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CRITICAL REVIEW OF PRE-CLINICAL EFFICACY STUDIES OF NAGAVALLI PATRA (*PIPER BETEL LINN*) IN VARIOUS DOSAGE FORMS

Vd Nishant G. Ingle[1]* and Prof. Vd. Vinaya R. Dixit[2]

[1]Assistant Professor Department of Rasashastra and Bhaishajya Kalpana, Ashvin Rural Ayurved College, Manchi Hill, Sangamner, Maharashtra.

[2]Associate Professor Department of Rasashastra, Tilak Ayurved Mahavidyalaya, Pune, Maharashtra.

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***Corresponding Author**
Vd. Nishant G. Ingle
Assistant Professor
Department of Rasashastra and Bhaishajya Kalpana, Ashvin Rural Ayurved College, Manchi Hill, Sangamner, Maharashtra.

INTRODUCTION

The Nagavalli (*Piper Betel Linn*) is an evergreen shade with glossy heart shaped leaves belong to the family Piperaceae. Betel leaf is traditionally known to be useful for the treatment of various diseases like bad breath, boils and abscesses, conjunctivitis, constipation, headache, itches, mastitis, mastoiditis, leucorrhoea, otorrhoea, swelling of gums, rheumatism, cuts and injuries.[1] betel leaves extract increases the salivation which increases the amount of peroxidase, lysozyme and antibodies to combat against bacterial growth in the oral cavity. Chewing of betel leaf not only accelerating the salivation but also enhances gastric juice, pancreatic lipase secretion which aids in digestion process. Betel leaf is in use from ancient times as a digestive edible in the form of Tambula. The leaf has the great potency to act as a natural anti-oxidant. The anti-oxidant property is correlated with different biological activities like hepatoprotective, anti-diabetic, anti-arthritis, anti-stroke and anti-cancer properties, since free radicals are involved in all these diseases.[2]

It is interesting to explore the evidence-based research done so far on Pharmaco- therapeutics of Nagavalli Patra.

AIMS AND OBJECTIVES

1) To review thoroughly the previous research work done on extracts of Nagavalli Patra

(*Piper betel linn*) and present the data in an applicable form.

2) To explore various dosage form prepared with Nagavalli (*Piper betel Linn*) and their respective Pharmaco-therapeutics actions.

MATERIALS

classical texts, various journals, research papers, articles and subject related information available on Scientific authenticate Websites.

METHODOLOGY

- Step 1 - The Ayurvedic and modern literatures available were reviewed thoroughly to accomplish above mentioned objectives.
- Step 2 – the complied data was classified and observation table was put forth.
- Step 3 – Inferences were drawn so as to derive analyzed information from above data.

The critical analysis of the noted observations was done so as to conclude regarding the keywords related to Nagavalli (*Piper Betel Linn*)

KEYWORDS

1. Active constituents
2. Dosage forms
3. Action on specific system
4. Type of study design used for research project
5. Conclusions noted by the researchers.

Conceptual study – Nagavalli Patra

तांबूलवल्ली तांबूली नागिनी नागवल्लरी।

तांबूलं विशदं रूच्यं तीक्ष्णोष्णं तुवरं सरम् ॥१०॥

वश्यं तिक्त कटु क्षारं रक्तपितकरं लघु।

बल्यं श्लैष्मास्यदौर्गद्र्यमलवात श्रमापहम् ॥११॥

(Bhavprakash Nighantu 3/10-11)

Ayurvedic Properties of Nagavalli (Piper Betel Linn)-

- Rasa- katu, tikta
- Guna-Laghu, Ruksha, Tikshna, Vishada.
- Veerya-Ushna

- Vipaka-Katu

A) Ayurvedic pharmacological activities

1) **Doshaghnata-** Kaphavatashamak
2) **Rogaghnata-** kantharoga, Mukharoga, Aruchi, Agnimandya, Vibandha, Krimiroga, Hriddaurbalya, Pratishay, swarabheda, kasa, swasa, stanashotha, grathishotha, parshwashool, Mandagnijanya Daubarlya, Dhwajabhanga.
3) **Karma-** Jantughna, Putihara, Uttejaka, Shothahara, Vedanasthapan, Mukhavaishadyakaraka, Durgandhanashak, Lalapraseekajanana, Rechana, Deepana, Pachana, Anulomana, krimighna, Hridya, Kaphaghna, Vajikara, Jwaraghna.

B) Chemical compounds and bioactive constituents of Piper betle[3]

Types of Chemical Compounds	Bioactive Constituents from Nagavalli
Phenolic	Chavicol, Hydroxychavicol, Chavibetol, Chavibetol Acetate and Eugenol
Ethanolic	Steroids, Diterpenes, Tannin, Cardial Glycosides, Flavonoids, Saponin, Phenols, Coumarin and Alkaloids
Methanolic	Steroids, Diterpenes, Tannin, and Saponin
Butanolic	Steroids, Diterpenes, Tannin, Flavonoids, Emodins and Alkaloids
Acetone	Steroids, Diterpenes, Tannin, Flavonoids, Saponin and Coumarin
Aqueous	Steroids, Diterpenes, Tannin, Cardial Glycosides, Flavonoids, Saponin, Phenols, Coumarin and Alkaloids

OBSERVATION TABLE

Sr. No.	Title	Type of extract / %	Dosage form	Action/ Acting Organ/System, In vitro/vivo/ clinical	Result
1	A review on antiasthamatic Activity of tradional medicinal plant[4]	-	Extract	Bronchodilator	
2	Antioxidant properties of *piper betel linn* leaf extract from six different Geographical domain of India.[5]	Banaras Calcutta Cuttack Desibagla Maharashtra Sofia. Solvent (80% methanol, 80% ethanol, 80% acetone, 80% ethyl acetate & distilled water)	Extract (Internal use)	Antioxidant In vitro	Culcutta variety showed highest antioxidant activity. Desibagla variety had maximum total phenol content.
3	A review on *Piper betel linn*[6]		Extract and essential oil (Internal, external & local application)	Anticancer- (In vivo) Antiallergic- (in vivo & clinical) Antifilarial- Antimalarial- Antibacterial- (in vitro) Antifungal- (in vivo) Antioxidant (in vivo) Antidiabetic Gastroprotective (in vivo) Wound healing activity (Clinical) Cyto toxic activity- (in vitro) Anti asthmatic effect (in vivo (guinea pigs))	Leaves of piper betel contains number of phytoconstituents and as a source of various therapeutic purposes.
4	A review on *Piper betel linn nature's promising medicinal*		Extract (Internal Use) ethanolic	Antinuclear property (in vivo)	This review suggests that leaves of piper betel have

	reservoir[7]		extract (Internal use) chloroform fraction (Local application) aqueous extract essential oil extract Extract aqueous extract	Anti-allergic (in vitro) Anti-filarial (in vivo) Anti-bacterial (in vitro) Anticancer activity (In vitro) Antinociceptive activity (In vivo) Anti-dermatophytic activity (In vitro) Anti-diabetic activity (In vivo) Anti-hypercholeste -rolemic activity (In vivo)	tremendous potential as a potent source for novel therapeutic usage.
5	Review of traditional use, Phytochemical and pharmacologica l activity of *Piper Betel L.*[8]	Ether Chloroform Ethanol Water extract	aqueous extract, methanolic extract & ethanolic extract ethanolic extract hydro- alcoholic extract ethanolic extract ethyl acetate extract ethanolic extract	Anti-bacterial activity (In vitro) Anti-microbial activity (In vitro) Analgesic and anti-inflammatory activity (In vivo) Anti-oxidant activity (In vivo) Anti-proliferation (Cell line study) Hepatoprotective (In vivo)	Piper betel has bioactivity as Anti-bacterial activity, Anti-microbial activity, Analgesic and anti- inflammatory activity, Anti- oxidant activity, Anti- proliferation, Anti-diabetic activity, Hepatoprotective.
7	The effects of leaf to water ration and heating time on the anti-fungal and antioxidant activities of betel leaf (Piper betel l,) extract[9]	Aqueous extract fresh leaf	Gel form (Topical application)	Anti-oxidant activity Antifungal Antitumor Antibacterial	Betel leaf extracts have highest antioxidant and antifungal activities against Candida Albicans

8	Golden heart of the nature: Piper betel L.[10]		Ethanolic extract (eye drops) Chloroform extract(lotio n) Ethanol and carbon tetra chloride Hot water extract	Antimicrobial Anti-inflammatory Aphrodisia Gastroprotective Antioxidant Antidiabetic Radioprotective Antifertility Immunomodulatory Cholinomimetic effect Hepato-protective	Betel leaf place its position in nature same as our heart in our body and role the same with lots of biological activities and has a tremendous strength to come out as a future green medicine hence Piper betel L leaf regard as 'Golden heart of nature'
9	Betel (Piper Betel L.) leaf essential oil extraction using steam distillation[11]	Oil extract Steam distillation	Extract	Anti-cancer Anti-bacterial Anti-microbial Insecticidal	
10	Effectiveness of Betel Leaves Extract (Piper betel Linn.) as Mosquito Anopheles spp Repellent[12]	Betel leaves extract in the conc of 20%, 40%,80% Solvent- Erlenmeyer solvent	Extract	Antibacterial Antifungal Insecticidal, Antioxidant Antiseptic Wound healing Strengthens teeth Cleanses throat	Most effective betel leaf extract againt anopheles' mosquito is 80% conc that is resulting93.75% protection power. It states that repellent is considered effective if the protection power is greater than 90%
11	Application of betel leaves 9Piper betel L.) extract for preservation of homemade chilli bo.[13]	95% ethanol (Betel leaves extract 10.75 mg ml 1.25 mg ml and 1.75 mg ml + distilled water) Peptone chlorophyll	Extract	Anti-microbial Antioxidant Antibacterial Antiseptic	
12	Traditional and functional uses of betel leaf (Piper betel L.) pertaining to food sector: a review.[14]	Essential oil Phenolic compounds, Ethanolic extract, Aqueous extract, Hydro chavicol	Extract	Aphrodisiac Antimicrobial Antioxidant Digestive and gastro Protective properties Wound healing	The various beneficial properties of betel leaf and its components in different forms may be utilized as a food ingredient, food preservative, sensory quality enhancer,

				Antidiabetic Anticancer Anticholinesterase	packaging material, etc. in food and beverage sectors.
13	Betel leaf extract (Piper betel L.) antihyperurice mia effect decreases oxidative stress by reducing the level of MDA and increase blood SOD levels of hyperuricemia wistar rats (I Ratus norvegicus)[15]	Betel leaf extract Ethanol 96%	Extract	Anti diabetic Antimutagenic Anti carcinogenic Anti-inflammatory Anti-bacterial Anti hyperuricaemia	Betel leaf extract as anti-hyperuricemia lower the uric acid and oxidative stress
14	Piper Betel Leaf: A reservoir of potential xenohormetic Nutraceuticals with cancer-fighting properties [16]	Phenolic components, Phyto chemicals		Antifungal Antimutagenic Antimicrobial Wound healing Antioxidant Chemo preventive Anti-ulcerogenic Anti-pro-oxidant	
15	A comprehensive review on the magical Indian folk medicine: piper betel Linn.[17]	Oil extract aqueous extract	Extract	Aromatic Antioxidant, Anti-microbial Analgesic Anti-viral Anti-cancer Seizure control Parkinson's Anti-depressant Hypoglycaemic Hypolipidemic Anti-inflammatory Gastro protective Anti-microbial Anti-platelet activity Anti-filarial activity, Oral hygiene	
16	Betel leaf extract efficacy on	Leaf extract with low 0.5mg	Extract	Wound healing Anti-	

	wound healing: a systematic review[18]	Highest conc 10%		bacterial Anti-inflammatory	
17	Effect of Piper Betel Linn extract on the growth of staphylococcus aureus[19]	Betel leaf extract, 70% methanol Distilled water and antibiotics methanol and chloroform extracts	Extract	Antibacterial (In vitro) Antioxidant	There is effect of betel leaf extract on the growth of staphylococcus aureus ATCC 25923
18	Antioxidant activity (phenol and flavonoid content) of three different cultivars of Piper betel L. (Piperaceae)[20]	Phenol content Fresh and matured leaves used Methanol	Aromatic oil, Minerals, glycosides, Enzymes, Vitamins, Essential amino acids, and tannins	Anti-inflammatory (In vitro) Antioxidant	
19	Antimicrobial, anti-oxidative and anti- hemolytic activity of Piper betel Leaf extracts[21]	Ethyl acetate Methanol Petroleum ether	Extract	Antimicrobial, anti-oxidative and anti-haemolytic	
20	Bioanalytical HPLC Method of Piper betel L. for quantifying phenolic compound, water soluble vitamin and essential oil in five different solvent extracts.[22]	Water, methanol, Ethanol, Chloroform and hexane	Essential oil, extract, phenolic compound		
21	Betel vine leaves- A green treasure house of useful chemicals[23]			Antioxidant	
22	The formulation of lotion preparations of betel leaf extract (Piper betel)[24]	Fresh betel leaves essential oil used, Water distillation, 70% ethanol	Extract	Antiseptic Antifungal	Lotion preparations from betel leaf extracts with 20% Arabic gum suspending agent had a physical quality that matched the required dosage criteria.

23	Isolation and identification of secondary metabolites of black betel (Piper betel L. var Nigra)[25]	Methanol Ethyl acetate n-hexane			TLC test showed the presence of alkaloids compounds.
24	Evaluation of antioxidant and anticancer effects of Piper betel L(Piperaceae) leaf extract on MCF-7 cells and preparation of transdermal patches of the extract.[26]	Maceration method extraction	Extract	Antioxidant Anticancer	Extract along with antioxidant activity also inhibits the viability and migration of MCF- 7 cells. Thus, the extract has promising; potential for development into anticancer agent for breast cancer.
25	Betel like scented Piper plants as diverse sources of industrial and medicinal aromatic chemicals.[27]			Aromatic	The diversity of betel like scented species and the chemical components could be useful for industries to produce favours, fragrances, cosmetics, drugs, perfumes and food preservatives.
26	Utilization of green betel leaves (Piper betel L.) extract as an additive material on paper soap production.[28]	leaf extract used. (External use-soap preparation)		Antiseptic	The best formulation of coconut oil paper soap was obtained with a composition of 2 ml of betel leaf extract
27	Extraction and qualitative analysis of Piper Betel Leaves for Antimicrobial Activities.[29]	Dry leaves used Aqueous extraction 70% ethanol	Extract	Antimicrobial Antibacterial	Betel leaves contain various bioactive compounds.
28	Antibacterial activity of Piper Betel Leaves[30]	Aqueous and ethanol extract	Extract	Antibacterial activity	The essential oil isolated from the leaves inhibited the growth of Staphylococcus aureaus and Streptococcus pyogenes.

29	The ignored Green Gold called as Betel Leaf[31]			Antibacterial Antiviral Antifungal	The betel leaves are very nutritive and contain a considerable amount of vitamins and minerals
30	Ethno Medicinal Uses of Piper Betel- A Review.[32]			Oral hygiene Anti-diabetic Cardiovascular Anti-inflammatory Anti-ulcer Antibacterial Anticancer Anti-allergic Wound healing Anti-hypercholesterolemi c Gastro-protective Anti-halitosis.	Study suggests that the leaves of Betel contains a number of important phytoconstituents to be used for therapeutic purposes.
31	Biochemical profiling of antifungal activity of betel leaf (Piper betel L,) extract and its significance in traditionalmedicine.[33]	Ethyl acetate Highest hexane Methanol Ethanol	Extract	Antifungal activity	Results highlight the potential of using betel leaf extract as a potent antifungal agent for farming and perhaps for food storage against different types of molds.
32	Dose dependent effect of Piper Betel Linn. Leaf extract on erythrocytes of experimental Mice[34]	Leaf extract	Extract	Anti-oxidant (In vivo)	The extract of piper betel leaf at the low dosage of 0.2 gm / day for 15 days provides better antioxidant potential as well as membrane stabilizing action in Swiss mice over controls
33	Therapeutic potential of Piper betel: An amazing Nature's medicinal reservoir[35]			Anticancer Antiallergic Anti-malarial Ant filarial Anti-microbial Protective & healing Immunomodulatory	Piper betel leaf has a great potential of medicinal and nutritional value.

				Anti-Oxidant Gastroprotective Hepatoprotective Platelet inhibition Anti-fertility Anti asthmatic Anti-halitosis Anti-haemolytic, etc	
34	A short review on piper betel (Betel Leaf's)[36]			Anti-diabetic Cardiovascular Anti-inflammatory Immunomodulatory Anti-ulcer Hapato protective Anti-infective	Betel leaf is tropical shade-loving perennial evergreen vine.
35	Extraction, fractionation and isolation of hydroxychavicol from the leaves of Piper betel[37]	Maceration extraction method		Antioxidant Antifungal Antimicrobial	
36	Chemistry behind the betel leaves and betel quid: Their health benefits and adverse health effect- A Review[38]			Antioxidant Antifungal Antimicrobial Anti inflammatory Anti-histamine Antimutagenic Anti-haemolytic Antiulcer Antibacterial Anti-diabetic Palpebral skin antiseptic Local anaesthetics action Anti-nociceptive Contraceptive	Review suggests that the leaves of Piper betel Linn. Contains number of Phyto-constituents and as a source for various therapeutic purposes. It may be concluded that though consumption of betel quid with tobacco poses serious health hazards, the leaves alone when consumed we have innumerable health benefits.

37	Evaluation of Antidepressant activity on extract of Piper betel leaves- A research[39]	70% ethanol 80% ethanol		Antidepressant (In vivo)	Piper betel has antidepressant activity.
38	Antimicrobial property of Piper betel leaf against clinical isolates of bacteria.[40]	Ethanol		Antimicrobial (In vitro) Antioxidant	Crude ethanol extract of Piper betel showed strong antimicrobial activity against the tested pathogenic bacterial strains.
39	Influence of piper betel leaf extract to prevent the premature spoilage of milk[41]	Dried betel leaves used. Distilled water		Spoilage prevention action.	The microbial spoilage of dairy products and its prevention of spoilage was found to be possible by the use of leaf extract of Piper betel.
40	Betel Leaf: The Green Gold.[42]			Antifungal Antioxidant Carminative Antiplatelet Digestive CNS depressant	Betel leaf contains various biologically active compounds which are responsible for its antioxidant, chemo preventive activities.
41	Antimalarial activity of Methanolic leaf extract of Piper Betel Linn.[43]	Methanol	Extract	Anti-malarial (In vivo) Antioxidant	The leaf extract of Piper betel demonstrated significant schizonticide activity in all the three models of the antimalarial evaluations. This study also suggests that Malaysian folkloric medicinal application of the extract of Piper betel leaves has a pharmacological basis.
42	Phenolic antioxidants from betel leaf (Piper betel Linn.) extract obtained with different solvents	Fresh leaves used. Methanol Ethanol Ethyl acetate		Antioxidant	Ethyl acetate was found to be the best solvent for the extraction of antioxidant

	and extraction time.[44]				compounds from betel leaves due to its nonpolar components.
43	Anatomical investigation on the leaves of Piper betel (L.) var. Sirugamani 1 (SGM1) links an ethnomedical important medicinal plant and its pharmacognosti c relevance.[45]	Fresh and dried leaves evaluated.			The result showed higher potassium content and thus the leaves may be useful in the maintenance of electrical excitability of nerves and muscles.
44	Exploration of multifunctional properties of piper betel leaves extract incorporated polyvinyl alcohol-oxidised maize starch blend films for active packaging application.[46]	90% ethanol	Extract	Antibacterial (In vitro) Antioxidant Biodegradable.	Polyvinyl alcohol is a well-known synthetic biopolymer, successfully blended with oxidised maize starch and betel leaves extract to enhance the biodegradability and hence reduce the cost of the material.

Following activities of piper betel Linn was studied previously

Sr no	Name of activity	No of Studies	Sr no	Name of activity	No of Studies
1	Bronchodilator	1	22	Anti-hepatotoxic	1
2	Antioxidant	21	23	Anti-mutagenic	3
3	Anticancer	9	24	Radioprotective	1
4	Antiallergic	4	25	Immunomodulatory	3
5	Antifiliarial	3	26	Anti-fertility	2
6	Antimalarial	3	27	Insecticidal	1
7	Anti-bacterial	8	28	Anti-septic	5
8	Antifungal	8	29	Aphrodisiac	2
9	Antidiabetic	9	30	Anti-hyperuricaemia	1
10	Gastroprotective	3	31	Chemo preventive	1
11	Wound healing	5	32	Anti-viral	1
12	Cyto toxic	1	33	Anti-platelet	2
13	Anti-asthamatic effect	2	34	Hypoglycaemic	1
14	Anti-nuclear property	1	35	Anti-depressant	2
15	Anti-nociceptive	1	36	Anti-oxidative	1
16	Anti-dermatophytic	1	37	Anti-haemolytic	2
17	Anti-hypercholesterolemic	2	38	Aromatic	1
18	Anti-microbial	11	39	Anti-ulcer	3
19	Anti-inflammatory	7	40	Anti- halitosis	2
20	Anti-proliferation	1	41	Cardiovascular	1
21	Hepatoprotective	3	42	Anti-infective	1
43	Contraceptive	1	45	CNS depressant	1
44	Anti-histaminic	1	46	Anti-tumour	1

It was noted that various dosage forms of piper betel linn were used to assess the pharmacotherapeutics

1) Extract

- essential oil extracted from Fresh betel leaves used for topical application- antiseptic/antifungal.
- Leaves extract used for soap paper preparation.
- Flower extract used for anti-diabetic activity.
- Ethanolic extract- eye drop- antimicrobial.
- Chloroform extract- lotion for baby- anti-inflammatory.

2) Gel
3) Lotion
4) Cream
5) Ointment
6) Juice

7) Paste
8) Soap paper
9) Eye drops.

RESULT AND DISCUSSION

1) Compiled information from total 44 articles, 46 activities and 9 dosage forms related to Piper betel Linn were noted. This comprehensive collection of data reflects the extensive pharmacological and therapeutic potential of piper betel linn across various medical applications.
2) Piper betel linn possess qualities (gunas) Such as Katu and Ushna which have the potential to balance kapha and vata doshas, while its tikta rasa can help balance pitta dosha. By restoring equilibrium among the doshas, Piper betel Linn promotes overall health and well-being.
3) Piper betel Linn interacts with multiple strotasa in the body including Annavaha, Pranavaha, Rasavaha, Mutravaha, Majjavaha, Medovaha, Raktavaha, and Mamsavaha. Eg Annavaha Strotasa- The Katu rasa and Ushna veerya of Piper betel Linn stimulates Agni, thereby enhancing digestion, metabolism and nutrient absorption. This promotes the proper assimilation of nutrients and elimination of waste products, supporting overall digestive health.
4) Piper Betel linn emerges as a valuable medicinal plant with a broad-spectrum therapeutic property rooted in both traditional Ayurvedic Principles and modern pharmacological research. its holistic approach to health and well-being, targeting multiple physiological system through a range of bioactive compounds, underscores its potential as natural remedy for various health conditions.

CONCLUSION

- The comprehensive review of 44 article, 46 activities and 9 dosage forms related to Piper betel Linn underscores its extensive pharmacological and therapeutic potential across various medical applications.
- Its qualities such as Tikta-katu rasa and Ushna Veerya contribute to balancing the three Doshas, Promoting overall health and well-being according to Ayurvedic Principles.
- Furthermore, Piper betel Linn interacts with multiple Strotasa, enhancing digestion, metabolism and nutrient absorption, thus supporting digestive health.
- Each dosage form presents unique advantages and applications, catering to different

preferences, conditions, and method of administration, the availability of various dosage forms allows for flexibility in treatment approaches, accommodating individual needs and preferences.

- Overall, Piper Betel Linn emerges as a valuable medicinal plant with broad spectrum therapeutic properties rooted in both Traditional Ayurvedic principles and modern pharmacological research.
- Further research and clinical studies are warranted to fully elucidate its mechanism of action, optimize its therapeutic use, and explore its potential integration into main stream healthcare practices.

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