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## *Tinospora cordifolia* Enhances Vyadhikshamatwa (immunity) in Children

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### ABSTRACT

**Background:** The immune system in children is constantly developing and they are at an increased risk of infections. It is vital to help enhance immunity by vaccination but more people are turning towards traditional medicines today. The vast flora of the world offers newer options to this effect and is worth exploring. *Tinospora cordifolia* (Guduchi) is one such plant which has been traditionally used for various health conditions and is also proven to be an immunomodulator. **Objective:** To evaluate the role of *Tinospora cordifolia* in status of Vyadhikshamatwa (immunity) in children. **Materials and Methods:** An open-labelled, placebo-controlled, randomized controlled trial was conducted in 400 children aged 1-15 years, with 200 each in control and test groups. Study drug and placebo were administered orally at a dose of 100 mg/kg body weight twice daily with honey for 2 months. Response was assessed by total leucocyte count (TLC), lymphocyte percentage and absolute lymphocyte count (ALC). Results were analysed statistically using repeated measures Analysis of Variance (ANOVA) for intra-group comparisons and unpaired t-test for inter-group comparisons using Statistical Packages for Social Sciences (SPSS) software version 20.0. **Results:** The test drug showed statistically significant increase in TLC (P<0.001), ALC (P<0.001) and lymphocyte percentage (P<0.001) as compared to placebo. Also the rate of infections in the trial group were significantly lesser during the study period (P<0.001). **Conclusion:** *Tinospora cordifolia* significantly improves immunity in children and can be used as an adjuvant to vaccination.

**Keywords:** *Tinospora cordifolia*, Vyadhikshamatwa, Children, Immunity.

### INTRODUCTION

The child's immune system is a constantly evolving one, right from foetal period upto adulthood. The development of the human immune system is a continuous process where both accelerated and retarded development is deleterious<sup>[1]</sup>. It is estimated that children constitute about 39% (440 million) of India's population and 13.6% of these are in the age groups of 0-6 years<sup>[2]</sup>. As it is now believed that foetal and childhood illnesses and exposures to pathogens can lead to adult diseases, it is crucial that we develop a good immune system right from foetal stage<sup>[3]</sup>. Vaccination is being followed universally as a means of improving immunity (*Vyadhikshamatwa*) against various infectious diseases. However, recently concerns have been raised about the possibility of numerous vaccines overwhelming the infant's immune system<sup>[4]</sup>. These very same apprehensions have led to more people relying on traditional systems of medicine like Ayurveda, Unani or Siddha.

Various plants have been described as *balya* (that which enhances bodily strength) and *rasayana* (that which promotes health, provides defense against disease, and promotes longevity) according to Ayurveda, such as *Yashtimadhu* (*Glycyrrhiza glabra*), *Guduchi* (*Tinospora cordifolia*), *Amlaki* (*Emblica officinalis*), and *Haritaki* (*Terminalia chebula*)<sup>[5]</sup>. Extensive research is being carried out on these plant products as they also have the potential to improve *Vyadhikshamatwa*. *Tinospora cordifolia*, also known as 'Guduchi' or 'Amrita', is a plant being used from centuries for its medicinal values and has been proven to have hypolipidemic, hypoglycemic, hepatoprotective, antibacterial, anti-inflammatory, antiosteoporotic, antiobesity, anticarcinogenic and antimutagenic effects<sup>[6-14]</sup>. It has also shown beneficial effects in lead exposure, diabetic foot ulcers and diabetic neuropathy and improves learning and memory<sup>[15-18]</sup>.

Studies have found that *Tinospora cordifolia* also acts as an immunomodulator in *in vitro* tests and in rats<sup>[19, 20]</sup>. Another study carried out in Human Immuno-deficiency Virus (HIV) positive patients showed this plant to reduce total leucocyte count (TLC), neutrophil and eosinophil counts<sup>[21]</sup>. To the best of our knowledge, however, the effect of *Tinospora cordifolia* on immune status in children has not been studied till date. Hence this study was carried out with the objective of evaluating the role of *Tinospora cordifolia* in status of Vyadhikshamatwa in children.

**MATERIALS AND METHODS**

This open-labelled, placebo-controlled, randomized controlled trial was conducted in Sri Dharmasthala Manjunatheshwara College of Ayurveda and Hospital, Udupi, after obtaining ethical clearance from the Institutional Ethics Committee (IEC). This study was a part of Ph.D. thesis but was not registered with the Clinical Trial Registry of India. The study was carried out for a period of eight months, from November 2013 to June 2014. Children aged 1-15 years of age and of either sex, attending the Kaumarabhritya (Paediatrics) out-patient department (OPD) and those whose parents were disposed to give consent to the study and willing for follow-up were included in the study. Children with genetic disorders, severe or chronic illnesses, congenital diseases, mentally challenged and those on other immunostimulant drugs were excluded from the study.

The sample size was calculated by the following formula:

$$n = 2 \left[ \frac{(Z_{1-\alpha/2} + Z_{1-\beta}) S^2}{d} \right]$$

where, n is the minimum sample size required in each group;  $Z_{1-\alpha/2}$  is the two-tailed standard normal distribution table value for 1% level of significance, which is 2.58;  $Z_{1-\beta}$  is the value of standard normal distribution table for 90% power, which is 1.28; S is the pooled standard deviation obtained from pilot study, which is 2320 cells/ cu mm blood, and d is the minimum clinically significant difference in the total leucocyte count, which was set at 1000 cells/cu mm blood.

Substituting in the above formula, we have n = 161 in each group. Assuming a 20% loss for follow-up, the sample size came up to n = 161 + 20/100(161) = 161 + 33 = 194. For better precision, we added another 6 to each group and a final sample size of 200 children in each group was considered to be adequate for this study.

More than 1250 children were screened during the study period of whom 400 were selected for the purpose of the study and 200 children each were allocated to control and test groups by simple randomization. The study objectives and procedures were explained to the parents/ guardians of the children in the local language and written informed consent was obtained from them after ensuring that their identity would not be disclosed at any point. The demographic details of the children, past and present history, immunization history, anthropometric measurements and laboratory investigations were done prior to administration of drugs (baseline). Fresh *Tinospora cordifolia* plants grown in the institute (Figure 1) were identified and collected, shade dried, cut and reduced to a fine powder. This powder was administered orally to children in test group at a dose of 100 mg/kg body weight twice daily after food with honey for 2 months. Placebo (wheat flour) was administered to children in control group

orally at the same dose twice daily after food with honey for 2 months. The total leucocyte count, absolute lymphocyte count (ALC) and lymphocyte percentage were repeated at 30<sup>th</sup> and 60<sup>th</sup> days of treatment in both groups. They were also asked to report any infections or adverse events occurring during the study period.



**Figure 1:** Leaf of *Tinospora cordifolia*

Results were analysed statistically using repeated measures Analysis of Variance (ANOVA) for intra-group comparisons and unpaired t-test for inter-group comparisons for quantitative data and Chi square test for descriptive data, using Statistical Packages for Social Sciences (SPSS) software version 20.0 (IBM, Corp.). The level of statistical significance was set at  $P < 0.05$ . Results were expressed as percentages and mean ± S.D.

**RESULTS**

Among the 400 children included in the study, majority were males (54.5% in test group and 55.5% in control group) and aged 1-5 years (37.5% in test group and 41.5% in control group) (Table 1). The effect of *Tinospora cordifolia* on laboratory parameters studied are shown in Table 2. There was a significant increase in TLC, ALC and lymphocyte percentage on 30<sup>th</sup> day ( $P < 0.05$ ) as well as 60<sup>th</sup> day ( $P < 0.01$ ) as compared to 0<sup>th</sup> day in the test group. The increase in these parameters was highly significant in test group as compared to control group ( $P < 0.001$ ). The rate of infections was significantly lower in test group ( $P < 0.001$ ) (Table 3). No significant adverse effects were reported in both groups during the study period.

**Table 1:** Characteristics of study subjects

Characteristics		Test group (N=200)		Control group (N=200)	
		N	%	N	%
Gender	Male	109	54.5	111	55.5
	Female	91	45.5	89	44.5
Age (in years)	1-5	75	37.5	83	41.5
	6-10	80	40	65	32.5
	11-15	45	22.5	52	26
Diet consumed	Vegetarian	13	6.5	25	12.5
	Mixed diet	187	93.5	175	87.5
History of immunization	Complete	148	74	167	83.5
	Incomplete	52	26	33	16.5

**Table 2:** Effect of *Tinospora cordifolia* on laboratory parameters (mean ± SD) in study subjects

Laboratory parameter		Assessment day			P value
		0 <sup>th</sup> day	30 <sup>th</sup> day	60 <sup>th</sup> day	
TLC (cells/cumm)	Test group (n=200)	4570 ± 112.32	6850 ± 789.35*	8970 ± 1450.12**	<0.001
	Control group (n=200)	4670 ± 167.23	4730 ± 185.98	4650 ± 187.95	
ALC (cells/μL)	Test group (n=200)	1948 ± 573.62	2189 ± 876.33*	3563 ± 989.05**	<0.001
	Control group (n=200)	1935 ± 620.13	1980 ± 651.32	1976 ± 713.24	
Lymphocyte percentage (%)	Test group (n=200)	24.8 ± 2.5	29.6 ± 5.8*	32.6 ± 9.7**	<0.001
	Control group (n=200)	26.5 ± 3.1	27.4 ± 2.9	26.9 ± 3.4	

Test used: Repeated measures analysis of variance (ANOVA) in intra - group comparison and unpaired t-test in inter - group comparison. \*P<0.05, \*\*P<0.01 as compared to 0th day in test group. SD: Standard deviation, TLC: Total leucocyte count, ALC: Absolute leucocyte count.

**Table 3:** Infections occurring during study period in study subjects

Infections	Test group (n=200)		Control group (n=200)		P value
	N	%	N	%	
Upper Respiratory Tract Infections	13	6.5	34	17	<0.001
Lower Respiratory Tract Infections	4	2	38	19	<0.001
Infective diarrhoea	0	0	5	2.5	<0.001
UTI	0	0	7	3.5	<0.001

Test used: Chi square test.

## DISCUSSION

Although maternal immunoglobulins (Ig) safeguard the neonate against diseases, their role is limited when compared with protection afforded by an infant’s active immune response. The innumerable pathogens encountered in the environment right after birth, render the development of active humoral and cellular immune responses in the newborn imperative. The production of functional T-lymphocytes in infants being comparable to that of older children and adults, nevertheless, they are deficient in generation of B-lymphocytes. Until about two years of age, this paucity continues and hence children in this age group are more susceptible to infections with *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* [4]. Vaccination helps develop immunity against the various pathogens but improper administration, inadequate storage, adverse reactions and failure of vaccines may hamper the process. Researchers are on the lookout for herbal medicines that can stimulate the immune system with less harm to the consumer and from this perspective the current study was carried out.

In our study, we found that *Tinospora cordifolia* had an immunostimulant action as evidenced by the increase in TLC, ALC and lymphocyte percentage and lower rate of infections after two months of treatment. A study conducted by Kalikar et al on HIV positive patients treated with *Tinospora cordifolia* extract, found that the patients reported lessening of symptoms and a reduction in TLC, neutrophil and eosinophil counts [21]. These findings are similar to those of the current study. However, they did not find any significant difference between the treatment and placebo groups. Nonetheless, the authors conclude that *Tinospora cordifolia* could be used as an adjunct to HIV/AIDS management. In yet another study done by Bansal et al, the effect of a nutraceutical prepared using various potent herbs described in Ayurveda (*Tinospora cordifolia* being one of them) on stress related changes in selected immunoglobulin levels in the

body was studied and it was found that this nutraceutical lowered the levels of stress-increased immunoglobulins [22]. This further substantiates the immunomodulator action of *Tinospora cordifolia*.

More et al found that *Tinospora cordifolia* led to activation of macrophages and as macrophages are the first line of defense in our body and play a crucial role in innate (nonspecific) and adaptive (specific) immunity, it is an important finding to support the immunostimulant action of the drug [19]. Study done by Aher et al on male Wistar rats using alcoholic extract of *Tinospora cordifolia* also reported an increase in the white blood cell (WBC) counts, bone marrow cellularity, serum Ig concentrations, further substantiating the immunomodulatory potential of this plant [20]. Furthermore, in *in vitro* and *ex vivo* studies done by Upadhyaya et al, aqueous extract of *Tinospora cordifolia* was found to boost the phagocytic activity of macrophages, remarkable augmentation in the production of cytokines, up-regulation of interleukin-6 (IL-6) and enhanced antigen specific recall response. The authors have attributed these actions to the glycoprotein isolated from the plant stem but the exact mechanism by which immunostimulation is brought about is still abstruse [23].

A limitation of the study could be that the effects on CD<sub>4</sub> and CD<sub>8</sub> counts and immunoglobulin levels were not studied, which would have indicated the type of immunity enhanced - cell mediated immunity (CMI) or antibody mediated immunity (AMI). The trial was carried out in a single centre and the results are specific to the particular geographic distribution; they cannot be generalized as a lot of other factors may influence immune status like nutrition, environmental challenges, exposure to pathogens and hormonal influences. Multicentric trials with large sample sizes are needed to further validate these findings and this study forms an important basis for such studies.

## CONCLUSION

The study confirms the earlier claims of immunostimulatory properties of *Tinospora cordifolia* and offers a newer horizon to explore for boosting immunity in health or in immunodeficiency states. It can be concluded that *Tinospora cordifolia* can be used as an adjuvant to vaccination in order to boost the immune system in children.

**Conflict of interest:** NIL

**Source of support (grants, equipment, drugs):** NIL

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