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"A CRITICAL REVIEW ON NIDIGDHIKADI LEHA IN THE MANAGEMENT OF RECURRENT UPPER RESPIRATORY TRACT INFECTION IN CHILDREN"

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Keywords:

Recurrent respiratory tract infections, Morbidity, Immune system, Children

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ABSTRACT: Upper respiratory tract infections are the major cause of childhood morbidity leading to limit the day to day activities and school absenteeism. Diseases like tonsillitis, cough, and cold account for the maximum respiratory tract morbidities. Studies document that, in developing countries, on average, every child has five episodes of acute respiratory infections per year accounting for 30%-50% of the total pediatric outpatient visits and 20%-30% of the pediatric admissions. Ayurveda states that in children, the Prana, Dosha, Dhatu, Bala, Ojas are under developed, and therefore, they are the most vulnerable group in terms of illness. Therefore they should be supported externally to potentiate their immune system. Good immunity has a substantial role in sustaining the body and preventing various infections. Although available conventional management provides symptomatic relief, there is no conclusive evidence that they shorten the duration of symptoms. The use of antibiotic is also not empirical. Therefore it is the need of hour to find some alternative to provide relief in symptoms, potentiate the immune system to resist the infections, and as a result, minimize the use of antibiotics. Ayurveda classics explain the upper respiratory tract infections under the heading of Kasa, Shwasa, Pratishyaya, peenasa, Mukha Roga with a comprehensive approach to the treatment. Nidigdhikadi leha is indicated for Kasa, Shwasa, Jwara, and peenasa. The present review provides evidence that the drug Nidighdhikadi leha may be used as a potent drug for the management of recurrent upper respiratory tract infections in children.

INTRODUCTION: Poor Immunity and recurrent infections are the major concern in children. Repeated infections and recurrence of any disease may adversely affect the physical and mental growth as well.

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Upper respiratory tract infections in children are the most common causes of significant morbidity and reason for a hospital visit. Common cold, cough, sore throat, tonsillitis, influenza, rhinovirus, sinusitis are the most common upper respiratory tract infections.

Recent estimates document 3.5% of the global burden of disease is caused by acute respiratory infections [1]. In developing countries, on average, every child has five episodes of acute respiratory infections per year, accounting for 30%-50% of the total pediatric outpatient visits and 20%-30% of the

pediatric admissions [1]. Recent community-based estimates from prospective studies report 70% of the childhood morbidities among children aged less than 5 years are due to acute respiratory infections [2]. The main focus of management is symptom relief of fever, nasal congestion, and coughing. For this purpose, a variety of adrenergic agonist, anti-cholinergic, anti-histamine preparations, anti tussives and expectorants are available in market. Although they provide symptom relief, there is no conclusive evidence that they shorten the duration of symptoms [3, 4].

Recently, the Food and Drug Administration issued an advisory statement warning against using over-the-counter medications for URTIs in children under two years of age [5]. Now a day, overuse of antibiotics is seen in general practice. Excessive and misuse of antibiotics causes anti-biotic resistance and emergence of superbugs which pose potent threat to mankind. Ayurveda states that in children the prana, dosha, dhatu, bala, ojas are all under developed and therefore, they are the most vulnerable group in terms of illness. Not all children are the same. They vary in terms of their vyadhikshamatva. Therefore they should be supported externally to potentiate their immune system. The good Immune system plays a very important role in sustaining the body and preventing various pathogenic infections. Therefore it is the need of hour to find some alternative to provide relief in symptoms, potentiate the immune system to resist the infections, and as a result, minimize the use of antibiotics. Ayurveda classics explains the similar instances of Upper Respiratory tract infections under the heading of Kasa, Shwasa, Pratishyaya, Mukha Roga with comprehensive approach to the treatment. A review of Ayurveda literature, reveals that Ojas (immunity) plays a substantial role in the prevention of such pathological states.

Ayurveda provides mounting references of drugs acting specifically on diseases of the respiratory system, including acute respiratory infections. These drugs also have immune potentiating action which may reduce the frequency and severity of the illness. Nidigdhikadi leha6 is one of such drugs indicated for Kasa, Shwasa, Jwara,and peenasa which are the features of upper respiratory tract infections.

With this aim, the present review is an attempt to provide evidence regarding the efficacy of Nidigdhikadi leha in the management of respiratory infections in children.

Aim and Objectives: To Search and re-evaluate the effect of evidence that the drug Nidighdhikadi leha may be used as a potent drug for the management of recurrent upper respiratory tract infections in children.

MATERIALS AND METHODS:

Data Sources and Review Process: Subject related published research articles from various journals were searched online through PubMed, Google Scholar, and Digital Helpline for Ayurvedic Research Articles (DHARA), AYUSH portal from online official websites, and data of the articles were analyzed by following PICOS format to confirm their safety and efficacy in the pediatric population.

Types of Studies: In this review online available scientific evidences were included like clinical and experimental study were evaluated for safety and efficacy of the drug.

Types of Interventions: This review article includes clinical trials and experimental study-based data for pharmacological actions of drugs and evidence for usefulness in upper respiratory tract infection in children in appropriate manner.

Types of Outcome Measure: Nidigdhikadi leha can be helpful to minimize the use of antibiotics. Frequent uses of antibiotic drugs results as poor immunity so dependency over corticosteroids antibiotics may be reduced. All the component of drug has immuomodulatory, anti-bacterial, anti oxidative, antimicrobial, analgesic and bioavailability enhancing effect therefore it posses to improvement in recurrent upper respiratory tract infection in children.

Data Extraction: For data analysis various experimental study and clinical trial of each component of the trial drug is studied carefully. Especially those study which can helpful to cure or good effect as bronchodilator, antitussive and immunomodulatory effect to minimize the recurrence with symptomatic relief in upper respiratory tract infection in children.

Study Selection and Exclusion: Clinical and experimental studies related to Kateri (*Solanum xanthocarpum*), Guduchi (*Tinospora cardifolia*), Sunthi (*Zingiber officinale*) and Pippali (*Piper longum*) from the various authorized journal were searched through Pubmed, Google scholar, AYUSH, DHARA, *etc.* were included after assessing the descriptions of the full-text articles. Effects of drugs related to other subjects were excluded from this review article.

Effect of Intervention: This article is based on a critical review of Nidigdhikadi leha in management of Upper Respiratory Tract Infection with its immune enhancing properties and effect on respiratory tract infections described in various ancient samhitas, textbooks, internet sources and research papers is analyzed thoroughly.

According to ayurveda classics Pranavaha Srotas is responsible for all respiratory illness. Pranavaha Srotas is main unit for lungs and heart. Any pathology or changes in anatomical structure causes Pranavaha Srotodusti.

Ayurveda classics also provide an explanation for the same in terms of Upper Respiratory tract infections under the heading of Kasa, Shwasa, Pratishyaya, Mukha Roga with complete approach to the remedy of the same.

It is established fact in Ayurveda that Ojas (immunity) plays an effective role in prevention of such pathological states. Ojas of an individual is usually challenged in the early life period because of physiological, structural, dietetic, and biochemical limitations.

Review Strengths: In this review, articles were searched through the most popular databases that comprise articles from Ayurvedic science. Full text articles published in English language and written in proper scientific manner with possible scientific discussion and justification were included in this study.

Review Limitations: There may be a chance of bias in the search and selection procedure used in this study. Here, an attempt was made to search the articles through possible keywords relating to the study. Some articles may be located in other databases.

Many articles of Ayurveda published earlier are still not available online. Therefore, studies from them could not be included in the study.

TABLE 1: INGREDIENTS OF NIDIGDHIKADI LEHA [7]

S. No.	Name of Drug	Latin Name	Part Used	Proportion
1	Nidigdhika	*Solanum xanthocarpum*	Fruit	1 Part
2	Nagar/Shuthi	*Zingiber officinale*	Rhizome	1 Part
3	Amrita/ Guduchi	*Tinospora cardifolia*	Stem	1 Part
4	Pippali	*Piper longum*	Fruit	1 Part

Nidigdhika:
Botaical Name: *Solanum xanthocarpum*

English Name: Yellow-berried Nightshade

Chemical Composition: B-carotene, diosgenin, carpesterol, solasodine, solamargine, B-solamargine, solasomine, solasodino-L-rhamnosyl-B-D-glucoside (solasurine), solanocarpine (solanine-S), tomtidenol *etc.* [8]

Therapeutic Properties and uses: Deepan, Pachan, Kasa-Shavasa-Jwarashamak, Peenasa, Garbhakari [9], Kasa-Shavasa-Jwara-Kaphashamak [10], Pratishyaya doshanashak, Kapha-Vata-Jwarashama [11], Hridyaroga, Swasa, Kasa, Asma, Parshvaruka [12].

Immunomodulatory Effect: The study examined the effects of *Solanum xanthocarpum* standard extracts on airway inflammation and oxidative stress parameters in an experimental model of asthma in rats. After 24h of last challenge, rats were anesthetized and blood and bronchoalveolar lavage fluid (BALF) were analyzed for, proinflammatory cytokines (TNF-α & IL-6), Th2 type cytokines (IL-4 & IFN-γ) and oxidative stress parameters malondialdehyde (MDA), reduced glutathione (GSH) and IgE levels. Ovalbumin-specific IgE levels were elevated in the immunized rats, which were reduced by 37% and 20% respectively in blood and BALF at the dose of 50 mg/kg of Solanum xanthocarpum extract. These findings were compared with the effects of the

standard drug prednisolone (10 mg/kg). Further, TNF-α, IL-6 & IL-4 were decreased maximum at dose 100 mg/kg, and IFN-γ was elevated maximum in both blood and BALF. The oxidative stress markers (MDA levels) were also lowered, whereas GSH levels were raised in rats treated with *Solanum xanthocarpum* extract at the dose of 100 mg/ kg [13]. The immunomodulatory activity of methanol extracts of fruits of *Solanum xanthocarpum* (Solanaceae) was examined on Cyclophosphamide induced immune-suppression model. Test drug showed marked protective activity by raising the reduced levels of total WBC count and RBC, Hb%, and neutrophils adhesion percent. Findings suggest the immunomodulatory effect of the extract [14]. The ethanol and water extracts of *Solanum xanthocarpum* fruit showed a higher level of immune effect than root and whole plant extracts tested for immunomodulatory function through cold water tolerance test, reaction response delay, and carbon test and CCl4 oxidative stress model in experimental animals. Findings suggest that *S. xanthocarpum* can be a powerful immune-modulatory agent [15].

Effect on Bronchial Asthma: Oral administration of 300 mg powder of the whole plant of *Solanum xanthocarpum* significantly improved the various parameters of pulmonary function to a significant level in patients suffering from mild to moderate asthma. Subjective relief from asthma symptoms was reported by patients an hour after administration of *S. xanthocarpum* powder. The effect lasted for about 6–8 hours. However, improvements observed were apparently less when compared to that of deriphilline or salbutamol [16]. Ethanolic extract of *Solanum xanthocarpum* (EESX) leaves demonstrated marked broncho-dilator activity in histamine-induced airway constriction and reversed allergen-provoked bronchospasm.

Further, EESX protected cells from compound 48/80 induced degranulation and prevented both acute and chronic inflammation in different models [17]. Apigenin, a flavonoid of *Solanum xanthocarpum* reversed airway hyperresponsiveness (AHR), inflammatory cell count in serum and BALF in ovalbumin induced asthma model of mice [18]. Ethanol extract of *Solanum xanthocarpum* demonstrated significant antihistaminic activity in histamine-induced contraction in goat tracheal chain preparation indicating antihistaminic (H1-receptor antagonist) action. Ethanolic extract of *S. xanthocarpum* at a dose of 50 and 100 mg/kg significantly reduced milk-induced eosinophilia.

Further, it showed significant mast cell stabilization as compared to standard drug Di-sodium chromoglycate at a dose of (50-100 mg/kg, i.p) [19]. Powder or decoction of whole dried plant of *Solanum xanthocarpum* is widely used by practitioners in southern India to treat respiratory diseases [20].

Anti-bacterial Effect: *Solanum xanthocarpum* can be regarded as a potential source of natural antimicrobials [21]. Methanolic extract of *S xanthocarpum* was found to have a maximum quantity of phenol and flavonoids. Further, the methanolic extract demonstrated exceptional antibacterial activity and performed the highest inhibitory effect against *Pseudomonas aeruginosa*, *S. typhi*, *Staphylococcus aureus*, and *E. coli*. The antimicrobial effect was probably due to the presence of high amount of phenolics and flavonoids, confirmed by low minimum inhibitory concentrations and low bactericidal concentration values. Also, the same extract was observed to show remarkable antioxidant activity [22].

Nutritional Effect: Studies have found that the leaves and seeds of *Solanum surrattennse* contain significant levels of nutrient content. It is also a good source of mineral content; therefore, the plant has high nutritional value and is recommended as a economic source of plant protein, energy and mineral nutrients such as calcium, magnesium, sodium and phosphorus [23].

Anti-inflammatory Effect: Carrageenan induced rat paw edema, histamine induced rat paw edema and cotton pellet granuloma in rats models were used to examine the anti-inflammatory activity of ethanol extract of *S. xanthocarpum* whole plant. Acute treatment didn′t show anti-inflammatory activity against carrageenan and histamine induced paw edema. However, administration of 100 mg/kg p.o for 7 days reduced the granuloma formation in cotton pellet granuloma model. Results provide pharmacological basis for the therapeutic use of *S. Xanthocarpum* for its anti inflammatory activity [24].

Anti-oxidant effect: The ethanol extracts of seeds and leaves of *S. xanthocarpum* exhibited anti-inflammatory and antioxidant activity. The acetones extract demonstrated significant anti-inflammatory activity over ethyl acetate and aqueous extract [25].

In another study, the ethanol, chloroform and ethyl acetate extract of leaves and stem of *Solanum xanthocarpum* Lam was studied for antioxidant activity and was compared with 2,2-diphenyl-1picrylhydrazyl radical (DPPH) and BHT as standard. By using DPPH scavenging assays, it was observed that all the ethanol extracts of leaves and stems exhibit antioxidant activity [26].

Anti-Histaminic Effect: The ethanolic extract of *Solanum xanthocarpum* possess antihistaminic mast cell stabilizing activity, decreased capillary permeability effect, and therefore can be effectively used for the treatment of asthma and allergic disorders. A dose-dependent effect was observed. The ethanolic extract showed a significant ($p<0.05$) effect in relaxing histamine pre-contracted isolated goat tracheal chain. Treatment with ethanolic extract (100 mg/kg), significantly reduced milk-induced eosinophilia in mice [27].

A polyherbal formulation (PHE) comprising the ethanolic extract of *Solanum xanthocarpum* Schrad & Wendl. (fruit), *Adhatoda vasica* Nees. (leaf), Curcuma longa Linn. (rhizome), *Clerodendrum, serratum* Linn. (root), and *Piper longum* Linn.(fruit) caused a significant reduction in the mortality of rats subjected to triple antigen-induced anaphylactical shock. Further, PHE exhibited remarkable protection of rat mesenteric mast cells in dose dependant manner from disruption by compound 48/80 [28].

NAGAR:
Botaical Name: *Zingiber officinale*

English Name: Ginger root, Dry Ginger

Chemical Constituents: The plant contains β-curcumene, α- D- curcumene, β-bourbornene, d-borneal, citral, d-camphene, citronellol, geraniol, gingerol, α, and β- Zingiberenes, Zingiberenes, Zingiberol, Zingerone, gingerols, paradol, gingerenone A, ginger glycolipids A,B, and C; [6] gingerdiol, gingerone B and C, *etc.* [29]

Therapeutic Properties and Uses: Vrisya, Swarya, Hridya, [30] Hridya, Vrisya, Vibandha-anahasulahara [31], Jivakanthasodhanam, Dipana, Rochna [32].

Bioavailability Enhancing Effect: Gingerol that can be efficiently used as anti-inflammatory agent, which is carried to reach the blood circulation by specially optimized nano vesicle called an ultra deformable vesicle, can thus be used to penetrate drugs across the biological permeability barriers, such as Stratum corneum with much better-releasing kinetics [33].

Anti-inflammatory Effect: Gingerol, Shogaol, and other structurally similar substances in ginger suppressed prostaglandin and leukotriene biosynthesis by inhibition of prostaglandin synthetase or 5-lipoxygenase. Further, they prohibited the synthesis of pro-inflammatory cytokines such as IL-1, TNF-α, and IL-8 [34]. Another study documented that rhizome hexane fraction extract of *Z. officinale* suppressed excessive production of NO, PGE (2), TNF-alpha, and IL-1beta [35].

Bronchodilatory Effect: A herbal capsule (AHF) containing *Curcuma longa, Zingiber officinale,* and *Alpinia galanga* extracts at a dose of 250 mg/kg showed significant protection of mast cell degranulation (40%) as compared to standard sodium cromoglycate (64%) while at doses of 62.5, 125, 250 mg/kg showed marked inhibition of total cells, eosinophils, neutrophils, lymphocytes, whereas inhibition of IgE, macrophages, and monocytes was observed at 125, 250 mg/kg [36].

Anti-oxidative Effect: The anti-oxidative properties of *Zingiber officinalis* and its constituent has been studied in various *in-vitro* and *in-vivo* tests. This property of ginger can restore the body's defense by enhancing the antioxidant status and further can protect humans across many chronic diseases [37]. The bioactive compounds [6]-gingerol, [8]-gingerol, [10]-gingerol, and [6]-shogaol from *Zingiber officinale* exhibited substantial scavenging activities against 1,1-diphenyl-2-picyrlhydrazyl (DPPH), superoxide, and hydroxyl radicals in anti oxidant assay All the compounds at a concentration of 6 microM have significantly inhibited ($P<0.05$)

f-MLP-stimulated oxidative burst in human polymorphonuclear neutrophils (PMN).

Further, they inhibited, production of inflammatory mediators (lipopolysaccharide-induced nitrite and prostaglandin E(2) production) significantly ($P<0.05$) in a dose-dependent manner [38].

Antimicrobial Effect: Ginger possesses potent antibacterial and, to some extent antifungal properties. *In-vitro* studies have revealed that active constituents from ginger inhibit the multiplication of colon bacteria. It inhibits the growth of *E. coli*, Proteus sp, Staphylococci, Streptococci and Salmonella. The ginger extract showed anti-microbial activity at levels equivalent to 2000 mg/ml of the spice. Ginger inhibited aspergillus, a fungus that produces aflatoxin. Fresh ginger juice showed inhibitory activity against *A. niger*, S. cerevisiae, Mycoderma SPP., and *L. acidophilus* [39].

The methanol and ethanol extracts of ginger are more effective against all tested bacterial strains than ginger aqueous extracts. *E. coli* and Shigella were also more susceptible to the ginger extracts. *E. coli* showed maximum susceptibility to the ginger ethanol extracts, while Shigella showed maximum susceptibility to both ginger methanol and ethanol extract [40]. The ginger extract showed potent antimicrobial activity of against all tested bacterial pathogens. Soybean oil extract of ginger showed the highest zone of inhibition against Salmonella spp. and the lowest zone of inhibition against *Escherichia coli*. Furthermore, Ginger extract showed a lower zone of inhibition against *Staphylococcus aureus* when compared to Gram-negative bacteria. Soybean oil extract of ginger has potent antimicrobial activity at boiling temperature and can be used in food preparation [41].

Antipyretic and Analgesic Effect: An ethanolic extract of the rhizomes of *Zingiber officinale* reduced carrageenan-induced paw swelling and yeast-induced fever in rats. The extract produced a lowering of blood glucose in rabbits. The extract significantly inhibited the growth of both Gram-positive and Gram-negative bacteria. Furthermore, using rat peritoneal leucocytes, dose-dependent inhibition of prostaglandin release effect was found [42]. In a study to evaluate the effect of ginger to improve acute migraine as an add-on therapy to standard treatment, patients treated with ginger demonstrated significant improvement in clinical response after 1 h ($p = 0.04$), 1.5 h ($p = 0.01$), and 2 h ($p = 0.04$). Additionally, ginger treatment exhibited a reduction in pain and relief on functional status at all times of assessment [43]. Treatment of primary dysmenorrhea in students with 1500 mg ginger powder for 5 days showed a statistically significant effect on relieving intensity and duration of pain [44].

Nutritional Effect: Ginger diet influenced the hematological parameters, biochemical indices, and immunological activities [45].

Anti-asthmatic Effect: Ginger and its isolated active components, [6]-gingerol, [8]-gingerol, and [6]-shogaol, relaxed Airway Smooth Muscles (ASM), and [8]-gingerol reduced airway hyperresponsiveness, in part by altering $[Ca^{2+}]i$ regulation. [6]-gingerol, [8]-gingerol, and [6]-shogaol induced rapid relaxation of pre-contracted ASM (100–300 μM), whereas [10]-gingerol failed to cause relaxation. In human ASM cells, exposure to [6]-gingerol, [8]-gingerol, and [6]-shogaol, but not [10]-gingerol (100 μM), blunted subsequent Ca^{2+} responses to bradykinin (10 μM) and S-(−)-Bay K 8644 (10 μM). In A/J mice, nebulization of [8]-gingerol (100 μM), 15 min before methacholine challenge, significantly reduced airway resistance [46].

Both ethanol and aqueous extracts of ginger significantly reduced goblet cell hyperplasia, infiltration of inflammatory cells in airways, and edema with vascular congestion in a mouse model of ovalbumin-induced allergic asthma. Also highly significant reduction was observed in total and differential count of eosinophils and neutrophils in BALF and eosinophil count in blood. Both extracts inhibited Th2-mediated immune response significantly, proved by a reduction in mRNA expression levels of IL-4 and IL-5. Significant inhibition of protein levels of IL-4 and IL-5 in BALF, along with total serum IgE levels, was also observed by both extracts [47].

Anti-tussive Effect: Oral administration of water extracted polysaccharides (WEP) from the Zingier Officinale rhizome, utilizing a traditional aqueous extraction protocol, in doses of 25 and 50 mg/kg

body weight significantly inhibited the number of citric acid-induced cough efforts in guinea pigs. Also, it did not alter the specific airway smooth muscle reactivity significantly. Findings prove that the traditional aqueous extraction method provides molecular entities, which induces antitussive activity without causing addiction [48].

Antiviral Effect: A study investigated the effect of hot water extracts of fresh and dried gingers on HRSV by plaque reduction assay in both human upper (HEp-2) and low (A549) respiratory tract cell lines. Fresh ginger was found to inhibit HRSV-induced plaque formation in both HEp-2 and A549 cell lines ($p<0.0001$) in a dose-dependent manner. Fresh ginger also inhibited viral attachment ($p<0.0001$) and internalization ($p<0.0001$). Further, fresh ginger of high concentration could stimulate mucosal cells to secrete IFN-β that might have contributed to counteracting the viral infection [49].

Guduchi (Amrita):
Botaical Name: *Tinospora cordifolia*

English Name: Heart leave moonseed, Gulancha tinospora

Chemical Constituents: Tinosporine, Tinosporon, Tinosporic Acid, Tinosporol, Tinosporide, Tinosporidine, Columbin, Chasmanthin, Palmarin, Berberine, Giloin, Giloinisin, 1, 2-Substituted Pyrrolidine, A Diterpenoid Furanolactone, 18-Norclerodanediterpene-O-Glucoside, Aryltetra-hydrofuranolignan, Octacosanol, Nonacosan-15-One And Sitosterol, Cordifolide, Unosporin, Heptacosanol, Cordifol, Cordifolon, Magnoflorine, Tembetarine, Cardiofoliosides A & B, Phenolic Lignan-3-4-Dihydroxy-3- Methoxybenzyl, 4-Hydroxy, 3-Methoxybenzyl, Tetrahydrofuran, Arabinogalactan [50].

Therapeutic Properties and Uses: Rasayani, Sangrahini, Agnideepan, vata-Jwaranashin [51], Visham-Jwaransham [52], Balya, Agnideepan, Rasayani, Pandu-Kamla-Kustha-Jwara-Kriminashak [53].

Anti-Inflammatory Effect: *Tinospora cordifolia* possesses significant anti-inflammatory effect against carrageenin-induced paw edema and in cotton pellet-induced granuloma in rats. In carrageenin-induced oedema, the effect of *T. cordifolia* was more than acetylsalicylic acid. In cotton pellet-induced granuloma, *T. cordifolia* was found to be less potent than phenyl butazone. Carrageenin induced hind paw oedema and cotton pellet-induced granuloma are the two standard experimental models of acute and subacute inflammation, respectively. This study provides evidence that these drugs may be effective in both acute and chronic inflammation [54].

Anti-bacterial Effect: The antibacterial activity of the extracts (aqueous, ethanol, and chloroform) from the stems of *Tinospora cordifolia* was studied against various gram negative (*Escherichia coil*, *Salmonella typhi*, *Proteus vulgaris*, *Enterobacter faecalis*) and gram positive (*Staphylococcus aureus* and *Serratia marcesenses*) bacteria. Among all the ethanolic extract exhibited remarkable antibacterial activity against the tested bacteria [55]. The aqueous extracts of *T. cordifolia* exhibited marked anti-bacterial activity against bacterial pathogens in HIV patients. The leaf aqueous extract showed maximum zone of inhibition against *Enterococcus faecalis* (28 mm) and *Salmonella typhi* (26 mm) whereas the stem aqueous extract caused maximum zone of inhibition against *Enterococcus faecalis* (23 mm) and Streptococcus pneumonia (24 mm) at 50 mg/ml concentration [56].

Immunomodulator Effect: G1-4A, a polysaccharide from Tinospora cordifolia significantly induced the surface expression of MHC-II and CD-86 molecules, secretion of pro-inflammatory cytokines, TNF-α, IL-β, IL-6, IL-12, IFN-γ, and nitric oxide lead to reduced intracellular survival of drug-sensitive (H37Rv) and multi drug-resistant strains of MTB, in *in-vitro* and aerosol mouse models of MTB infection.

Further, the bacillary burden was also decreased significantly in the lungs of MTB infected BALB/c mice treated with G1-4A, along with up-regulation of the expression of TNF-α, INF-γ, and NOS_2 in the mouse lung with simultaneously increased levels of Th1 cytokines (IFN-γ, IL-12) and reduced levels of Th2 cytokine (IL-4) in the serum. Also, a combination of G1-4A with Isoniazid (INH) showed better protection against MTB when compared to that due to INH or G1-4A alone, which suggests its potential as adjunct therapy [57]. *Tinospora cordifolia* and its constituent α-D-glucan

stimulate NK cells, B cells, and T cells along with simultaneous production of various immune-stimulatory cytokines [58].

A randomized controlled study on *Tinospora cordifolia* plant extract as an adjuvant in surgical treatment of diabetic foot ulcers is proved to be highly beneficial in immunomodulation for ulcer healing [59]. The ethyl acetate, water fractions and hot water extract of *Tinospora cordifolia* exhibited remarkable immunomodulatory activity with increased percentage phagocytosis. Among different compounds, cordifolioside A and syringin were found to possess immunomodulatory activity. Other isolated compounds- 11-hydroxymustakone, N-methyl-2-pyrrolidone, N-formylannonain, magnoflorine, and tinocordiside exhibited significant increase in phagocytic activity and nitric oxide, and generation of reactive oxygen species also increased at concentration 0.1–2.5 μg/ml [60].

Direct treatment with *Tinospora cordifolia* to macrophage cell line J774A cells showed activation assessed in biochemical assays. Enhanced secretion of lysozyme by J774A on treatment with *Tinospora cordifolia* and lipopolysacharide was observed, indicating the activated state of macrophages. Enhanced lysozyme production was reported at different time intervals (24 h and 48 h). The susceptibility of bacteria was evidenced by raised inhibitory effects of *T. cordifolia* (direct effect) and *T. cordifolia* treated cell supernatant (indirect effect) on the bacteria (*E. coli*). Findings prove that *T. cordifolia* has potential to be used as immune-modulator for the activation of macrophages [61].

Immunomodulatory activity of *Tinospora cordifolia* alcoholic extract was investigated using Delayed Type Hypersentivity (DTH), α-esterase cells, effect on the bone marrow cellularity and zinc sulphate turbidity test. There was a marked increase in footpad thickness after treatment with *T. cordifolia* alcoholic extracts (100 mg/g,p.o), which indicated immunomodulatory effects of the test drug. Further significant increase in the WBC counts and bone marrow cells indicated a stimulatory effect on haeomopoetic system. Furthermore, *T. cordifolia* treated rats serum exhibited more turbidity (cloudy) in zinc sulphate turbidity test, which showed the increase in immunoglobulin level when compared to vehicle, SRBC sensitized, and cyclophosphamide treated group [62]. *T. cordifolia* stem extracts and the isolated compounds of the plant exhibited remarkable immune stimulatory activity in several ways. Isolated compounds of *T. cordifolia* like, N-methyl-2-pyrrolidone and 11-hydroxymustakone, Magnoflorine and Tinocordiside enhanced Reactive Oxygen Species (ROS) generation which induces augmentation of the immune response. *T. cordifolia* extract increased the phagocytosis and intercellular killing capacity by enhancing the survival rate and polymorphonuclear leucocyte function in HIV patients. Further, (1,4)-α-D-glucan from *T. cordifolia* activated the immune system by stimulating macrophages via TLR6 signaling and NF-κB activation mechanism, resulted to cytokine and chemokine production. Furthermore, Immunoductatory protein (ImP) obtained from the dry stem powder of *Tinospora cordifolia* is significant for augmenting the various immunological activities in the human body [63].

Effect in Allergic Rhinitis: *Tinospora cordifolia* (TC) extract significantly reduced all symptoms of allergic rhinitis as compared to placebo. After TC administration, eosinophil and neutrophil count were decreased, and goblet cells were absent in the nasal smear [64].

Pippali:

Botaical Name: Piper longum

English Name: Indian long Piper

Chemical Composition: Essential oil, mono and sesquiterpenes, caryophyllene, piperine, piperlongumine, piperlonguminie, pipernonaline, piperundecalidine, pipercide, sesamin, β-sistoserol, four aristolactams (cepharanone B, aristolactum, AII, piperlactum A and piperolactam B, five 4,5-dioxoaporphines *etc.* [65]

Therapeutic Properties and Uses: Dipana, Rechana, Vrisya, Rasayana. Medhya, Agnivardhan [66], Vrisya, Medha-aganivardhani [67], Dipan, Rechana, Plihasulamarutan [68].

Bio-availability Enhancing Effect: Co-administration of piperine, significantly enhanced bioavailability of beta lactam antibiotics, amoxycillin trihydrate and cefotaxime sodium in rats. The improved bioavailability is reported in

various pharmacokinetic parameters *viz.* t_{max}, Cmax, t(1/2) and AUC, of these antibiotics. The increased bioavailability could be attributed to the effect of piperine on microsomal metabolising enzymes or enzymes system [69]. Piperine of *P. longum* exhibited the bioavailability enhancing activity in structurally and therapeutically varied drugs. It is may be by modulating membrane dynamics due to its easy partitioning and therefore enhancing the permeability of other drugs and solutes [70].

Immunomodulatory and Anticancer Activity: Alcoholic extract of *Piper longum* (10 mg/dose/animal) and piperine (1.14 mg/dose/animal) was able to inhibit the solid tumor development in mice induced with DLA cells and increased the life span of mice bearing Ehrlich ascites carcinoma tumor. Administration of *Piper longum* extract and piperine increased the total WBC count in Balb/c mice. On 5th day of immunization, there was a significant increase in number of plaque-forming cells by extract and piperine. *Piper longum* extract and piperine administration also increased the Bone marrow cellularity and alpha-esterase positive cells [71].

Trikatu group of drugs (*Piper longum* as one of the ingredients) increased bioavailability of the drugs either by facilitating rapid absorption from the gastrointestinal tract, or by protecting from being metabolized during its first passage through the liver after absorption, or by a combination of both mechanisms [72]. An Ayurvedic compound containing *Piper l*ongum fruit (*Pippali rasayana*) was tested in mice infected with *Giardia lamblia*, observed to activate macrophages, as indicated by increase in both macrophage migration index and phagocytic index, which suggests its immunostimulatory activity [73].

Antimicrobial Activity: The study investigated the antimicrobial activity of various solvent extracts of fruit of *Piper longum* L. against different bacteria (gram-positive and gram-negative) by using the disk diffusion method. Among all the gram-positive strains, *Staphylococcus aureus* was observed markedly sensitive with 500 mg/ml ethyl acetate extract. Among gram-negative bacteria, *Vibrio cholera* and *Pseudomonas aeruginosa* were highly sensitive. The ethyl acetate extract was highly sensitive, whereas the petroleum ether was resistant towards all the tested bacterial strains [74, 28]. Extracts from the fruits of Piper species, including *P. longum* Linn. were examined against bacterial pathogens, such as *S. albus, S. typhi, Pseudomonas aeruginosa, E. coli,* and *B. megaterium* and fungus, *Aspergillus niger*. All the extracts exhibited a good antibacterial activity as compared to Streptomycin. Some of the extracts also showed antifungal activity [75].

Bronchodilator Effect: The effect of petroleum ether, alcoholic, and decoction of fruits of piper logum was studied for antihistamic activity using guinea pig ileum preparation. Histamine-induced bronchospasm in guinea pigs and haloperidol-induced catalepsy in mice.

Its anti-allergic activity was elevated using milk-induced leukocytosis in mice. The extract showed significant ($p<0.01$) activity and an increase in dose of extract increased the % protection in histamine-induced bronchospasm [76].

Analgesic Effect: The aqueous extract of *P. longum* root powder (200, 400, and 800/kg) was given orally to mice and rat to study its analgesic property. In the rat the delay in reaction time to thermal stimulant was assessed.

In mice the amount of writhing to the chemical stimulus was assessed. *P. longum* root extract at the doses, 400 and 800 mg/kg doses of exhibited significant NSAID type of analgesia ($P < 0.001$). Both *P. longum* (800 mg/kg) and ibuprofen (40 mg/kg) demonstrated 50% protection against writhing. There was delay in reaction time to thermal stimulus for different doses of *P. longum*. Results demonstrated that *P. longum* root extract has a potent non-steroidal anti-inflammatory drug type and weak opioid-type analgesic effect [77].

Anti-allergic Effect: Piperine acts by mast cell-stabilizing activity, demonstrated immune-modulatory and anti-inflammatory activity, and hence can be a potent treatment for Allergic Rhinitis.

Following nasal challenge, piperine (10, 20, and 40 mg/kg, p.o.) exhibited a significant dose-dependent improvement in sneezing, nasal rubbing and redness of nose ($p < 0.001$). Piperine also

significantly reduced histamine, NO concentration, Mast cell degranulation (MSD), and paw edema dose-dependently, and lowered the expression of IL-6, IL-1β, and IgE. Histopathology exhibited inhibition of eosinophil infiltration and hyperplasia [78]. Piperine-treated groups showed reduced eosinophil infiltration, allergic airway inflammation and airway hyper responsiveness, led by inhibition of the production of Th2 cytokines (IL-4, IL-5), IgE and histamine.

Furthermore, marked reduction of thymus and activation regulated chemokine, eotaxin-2 and interleukin-13 mRNA expression in lung tissue was found in piperine treated [79].

Anti-tussive Effect: The anti-tussive activity of extract of *Piper longum* was investigated by comparison with market preparation and reference standard Codeine phosphate. Acetic acid induced cough models in guinea pigs were used. The percentage suppression of bouts of cough for *P. longum* extract was very significant (92.15%), compared to standard and other market preparation. Study supports the traditional use of *P. longum* churna for the treatment of cough [80].

Anti-inflammatory Effect: *Piper longum* dried fruit's oil was studied for its anti-inflammatory activity in rats. The dried fruit's oil demonstrated inhibition of carrageenan-induced rat paw edema indicating potent anti-inflammatory activity when compared with the standard ibuprofen [81].

Anti-oxidant Effect: A combination of spices and herbs, including *Piper longum* as one of the ingredients in combination named as Amrita Bindu, were tested for anti-oxidant activity.

Rats with Amrita Bindu pretreatment exhibited lower free radicals, lipid peroxidation and protein carbonyls along with higher levels of antioxidant. Findings suggest that Amrita Bindu, has antioxidant potential against free radical-induced oxidative injury [82].

TABLE 2: SHOWING PHARMACOLOGICAL PROPERTIES, INDICATIONS AND FORMULATIONS OF NIDIGDHIKADI LEHA

S. no.	Name	Pharmacodynamics	Indications	Formulations
1	Nidigdhika/Kateri[83] (*Solaum xanthocarpum*)	Rasa- Katu-Tikta Guna- Ushana Virya- Ushana Vipaka- Madhura Dosha shamakta - Vatashamaka	Kasa, Shavasa, Jwarashamaka, Peenasa, Kaphanashaka	Kantakaryava leha Pancatiktaka Ghrita Vyaghriharitiki Vyaghri Taila Vasa-Kantkari Aveleha
2	Nagar/Shuthi[84] (*Zingiber officinale*)	Rasa- Katu Guna-LaghuSnigdha Virya- Ushana Vipaka- Madhur Dosha shamakta Vatakaphashamaka	Kasa, Swasa, Jwara, Kaphashmaka, Sula	Ardraka Khanda Panchasama Churna Samasharkar Churna Trikatu Churna Panchkola Churna Sobhagyasunthi
3	Amrita/ Guduchi[85] (*Tinospora cordifolia*)	Rasa- Tikta-Katu Guna- LaghuSnigdha Virya- Ushana Vipaka- Madhur Dosha shamakta – Tridoshahara	Kasa, Jwara, Rasayana, Kaphashamaka	Guduchyadi churna Guduchyadi kvath Guduchyadi lauha Guduchi Satva Amritarishta Guduchitaila Guduchyadi taila Sarvajwarahara lauha Dashamoolarishta Kaishor guggulu
4	Pippali[86] (*Piper longum)*	Rasa- Tikta-Katu Guna-Laghu- Snigdha Virya- Sheeta Vipaka- Madhur Dosha shamakta – Tridoshahara	Swasa, Jwara, Rasayana, Kaphashamka, Sula	Pippali khanda Guda pippali Pippaliyadi churna Pippali rasayanam Pippalyasava Verdhamana pippali Pippali ghritam

TABLE 3: SHOWING PHARMACOLOGICAL ACTIONS OF INGREDIENTS OF NIDIGDHIKADI LEHA

S. no.	Drug Name	Pharmacological Action
1	Nidigdhika/Kateri (*Solaum xanthocarpum*)	Immunomodulatory Effect[13,14,15] Effect on Bronchial Asthma[16,17,18,19,20] Anti-Bacterial Effect[21,22] Nutritional Effect[23,24] Anti Oxidative Effect [25, 26] Anti Histaminic [27, 28]
2	Nagar/ Shuthi (*Zingiber officinale*)	Bioavailability Enhancing Effect[33] Anti-Inflammatory Effect[34,35] Bronchodilator Effect[36] Anti Oxidative Effect [37, 38] Antimicrobial Effect[39,40,41] Antipyretic and Analgesic Effect [42, 43, 44] Nutritional Effect[45] Antiasthmatic Effect[46,47] Antitussive Effect[48] Antiviral Effect[49]
3	Amrita/ Guduchi (*Tinospora cordifolia*)	Anti-Inflammatory Effect[54] Anti Bacterial Effect[55,56] Anti allergic Rhinitis[64] Immunomodulator Effect [57, 58, 59, 60, 61, 62, 63]
4	Pippali (*Piper longum)*	Bio-Availability Enhancing Effect[69,70] Immunomodulatory and Anti Cancer [71,72,73] Antimicrobial Activity[74,75] Brochodialator Effect[76] Analgesic Effect[77] Anti allergic Activity[78,79] Antitussive Effect[80] Anti-Inflammatory Effect[81] Anti Oxidative Effect[82]

DISCUSSION: Recurrent upper respiratory tract infections are very common in children; they adversely affect their day-to-day activities and academic performance. The available management like, first-generation antihistamines, antipyretics (paracetamol) or anti-inflammatory agents (ibuprofen), cough suppressants such as dextromethorphan, expectorants (guaifenesin), and decongestants such as pseudoephedrine and phenylpropanolamine provide symptomatic relief but do not reduce the duration of illness neither they reduce the frequency of illness. The indications of the drug Nidigdhikadi leha in Chakradutta 7 is jwara (fever) along with kasa (cough), shwasa (dyspnoea), peenasa (rhinitis), indicating the symptoms of respiratory infections. The review of effect of ingredients of drug suggests that these drugs are having immunomodulatory, [13-15, 57-63, 71-73] anti-bacterial [21, 22, 55, 56], antioxidative [25, 26, 37, 38, 82], antimicrobial [39-41], [74-75], analgesic [77] and bioavailability enhancing effect [33, 69-70]. The immunomodulatory effect may show sustained effect of the drug and may reduce the frequency and severity of illness.

Anti-inflammatory [34-35,54,81], Bronchodilator effect [36, 76], anti histaminic [27-28], and anti-asthmatic [16-20, 46-47] property may help in alleviating the symptoms and provide relief. Anti-allergic [78-79] and antitussive [48, 80] effects can help in relieving the symptoms. Also, the drugs are having nutritive [23-24, 45] effects which may add in better growth and development and improve the immune system of the child.

CONCLUSION: Present review reveals that the ingredients of Nidigdhikadi leha possess immuo-modulatory, anti-bacterial, antioxidative, antimicrobial, analgesic, and bioavailability enhancing effect. Also, the ingredient affects bronchial asthma, antitussive and anti-allergic effect and has high nutritive value. Therefore, Nidigdhikadi leha can be a potent remedy for the management of recurrent upper respiratory tract infections in children.

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