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RESEARCH ARTICLE

CLINICAL STUDY TO EVALUATE THE IMMUNOMODULATORY EFFECT OF BALCHATURBHADRA SYRUP IN LOWERING DOWN MORBIDITY OF CHILDREN

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Abstract

Objectives: To evaluate the efficacy of Balchaturbhadra Syrup in lowering down morbidity of children.

Study Design: Single-Arm Open-Label Study

Subjects: This Present clinical study was conducted on 55 children who were randomly selected from the surveyed area, school, and OPD /IPD of Post Graduate Institute of Ayurved, Dr. S. R. Rajasthan Ayurved University, Jodhpur.

Outcome Measures: A paired t-test was carried out to test significance before and after treatment.

Result: Balchaturbhadra Syrup had shown significant improvement in morbidity features in children.

Conclusion: Balchaturbhadra Syrup was found effective in children suffering from various types of recurrent illnesses. Therefore, morbidity scores were effectively reduced.

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Introduction: -

The under-five age group is a crucial and susceptible segment of society because its morbidity profile has a significant impact on the whole nation's progress. There are certain preventive factors for frequent childhood morbidities, even though the morbidity pattern differs from nation to nation. The child's health and development are influenced by a variety of sociocultural factors, including age, gender, the mother's literacy level, the family's socioeconomic situation, the child's immunization status, and feeding practices. UNICEF views this as the best indication of social development in terms of rates of morbidity and mortality in children under the age of five ^[1]. Due to their susceptibility to morbidities and mortalities as well as their relevance as possible future assets for any nation, children under the age of five play a significant role in any plan relating to health care. Despite economic progress and increased attempts to improve basic healthcare India is known for having healthcare disparities. From an estimated rate of 93 deaths per 1000 live births in 1990 to 39 deaths per 1000 live births in 2017, the under-five mortality rate has fallen globally by 58%. This translates to 1 in 11 children dying before they had 5 in 1990 to 1 in 26 in 2017. ^[2] Around 14 times higher than the average rate in high-income nations (5 deaths per 1000 live births), the under-five mortality rate in low-income countries in 2017 was 69 deaths per 1000 live births. The target is for all

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nations to lower the death rate for children under five years of age to at least 25 per 1,000 live births. The Sustainable Development Goals (SDG) target for under-five mortality has already been achieved by 117 Member States, and if current trends continue, 26 additional nations are anticipated to do the same by 2030^[3]. India has pledged to reduce the under-five mortality rate to 25 deaths per 1,000 live births by 2030 as part of the Sustainable Development Goals outlined by the United Nations. By 2025, India's National Health Profile has set a goal of 23^[4]. The statistics of childhood morbidities have essentially remained the same despite numerous government measures, such as the national immunization scheme and other infection control programs. Additionally, immunizations are disease-specific, and additional infectious diseases are always emerging at the same time. So, the greatest threat to human health is the rise of superbugs because of the misuse of antibiotics. Therefore, exploring wealth with the help of traditional medicine for human benefit is urgently required.

Balchaturbhadrachurna was selected for the present study which was described in Chakradatta^[5], Bhaishajya Ratnavali^[6], and Yog Ratnakar^[7]. For increasing the palatability among children this was prepared in syrup form. As per textual reference, it is highly efficacious to manage the Jwara, Swasa, Kasa, Vaman, and Atisar. Various experimental and clinical studies on individual Herbs of this formulation have shown its effects on the immune system, anti-inflammatory, anti-spasmodic, anti-asthmatic, anti-bacterial, anti-diabetic, antioxidant, anti-fungal, hepatoprotective, and analgesic properties. To keep all these in the brain this drug was selected for the present study.

Aims and Objectives: -

1. To evaluate the efficacy of the Balchaturbhadrachurna Syrup in the lowering of morbidity in children.
2. To evaluate the immunomodulatory effect of Balchaturbhadrachurna Syrup.

Institutional ethics committee clearance-

The institutional ethics committee of the University Post Graduate Institute of Ayurved Studies and Research, approval was obtained before starting this study vide letter no. DSRRAU/UPGIAS&R/IEC/20-21/408, Dated: 12/06/2022

Clinical trial registry of India registration-

To obtain a registration number through the Clinical Trial Registry of India (CTRI) the details of the present study were submitted online to the CTRI website with the reference number REF/2022/08/056924. Registration No. CTRI/2022/09/045142 was allotted to the present study by CTRI in September 2022 before the start of the trial.

Materials and Methods: -

The following materials and methods were required for conducting the present clinical trial. The research work was planned at two levels.

Level 1 – Cross Section Demographic Study.

Level 2 - Clinical Study

Cross-section demographic study –

To assess the morbidity status of children residing in rural areas of Jodhpur, a survey was conducted on 1000 children living in the surroundings of the Post Graduate Institute of Ayurved, Dr. S. R. Rajasthan Ayurved University, Jodhpur.

Clinical study –

The study was conducted on 55 children which was randomly selected from the surveyed area, from the school, and OPD/IPD of Post Graduate Institute of Ayurved, Dr. S. R. Rajasthan Ayurved University, Jodhpur.

Inclusion Criteria: -

1. Children age group from 1 Year to 05 years.
2. Children were suffering from recurrent URTI.
3. Children were suffering from recurrent GIT Disease.
4. Children who had other recurrent diseases.

Exclusion Criteria: -

1. Children aged below 1 year and above 05 years of age.
2. Children had a history of hypersensitivity to a trial drug or their ingredient.
3. Children had a history of participation in any trial past 6 months.
4. Children suffering from chronic respiratory illnesses like tuberculosis, pleural effusion, bronchiectasis, lung carcinoma, COPD, and Chronic lung disease were excluded.
5. Children suffering from chronic GIT disorders like abdominal tuberculosis, chronic ailments, and any tumors were excluded.
6. Children suffering from Diabetes Mellitus, any malignant conditions, genetic disorders, and congenital disorders were excluded.

Withdrawal Criteria: -

1. During a clinical trial, if a child develops any serious condition that requires urgent treatment refer to a higher center.
2. A child her/his parents/guardian wanted to withdraw from the clinical trial.

Trial Drug – Balchaturbhadrha Syrup

Balchaturbhadrha syrup is the combination of four ingredients Musta, Pippali, Ativisha, and Karkatshringi. All Ingredients of trial drugs were procured from the local market and identified by a Pharmacognosist of the Post Graduate Department of Dravyaguna, PGIA, Jodhpur. After proper identification, all ingredients were cleaned and dried. Add 8 times water to make Kwath then boil to reduce to ¼ After that filter with a cotton cloth. For making in the form of syrup that is easily Palatable to children honey and sugar are added. After that Balchaturbhadrha Syrup was prepared under the aseptic condition in a pharmacy attached to the Post Graduate Institute of Ayurved, Jodhpur under the supervision of the Director, Pharmacy, PGIA, DSRRAU, Jodhpur. During the preparation of the drug, all related SOPs were strictly followed. After the preparation, the medicine is stored in an airtight container.

Presentation

The prepared syrup was packed in sterile bottles of 100- and 200-ml capacity and labeled with the date of manufacturing, batch no., and drug license number.

Dose and Duration of Drug Trial- As per Young Formula (1.0 ml/kg/day in three divided doses) for 45 days.

Follow-up: -

Follow-up was taken completion of every fortnight during and after the completion study. A total of 3 follow-ups were done before the completion of the study and two follow-ups were done on 90, and 135 days after the completion of the trial.

Table No.1: - Administration of drug and grouping.

Name of Drug	Balchaturbhadrha Syrup
Number of Patients	55
Type of Study	Single Arm Open-Label Study
Duration of Drug Trial	45 Days
Dose	As per Young Formula (1.0 ml/kg/day in three divided doses)
Anupana (Vehicle)	Luke Warm Water
Route	Oral

Observation of Clinical Study-**Table No.2: - Clinical study Observation.**

Observations	Maximum morbidity	Percentage
Age	4-5 year	33.33
Sex	Male	70.59
Religion	Hindu	94.12
Habitat	Urban	70.59
Socio-economic status	Middle class	98.04

Breast Feeding	Immediately after birth	96.08
Duration of Breastfeeding	4- less than 6 months	62.75
Immunization	Complete	94.12
Prakriti	Vata-Kapha	56.86
Satva	Madhyam	92.16
Sara	Twak Sara	47.06
Agni	Mandagni	64.71
Diet	Vegetarian	82.35

Table No. 3: - Showing all morbidity features-wise distribution of children in a clinical trial.

Sr. No.	Morbidity Feature	No. of children	Percentage
1	Nasal Obstruction	26	50.98%
2	Running Nose	37	72.55%
3	Sore Throat	14	27.45%
4	Dyspnoea	5	9.80%
5	Cough	13	25.49%
6	Fever	10	19.61%
7	Diarrhoea	5	9.80%
8	Enlargement of Tonsils	9	17.65%
9	Abdominal pain	10	19.61%
10	Constipation	9	17.65%
11	Vomiting	11	21.57%
12	Anorexia	10	19.61%

Result: -

A paired t-test was carried out to test significance before and after treatment.

Table No.4: - Showing statistical presentation of all morbidity features after treatment.

Sr No	Morbidity Feature	Mean		SD		Mean Diff	Gain %	t-Value	P-Value	Remark
		BT	AT	BT	AT					
1	Nasal Obstruction	7.12	3.67	3.67	2.46	3.45	48.46	4.582	<0.001	HS
2	Running Nose (character)	5.15	2.09	2.37	2.97	3.06	59.42	6.599	<0.0001	ES
3	Running Nose (Frequency)	5.27	2.17	2.33	2.89	3.10	58.82	6.199	<0.0001	ES
4	Sore Throat	4.82	2.56	2.58	1.53	2.26	46.89	5.272	<0.001	HS
5	Dyspnoea	4.58	2.62	2.21	2.09	1.96	42.79	5.714	<0.001	HS
6	Cough character	5.89	1.97	3.01	2.31	3.92	66.55	6.894	<0.0001	ES
7	Cough Frequency	5.29	1.67	2.19	2.09	3.62	68.43	7.308	<0.0001	ES
8	Fever Character	4.67	1.12	3.36	2.48	3.55	76.02	9.697	<0.0001	ES
9	Fever Frequency	4.89	1.09	2.06	2.19	3.80	77.71	7.082	<0.0001	ES
10	Diarrhoea Consistency	4.37	1.40	3.59	3.48	2.97	67.96	10.757	<0.0001	ES
11	Diarrhoea Frequency	4.49	1.46	2.10	2.41	3.03	67.48	9.298	<0.0001	ES
12	Enlargement of Tonsils	4.98	3.28	3.37	2.35	1.70	34.14	3.827	<0.05	Sig
13	Abdominal pain	4.20	2.67	2.49	2.51	1.53	36.43	3.972	<0.05	Sig

14	Constipation	6.73	5.13	2.21	2.39	1.60	23.82	0.276	>0.05	NS
15	vomiting	4.68	2.43	3.45	1.30	2.25	48.08	4.816	<0.001	HS
16	Anorexia	4.76	2.87	2.73	1.05	1.89	39.71	3.682	<0.05	Sig

Abbreviation- HS- Highly Significant, ES- Extremely Significant, NS- Non-Significant, Sig- Significant, BT- Before treatment, AT- After treatment and SD- Standard deviation.

Discussion regarding the Observation of Clinical Study: -

In the present clinical study, a total of 55 children were registered [Table no. 1], and out of those 4 children discontinued the medicine during the defined period. Therefore, the study was completed on 51 children.

Age-

Out of 51 patients, a maximum of 17 (33.33%) was found in the age range of 04 years to 05 years [Table no.2] because morbidity higher occurrence in pre-school-age children (4-5 years), which may be caused by unhealthy eating habits and excessive exposure to the environment, both of which can lead to infections.

Sex-

The maximum 36 (70.59 %) were male children [Table no.2] because it turns out that girls' serum IgM levels were typically higher and considerably different from boys. (1980, Herna Roode). Boys were therefore more frequently found with morbid traits than females.

Religion-

The maximum 48 (94.12%) was found to be Hindu religion [Table no.2] because Hindus are more susceptible to infectious diseases because the research area's prevalence having the Hindu community could be the explanation.

Family-

The maximum 31 (60.78%) enrolled in the study belonged to Joint families [Table no.2] because Joint families have their demerits like less time for care for children because of the large size of the family.

Habitat-

Most children 36 (70.59 %) were from urban areas [Table no.2] because the survey area covered urban areas like Mandore, CHB, etc. where the maximum number of patients was randomly selected for a clinical trial.

Socio-economic status –

The maximum of 50 patients (98.04%) came from the Middle Class [Table no.2] because this type of distribution may be the result of the way that middle-class and poor families approach government health facilities and care. These children's immune systems and immunities have not evolved as well as they should, in part because they lack access to food and medical treatment. ^[8]

Breast Feeding-

The majority of children 49 (96.08%) had reported starting their breastfeeding initiation Immediately after birth [Table no.2] because the study found that most mothers prefer breastfeeding over another type of feeding. Start feeding term babies as soon as possible because they have good swallowing and sucking coordination. Preterm babies can grasp their nips from around 28 weeks of gestation onward, and between 32 and 35 weeks of pregnancy, coordination of sucking, swallowing, and breathing occurs. At 36 weeks of gestation, the majority of infants can start receiving a full supply of breast milk. (Nygqvist KH, et al. 1999). It has long been believed that extra protection is provided by maternal colostrum, which is generated in the first few days following delivery and has both immune and nonimmune qualities. ^[9]

Duration of Feeding-

The maximum number of patients, 32 (62.75%) had given a history of Breastfeeding for 4 - less than 06 months [Table no.2]. WHO revised infant feeding guidelines, and recommended exclusive breastfeeding for 6 months of life to protect infants from morbidity and mortality.

Weaning –

The majority of children, 40 (78.43%) were given complementary food during 06- 12 months of age. [Table no.2]

Immunization-

It was observed that most children i.e., 48 (94.12%) were completely immunized as per the given schedule (BCG, OPV, DPT, Hep-B, MEASLES, MMR, OTHER) [Table no.2] because the rate of morbidity rises when immunization is either absent or partially immunized^[9] but the study data does not match that because, for the clinical study, the patient was collected randomly from the survey area in which the maximum number of children (883 out of 1000) was immunized.

Diet-

A maximum of 42 (82.35%) children were vegetarian diet because the individual's diet and nutrition matter, there is no clear link between the type of diet one consumes and repeated infections and immunity. The weak immune system is caused by poor diet intake.

Prakriti-

Most children had Vata-kapha Prakriti 29 (56.86%) [Table no.2] because Ayurveda states that because of the prominence of the Kapha Dosha in Balyavastha, children are more likely to experience Kapha Sthan (Uraha) GataVyadhi (URTI) and low Vyadhikshamatvam may be caused by Aparipakva Dhatu and Alpa Ojas. According to another source, Vata Prakriti children also have Alpa Bala^[10], therefore Vata-Kapha Prakriti may be more renowned for having a high morbidity rate in children.

Satva-

A maximum of 47 (92.16%) of the registered children had Madhyam Satva [Table no.2] because this data was consistent with the Ayurvedic idea that children are more delicate than younger persons^[11] and have Alpa-Satva and Madhyam Satva.^[12]

Sara-

In registered children, a maximum of 24 (47.06%) were found with Twak Sara [Table no.2] because This information correlates with Ayurvedic theory because Asthi, Mamsa, and Rakata Sara Purusha contain the maximum Vyadhikshamatava.^[13]

Agni-

The maximum of 33 children (64.71%) had Mandagni. Vishamagni and Mandhyamagni, collectively known as Agni Dushti, are the primary causes of Ama formation, which ultimately results in Vyadhikshamatava Hrasa (Loss of Immunity).^[14]

Morbidity pattern-

It was observed that out of 51 registered children, a maximum of 37 (72.55%) children suffered from recurrent episodes of running nose, followed by 26 (50.98%) with nasal obstruction, 14(27.45%) with a sore throat, 13(25.49%) with recurrent cough, 11(21.57%) with recurrent vomiting and 10(19.61%) with anorexia, abdominal pain, and recurrent fever, 9(17.65%) of enlargement of tonsils, constipation respectively and minimum 5(9.80%) of recurrent diarrhoea and dyspnoea [Table no.3]. According to WHO data^[15] upper respiratory tract infection is a leading cause of morbidity in children. The most common symptoms of URTI include recurrent cough, running nose, nasal blockage, etc.

Discussion regarding the effect on individual morbidity symptoms: -

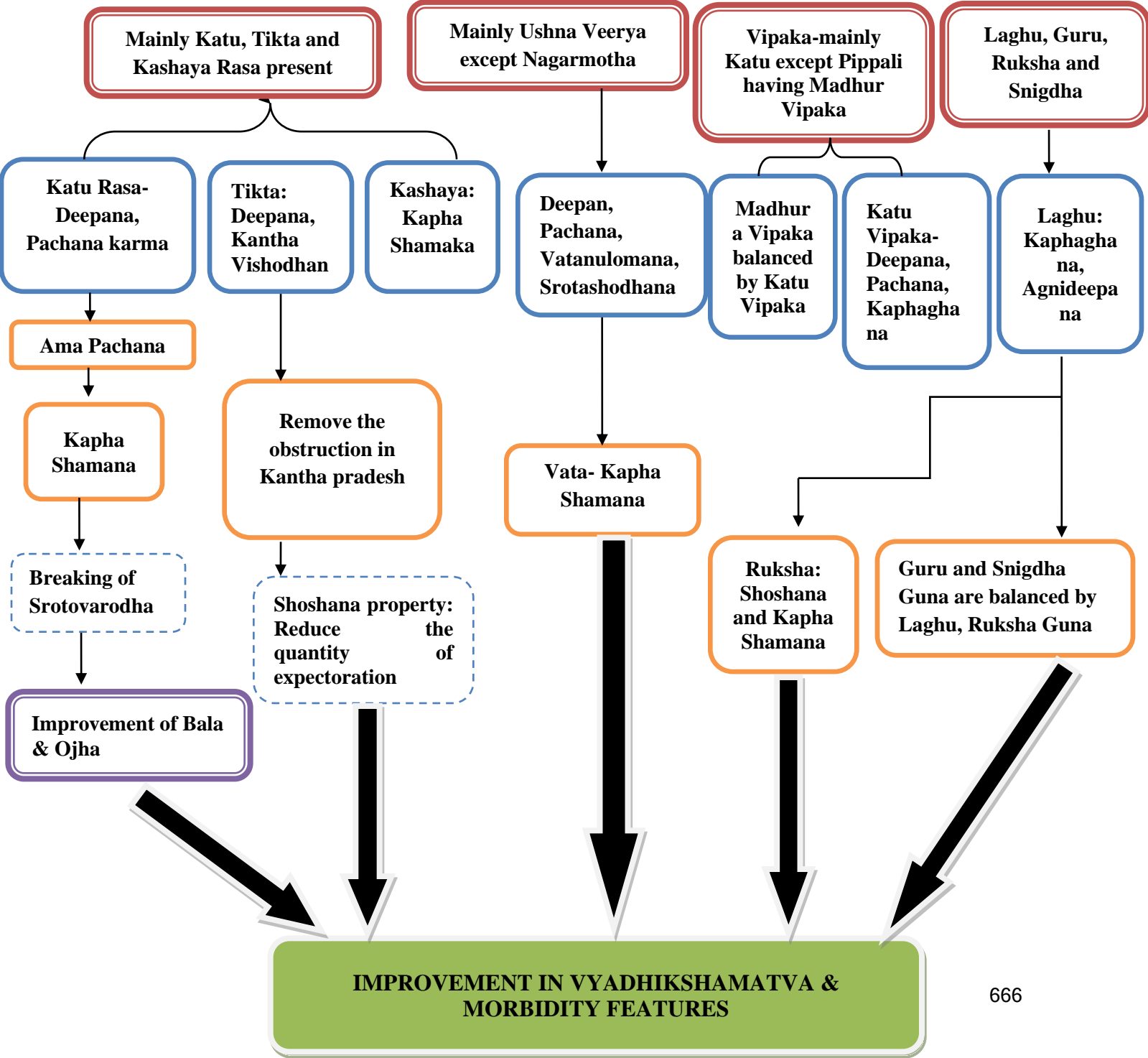
Trial Drug (Balchatubhadra Syrup) gives an extremely significant improvement in running nose (character), running nose (frequency), cough character, cough frequency, fever character, fever frequency, diarrhoea consistency, and diarrhoea frequency. In nasal obstruction, sore throat, dyspnoea, and vomiting statistically highly significant results were found. In enlargement of tonsils, abdominal pain, and anorexia statistically significant results were found. In constipation, statistically non-significant results were found.

Discussion regarding the Mode of Action of the trial Drug

The polyherbal Trial drug "Balchatubhadra Syrup" is a combination of drugs having Rasayana (Pippali), Amapachaka (eg. Pippali, Ativisa, Nagarmotha), Kasahara (e.g., Pippali, Ativisha, Musta, Karkatshringi), Swasahara (e.g., Pippali, Musta, Karkatshringi), Jawarahara (e.g., Pippali, Musta, Ativisha, Karkatshringi),

Atisarahara (e.g. Musta, Ativisha, Karkatshringi), Deepana, Pachana (e.g. Pippali, Ativisha, Musta, Karkatshring), Balya (eg. Pippali, Musta) Krimighan (e.g., Pippali, Musta) properties.

Flow Chart Mode of action of Balchatubhadra Syrup



Role of Madhu in Balchaturbhadra Syrup –

The classics of Ayurveda frequently use the ingredient honey. It is a Madhura in Rasa with Kashaya Anurasa that balances the Kapha and Pitta Doshas and is simple to digest. Honey is regarded by Acharya Sushruta as the best Yogavahi, ^[16] the material with the capacity to permeate the deepest tissue. As a result, it serves as a catalyst and aids in the quick delivery of numerous Ayurvedic medications to the target location without altering their original qualities. The fact that Acharya Charaka listed it as one of the Pathya Dravyas demonstrates how beneficial honey is to the body. It is the most strong and effective Yogavahi Dravya since it is made from a variety of flowers and herbs. It is known as "Param Yogavahi" since administering Madhu with different formulations. improves their therapeutic properties when used especially to treat Kapha problems.

Ingredients of the trial drug "Balchatubhadra Syrup" showed Katu, Tikta, Kashaya (37.5, 37.5, and 25 % respectively), Laghu Guna (50%), KatuVipaka (75%), Ushna Virya (50%) and Vata- Kaph, Pitta Kapha and Tridosh shamak (50, 25, 25% respectively) effect. In Balyavastha children mainly Kapha Dosha Predominant Katu, Tikta, and Kashaya Rasa, Laghu Guna, and Ushna Virya neutralize Kapha Dosha.

Drug having Rasayana properties improves the quality of Rasa Dhatu and thereby all Dhatus and the whole body. These are especially mentioned for the enhancement of Bala and the prevention of old age and disease. The ingredients Pippali of the trial drug Balchaturbhadra have Rasayana properties ^[17]. Thus, improving the resistance power of children by means of Dhatu poshana and finally increasing the Vyadhikshamatva.

All Ingredients of trial drugs like Pippali, Ativisha, Nagarmotha, and Karkatshringi have Deepana, and Pachana properties ^[18,19,20,21,22,23], thus improving the appetite and digestive power of the children. This is responsible for improved quality of Rasa Dhatu which in term responsible for providing the nutrition to subsequent Dhatus and finally improving the status of Ojas or Bala or Immunity.

The Pranavaha Srotas, play a major role in upper respiratory tract infections. Kaphavatapradhan and Alpa Pitta are the Doshas involved in this illness. Rasa and Rakta Dhatu, together with Pranavaha, Annavaha, and Udakavaha Srotas, are involved in Dushya. Given the aforementioned considerations, the drug of choice, in addition to having mainly Vata Kaphahar activity, should also have a high propensity to act on Pranavaha SrotasVyadhi

Oedematous and subsequently inflammatory alterations in the upper respiratory tract are the origin of morbidity symptoms including a sore throat, nasal obstruction, and swollen tonsils. All five of the drugs Pippali ^[24], Ativisa ^[25], Nagarmotha ^[26], Karkatshringi ^[27], and Madhu ^[28] have anti-inflammatory activity. In numerous clinical investigations, Madhu, and Pippali demonstrated mast cell stabilizing and anti-histaminic action. A blockage in the airways may be the cause of symptoms like dyspnea. Karkatshringi has broncho-dilation activity.

The primary causes of cough in URTIs are postnasal drip and infections of the throat and respiratory tract. Cough alleviation is brought on by the anti-inflammatory and antibacterial properties of the ingredients (Pippali, Musta, Ativisha, Karkatshring, and Madhu).

A number of compounds, including Pippali ^[32], Musta ^[29], Karkatshring ^[33], Ativisha ^[30], and Madhu ^[31], have shown antibacterial or antimicrobial activity. As a result, it may be concluded that it is very helpful for fever, sore throat, enlarged tonsils, and URTIs. The antiviral action of Musta and Madhu may have alleviated URTI symptoms. Fever improved because of an ingredient called Ativisha that has Antipyretic properties.

Ingredients in trial medications including Pippali^[34], Ativisha^[35], and Madhu^[36] have immunomodulatory activity; as a result, the trial medication had a significant role in improving URTI symptoms. By boosting immunity, immunomodulatory action not only alleviated URTI but also decreased morbidities.

Efficacy of the trial drug to reduce morbidity features like diarrhea, because of antidiarrheal properties of ingredients of a trial drug like Musta^[37], Ativisha^[38], and Karkatshring^[39].

Efficacy of the trial drug to reduce morbidity features like vomiting because of the antiemetic properties of ingredients of a trial drug like Ativisha^[40], and Karkatshring^[41] Musta ^[40]

- The trial drug's antioxidant, immunomodulatory, anti-inflammatory, etc. effects overall may be responsible for the immunomodulating effect of the trial drug and its long-lasting effects.

The ingredients of the Trial drug individually exhibit an Immunomodulatory effect, Antioxidant effect, Antimicrobial or Antibacterial effect, Anti-inflammatory effect, Antipyretic effect, Anti-viral effect, Bronchodilatory effect, Mast cell stabilizing effect, and Antihistaminic effect. The combined effect of the drug reduces the morbidity rate using promoting the general health of patients.

Conclusion: -

Balchaturbhadra Syrup was found extremely significant in Running Nose (character), Running Nose (Frequency), Cough character, Cough Frequency, Fever Character, Fever Frequency, Diarrhea Consistency, and Diarrhea Frequency. In Nasal Obstruction, Sore Throat, Dyspnea, and vomiting statistically Highly significant results were found. In Enlargement of Tonsils, Abdominal pain, and Anorexia statistically significant results were found. Thus, it was concluded that this Balchaturbhadra Syrup was a very potent Ayurvedic medicine that was not only controlling the symptoms of these recurrent illnesses but also lowering down the morbidity status too.

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