm.nih.gov/27011727/> [last accessed on April1,2025].
40. Vedhanayaki G, Shastri GV, Kuruvilla A. Analgesic activity of Piper longum Linn. root. Indian J Exp Biol. 2003; 41: 649-651. Available from: <https://pubmed.ncbi.nlm.nih.gov/15266916/> [last accessed on April1,2025].
41. S Kumar, P Arya, C Mukherjee, BK Singh, N Singh, VS Parma r, et al. Novel aromatic ester from *Piper longum* and its analogues inhibit expression of cell adhesion molecules on endothelial cells. Biochemistry. 2005; 44:15944-15952. Available from:
- <https://pubmed.ncbi.nlm.nih.gov/16313198/> [last accessed on April1,2025].
42. DM Tripathi, N Gupta, V Lakshmi, KC Saxena, AK Agrawal Antigiardial and immunostimulatory effect of Piper longum on giardiasis due to *Giardia lamblia*. Phytother Res.1999; 13 : 561-565. Available from: <https://pubmed.ncbi.nlm.nih.gov/10548746/> [last accessed on April1,2025].
43. Kaushik P, et al. *In vivo* and *in vitro* Antihistaminic Studies of Plant *Piper longum* Linn.; International Journal of Pharmacology 2012;8:192-7. Available from: <https://scialert.net/fulltext/?doi=ijp.2012.192.197> [last accessed on April1,2025].
44. AM Ali, NM Alam, MS Yeasmin, AM Khan, MA Sayeed Antimicrobial screening of different extracts of *Piper longum* Linn. Res J Agr Bio Sci. 2007; 3: 852-857. Available from: https://www.researchgate.net/publication/322096928_Antimicrobial_Screening_of_Different_Extracts_of_Piper_longum_Linn [last accessed on April1,2025].
45. Gupta OP, Nath A, Gupta SC and Srivastava TN. Preparation of semi synthetic analogues of piper amides and their antitubercular activity. Bull. Med. Ethnobot. Res. 1980;1(1):99. Available from: https://scholar.google.com/scholar_lookup?journal=Bull%20Med%20Ethnobot%20Res&title=Preparation%20of%20semi%20synthetic%20analogue%20of%20Piper%20amides%20and%20their%20antitubercular%20activity&author=OP%20Gupta&author=A%20Nath&author=SC%20Gupta&author=TN%20Srivastava&volume=1&publication_year=1980&pages=99-106&
46. Bezerra DP, Pessoa C, Moraes MO, Alencar NM, Mesquita RO, Lima MW, et al. *In vivo* growth inhibition of sarcoma 180 by piperlonguminine, an alkaloid amide from the *Piper* species. J Appl Toxicol 2008;28:599-607. Available from: <https://pubmed.ncbi.nlm.nih.gov/17975786/> [last accessed on April1,2025].
47. DM Tripathi, N Gupta, V Lakshmi, KC Saxena, AK Agrawal Antigiardial and immunostimulatory effect of Piper longum

- on giardiasis due to *Giardia lamblia*. Phytother Res.1999;13:561-565. Available from: <https://pubmed.ncbi.nlm.nih.gov/10548746/> [last accessed on April1,2025].
48. IB Koul, A Kapil Evaluation of the liver protective potential of piperine, an active principle of black and long peppers. Planta Med.1993; 59: 413-417. Available from: <https://pubmed.ncbi.nlm.nih.gov/8255933/> [last accessed on April1,2025].
49. AJ Christina, GR Saraswathy, SJ Robert, R Kothai, N Chidambaranathan, G Nalini, *et al*. Inhibition of CCl4 induced liver fibrosis by *Piper longum* Linn. Phytomedicine. 2006; 13:196-198. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0944711305000310?via%3Dihub> [last accessed on April1,2025].
50. Z Jin, G Borjihan, R Zhao, Z Sun, GB Hammond, T Uryu. Antihyperlipidemic compounds from the fruit of *Piper longum* L. Phytother Res. 2009; 23:1194-1196. Available from: <https://pubmed.ncbi.nlm.nih.gov/19172581/> [last accessed on April1,2025].
51. S Pattanaik, D Hota, S Prabhakar, P Kharbanda, P Pandhi. Effect of piperine on the steady-state pharmacokinetics of phenytoin in patients with epilepsy. Phytother Res.2006; 20 :683-686. Available from: <https://pubmed.ncbi.nlm.nih.gov/16767797/> [last accessed on April1,2025].
52. M Singh, C Varshneya, RS Telang, AK Srivastava. Alteration of pharmacokinetics of oxytetracycline following oral administration of *Piper longum* in hens. J Vet Sci. 2005; 6: 197-200. Available from: <https://pubmed.ncbi.nlm.nih.gov/16131821/> [last accessed on April1,2025].
53. A Khajuria, N Thusu, U Zutshi. Piperine modulates permeability characteristics of intestine by inducing alterations in membrane dynamics: influence on brush border membrane fluidity, ultrastructure and enzyme kinetics. Phytomedicine.2002; 9 : 224-231. Available from: <https://www.sciencedirect.com/science/article/abs/pii/S0944711304701063> [last accessed on April1,2025].
54. D Chanda, K Shanker, A Pal, S Lugman, DU Bawankule, D M ani, *et al*. Safety evaluation of Trikatu, a generic Ayurvedic medicine in Charles foster rats. J Toxicol Sci. 2009; 34: 99-108. Available from: <https://pubmed.ncbi.nlm.nih.gov/19182439/> [last accessed on April1,2025].
55. Kumar S, Kamboj J, Sharma S. Overview for various aspects of the health benefits of *Piper longum* linn. fruit. Journal of acupuncture and meridian studies. 2011 Jun 1;4(2):134-40. Available from: <https://www.sciencedirect.com/science/article/pii/S2005290111600204?via%3Dihub> [last accessed on April1,2025].
56. Gagandeep Kour, Suresh Chaubey, Dinesh Chandra Singh, Rajesh Kumar Mishra. Ativisa (*Aconitum Heterophyllum* Wall Ex. Royle): A Comprehensive Review on Propagation, Traditional Uses and Pharmacology. AYUSHDHARA, 2020;8(2):3168-3177. Available from: <https://ayushdhara.in/index.php/ayushdhara/article/view/714/599> [last accessed on April1,2025].
57. Anonymous. The Ayurvedic Pharmacopoeia of India. Part I. 1st ed., Vol. 3. New Delhi: Government of India, Ministry of Health and Family Welfare, Department of Indian Systems of Medicine and Homoeopathy; 2001:129-30.
58. Prasad SK, Jain D, Patel DK, Sahu AN, Hemalatha S. Antisecretory and antimotility activity of *Aconitum heterophyllum* and its significance in treatment of diarrhea. Indian J Pharmacol 2014;46:82-7. . Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3912813/> [last accessed on April1,2025].
59. Verma S, Ojha S, Raish M. Anti-inflammatory activity of *Aconitum heterophyllum* on cotton pelletinduced granuloma in rats. J Med Plants Res 2010;4:1566-9. Available from: https://www.researchgate.net/publication/216795242_Anti-inflammatory_activity_of_Aconitum_heterophyllum_on_c

- [otton pellet-induced granuloma in rats](#) [last accessed on April1,2025].
60. Subash AK, Augustine A. Hypolipidemic effect of methanol fraction of *Aconitum heterophyllum* wall ex Royle and the mechanism of action in diet-induced obese rats. J Adv Pharm Technol Res 2012;3:224-8. Available from: <https://pmc.ncbi.nlm.nih.gov/articles/PMC3560128/> [last accessed on April1,2025].
61. Konda VG, Eerike M, Raghuraman LP, Rajamanickam MK. Antioxidant and nephroprotective activities of *Aconitum heterophyllum* root in glycerol induced acute renal failure in rats. J Clin Diagn Res 2016;10:FF01-2. Available from: <https://pubmed.ncbi.nlm.nih.gov/27134892/> [last accessed on April1,2025].
62. Aggarwal BB, Ichikawa H, Garodia P, Weerasinghe P, Sethi G, Bhatt ID, Pandey MK, Shishodia S, Nair MG. From traditional Ayurvedic medicine to modern medicine: identification of therapeutic targets for suppression of inflammation and cancer. Expert opinion on therapeutic targets. 2006 Feb 1;10(1):87-118. Available from: <https://pubmed.ncbi.nlm.nih.gov/16441231/> [last accessed on April1,2025].
63. Munir M, Khan MA, Ahmed M, Bano A, Ahmed SN, Tariq K, Tabassum S, Mukhtar T, Ambreen M, Bashir S. Foliar epidermal anatomy of some ethnobotanically important species of wild edible fruits of northern Pakistan. J Med Plants Res. 2011 Oct 30;5(24):5873-80. Available from: https://www.researchgate.net/publication/286947662_Foliar_epidermal_anatomy_of_some_ethnobotanically_important_species_of_wild_edible_fruits_of_northern_Pakistan [last accessed on April1,2025].
64. Ahmad S, Ali M, Ansari SH, Ahmed F. Phytoconstituents from the galls of *Pistacia integerrima* Stewart. Journal of Saudi chemical society. 2010 Oct 1;14(4):409-12. Available from: https://www.researchgate.net/publication/250781296_Phytoconstituents_from_the_galls_of_Pistacia_integerrima_Stewart [last accessed on April1,2025].
65. Islam M, Ahmad H, Rashid A, Razzaq A, Akhtar N, Khan I. Weeds and medicinal plants of Shawar valley, district Swat. Pak. J. Weed Sci. Res. 2006;12(1-2):83-6. Available from: https://www.researchgate.net/publication/285344841_Weeds_and_medicinal_plants_of_Shawar_Valley_District_Swat [last accessed on April1,2025].
66. Farrukh Hussain FH, Shah SM, Hasan Sher HS. Traditional resource evaluation of some plants of Mastuj, District Chitral, Pakistan. Pakistan Journal of Botany.2007; 39(2):339-354. Available from: https://www.researchgate.net/publication/286951135_Traditional_resource_evaluation_of_some_plants_of_Mastuj_District_Chitral_Pakistan [last accessed on April1,2025].
67. Abbasi AM, Khan MA, Ahmad M, Zafar M, Khan H, Muhammad N, Sultana S. Medicinal plants used for the treatment of jaundice and hepatitis based on socio-economic documentation. African Journal of Biotechnology. 2009;8(8): 1643-1650. Available from: https://www.researchgate.net/publication/228348321_Medicinal_plants_for_the_treatment_of_jaundice_and_hepatitis_based_on_socio-economic_documentation [last accessed on April1,2025].
68. Thakur S, Asrani RK, Patil RD, Thakur M. Antimicrobial Potential of Medicinal Plants of Himachal Pradesh Against Pathogenic *Escherichia Coli*, *Salmonella Gallinarum* and *Salmonella Typhimurium*. Veterinary Research 2018;6(04):67-71. Available from: https://www.researchgate.net/publication/339874362_Antimicrobial_Potential_of_Medicinal_Plants_of_Himachal_Pradesh_Against_Pathogenic_Escherichia_Coli_Salmonella_Gallinarum_and_Salmonella_Typhimurium [last accessed on April1,2025].
69. Ismail M, et al. Analgesic, anti GIT motility and toxicological activities of *Pistacia integerrima* Stewart ex Brandis bark in mice. Journal of Medicinal Plants Research 2012;6.14:2827-31. Available from: https://www.researchgate.net/publication/271184809_Analgesic_anti_GIT_motility_and_toxicological_activities_of_Pistacia_integerrima_Stewart_ex_Brandis_bark_in_mice

[Pistacia integerrima Stewart ex Brandis bark in mice](#)

[last accessed on April1,2025].

70. Joshi UP, Mishra SH. In vitro antioxidant and hepatoprotective activity of isolated compounds from Pistacia integerrima. Australian Journal of Medical Herbalism. 2010 Jan;22(3):94-9. Available from: https://www.researchgate.net/publication/285806136_In_vitro_antioxidant_and_hepatoprotective_activity_of_isol

[ated compounds from pistacia integerrima](#)

[last

accessed on April1,2025]

71. Viquar U, Ahmad T, Firdaus N, Ansari A, Kazmi MH. Compound Unani formulations used in Zeeq-un-Nafas (Bronchial Asthma) with their therapeutic importance: An overview. Int J Unani Integr Med. 2021;5:1-0. Available from: <https://www.unanijournal.com/archives/2021/vol5issue2/A/5-1-7> [last accessed on April1,2025].