

Clinical evaluation of efficacy and safety of appetizer syrup as appetite stimulant in children with non-pathogenic anorexia

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Anorexia, *i.e.*, lack of desire to eat or loss of appetite is a common cause of parental concern in pre-school and school-going children. Many herbs and herbal formulations have been traditionally used in India as ‘appetizers’ in children with non-pathological anorexia and over 100 phyto-constituents are claimed to have appetite-stimulant effects, though efficacy and safety of many of these formulations needs to be evaluated with well-controlled clinical trials. Appetizer syrup (Mfd: Dabur India Limited) is an *Ayurvedic* polyherbal formulation proposed to stimulate appetite in children with non-pathogenic anorexia. It comprises herbs such as *Kismis* (*Vitis vinifera* L.), *Pipalli* (*Piper longum* L.), *Anar* (*Punica granatum* L.), *Amla* (*Embllica officinalis* Gaertn), etc., that are traditionally known to be useful in digestive impairment and are documented to possess appetite stimulant and strength promoting properties. Present trial was a double-blind, randomized, placebo-controlled parallel group clinical study to evaluate the efficacy and safety of Appetizer Syrup in children with non-pathogenic anorexia. Results were assessed from baseline to study completion on basis of the appetite stimulating effects of the formulation and the benefits secondary to appetite stimulation like changes in anthropometric measurements and academic performance.

Keywords: Non-pathogenic anorexia, Appetite stimulant, Children, Herbal, *Ayurveda*

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Anorexia, *i.e.*, lack of desire to eat or loss of appetite, is a common cause of parental concern in pre-school and school-going children. A variety of factors, both physiological and psychological, determines one’s hunger, desire to eat and satiety¹, which may or may not be associated with an underlying intestinal or extra-intestinal disease. Intermittent anorexia without any underlying cause (non-pathological anorexia) is common in childhood, which may adversely affect the childhood growth and development due to inadequate nutritional intake during an age of higher requirements. It is recognized that a diminished nutritional status may be a contributing factor for decreased immune function, delayed wound healing, and disturbed drug metabolism influencing prognosis^{2,3}. Appetite stimulants such as megastore acetate (MA), cyproheptadine hydrochloride (CH), cannabinoids, anabolic and growth hormones and serotonin have been used to help overcome decreased appetite and malnutrition in children with various chronic illnesses^{3,4}. Many of these have substantial side effects

and may not be suitable for prolonged use. Serotonin (5-HT) too is believed to have an inhibitory influence over feeding behavior⁵. Recent times have seen a renewed interest of herbal and other complementary therapies in the management of various chronic diseases⁶. Traditional Medicines derived from medicinal plants are used by about 60 % of the world’s population. Many herbs and herbal formulations have been traditionally used in India as ‘appetizers’ in children with non-pathological anorexia and over 100 phyto-constituents are claimed to have appetite-stimulant effects⁷⁻¹⁰, though efficacy and safety of many of these formulations needs to be evaluated with well-controlled clinical trials. Appetizer syrup (Mfd: Dabur India Limited) is an *Ayurvedic* polyherbal formulation proposed to stimulate appetite in children with non-pathogenic anorexia. It comprises of ingredients such as *Kismis*, *Pipalli*, *Anar*, *Amla*, etc., that are traditionally known to be useful in digestive impairment and are documented to possess appetite stimulant and strength promoting properties^{6,11-13}. Present trial conducted between the years 2004-2005 was a double-blind, randomized, placebo-controlled

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parallel group clinical study conducted to evaluate the efficacy and safety of Appetizer Syrup (DRF/AY/4008) in children with non-pathogenic anorexia. Results were assessed from baseline to study completion basis of the appetite stimulating effects of the formulation and the benefits secondary to appetite stimulation like changes in anthropometric measurements and academic performance.

Aim

To evaluate the clinical efficacy and safety of a polyherbal appetite stimulant - Appetizer syrup

Objectives

1. Evaluation of the primary effects of appetizer syrup on pattern of changes in rated hunger, fullness and associated factors.
2. Evaluation of the secondary effects of this drug appetizer syrup on growth, using anthropometric parameters as indicators.
3. Evaluation of safety profile and identification of adverse effects, if any, associated with use of any of the study products.

Material and methods

Study product

Appetizer syrup was prepared using standard methodology for preparing syrups. Hot and cold infusions of herbs were used. The composition details of Appetizer syrup (Mfd: Dabur India Limited) are given in Table 1.

Study design

Prospective double-blind, placebo-controlled, randomized, parallel study

Number of subjects

A total of 100 children with complaints of reduced appetite were recruited as per the inclusion/exclusion criteria

Inclusion criteria

1. Male and female children in age range 3-12 yrs.
2. History of poor appetite with or without reduced food intake.
3. Willingness to provide informed consent and to come for regular follow-up evaluation as and when required.

Exclusion criteria

1. Subjects with compromised renal and liver function.

2. Subjects with any chronic infection or significant systemic disease.
3. Subjects with known history of food allergies.
4. Subjects with dysphagia due to inflammatory conditions of oral cavity (ulcers) or neuromuscular dysfunction.
5. Subjects not willing to sign informed consent
6. Subjects not willing to come for follow-up as and when required.

Methodology

The study was conducted at RA Podar Ayurvedic Hospital, Worli, Mumbai, Maharashtra with approval from Institutional Ethics Committee of RA Podar Medical College (*Ayurveda*), Worli, Mumbai (Approval Date & No: 07 August 2004 & NO/RAP/store/4784/2004). The study was registered retrospectively with the CTRI, Clinical Trial Registry of India vide Reg. No/2015/12/006465.

Healthy male and female children in the age range of 03-12 yrs, attending OPD Department of Kayachikitsa, RA Podar Ayurvedic Hospital, Mumbai were screened for eligibility. On screening/ baseline visit, a written informed consent was obtained from children's parent/legally accepted guardian for their participation in the study. Assessment of inclusion and exclusion criteria was made. Screened subjects were administered a single oral dose of Albendazole 400 mg one week before the enrollment. Thereafter, they were randomized to receive either appetizer syrup or the placebo syrup.

Blinding

For the purpose of blinding, the study drug was supplied in a pre-encoded syrup form along with a similarly packed placebo formulation as- Group I- appetizer syrup (coded as 201) and Group II- placebo syrup (coded as 102).

Dosage and treatment schedule

Recruited subjects were randomized to receive either appetizer syrup or placebo syrup according to computer generated randomization list. Both the study products were advised to taken orally at doses of 5 mL twice daily for 2 months.

Analysis

All enrolled cases were evaluated on day 0 (baseline), day 15 (± 3 days), day 30 (± 3 days) and day 45 (± 3 days) for following efficacy and safety parameters.

Table 1—Composition details of appetizer syrup quantity of actives (in mg) used for preparing 5mL of ayurp

S.No.	Name of Ingredient	Botanical name	Quantity (mg)/ per 5 mL of syrup	Benefits as per <i>Ayurveda</i>
1.	<i>Kismis</i>	<i>Vitis vinifera</i> L.	35	<i>Agnimandya</i> (Digestive Impairment)
2.	<i>Anar seed</i>	<i>Punica grantum</i> L.	35	<i>Agnimandya</i> (Digestive Impairment)
3.	<i>Elaichi</i>	<i>Elettaria cardamomum</i> (L.) Maton.	25	<i>Deepana</i> (Appetizer), <i>Aruchi</i> (Tastelessness)
4.	<i>Haritaki</i>	<i>Terminalia chebula</i> Retz.	25	<i>Deepana</i> (Appetizer), <i>Aruchi</i> (Tastelessness), <i>Udararoga</i> (Diseases of Abdomen), <i>Rasayana</i>
5.	<i>Ajwain</i>	<i>Trachyspermum ammi</i> (L.) Sprague	25	<i>Adhmana</i> (Flatulence), <i>Udararoga</i> (Diseases of Abdomen)
6.	<i>Jeera sveta</i>	<i>Cuminum cyminum</i> L.	25	<i>Agnimandya</i> (Digestive Impairment)
7.	<i>Chavya</i>	<i>Piper retrofractum</i> Vahl.	25	<i>Pachan</i> (Digestive), <i>Adhmana</i> (Flatulence)
8.	<i>Sowa</i>	<i>Anethum sowa</i> Roxb.	25	<i>Deepan</i> (Appetizer), <i>Pachan</i> (Digestive), <i>Adhmana</i> (Flatulence), <i>Sula</i> (Pain)
9.	<i>Mulethi</i>	<i>Glycyrrhiza glabra</i> L.	25	<i>Sheetal</i> , <i>Rasayana</i> (Rejuvenator), <i>Balya</i> (Strength promoter)
10.	<i>Palash seed</i>	<i>Butea monosperma</i> (Lam.)	25	<i>Agnimandya</i> (Digestive Impairment)
11.	<i>Mustak</i>	<i>Cyprus rotundus</i> L.	25	<i>Deepan</i> (Appetizer), <i>Pachan</i> (Digestive)
12.	<i>Guruchi</i>	<i>Tinospora cordifolia</i> (Thunb.) Miers	25	<i>Agnimandya</i> (Digestive Impairment)
13.	<i>Amla Dry</i>	<i>Phyllanthus emblica</i> L.	10	<i>Deepan</i> (Appetizer)
14.	<i>Dalchini</i>	<i>Cinnamomum zeylanicum</i> J.Presl	10	<i>Ruchya</i> (Appetite stimulant)
15.	<i>Pippali</i>	<i>Piper longum</i> L.	10	<i>Deepana</i> (Appetizer), <i>Ruchya</i> (Appetite Stimulant), <i>Udararoga</i> (Diseases of Abdomen)
16.	<i>Sunthi</i>	<i>Zingiber officinale</i> Roscoe	10	<i>Agnimandya</i> (Digestive impairment), <i>Adhmana</i> (Flatulence), <i>Udararoga</i> (Diseases of Abdomen)
17.	<i>Maricha</i>	<i>Piper nigrum</i> L.	10	<i>Deepana</i> (Appetizer), <i>Ruchya</i> (Appetite Stimulant)
18.	<i>Lavang</i>	<i>Syzygium aromaticum</i> (L.) Merrill & Perry	5	<i>Deepana</i> (Appetizer), <i>Pachana</i> (Digestive), <i>Ruchya</i> (Appetite stimulant), <i>Adhmana</i> (Flatulence), <i>Amlapitta</i> (Hyperacidity)

Contains Preservatives, Colours and other Permitted Excipients

Efficacy parameters

- a) Subjective evaluation during each visit, based on history from parents and rating on a visual analogue scale following parameters were considered for efficacy evaluation:
- History regarding various food habits directly or indirectly related to appetite, e.g. general desire to eat, quantity of food intake, left over in the plate, number of meals taken per day and range of food taken.
 - History related to bowel habits (regularity and consistency of stools) and sleep (sound/ disturbed & duration). Leading questions were asked in this regard.
 - Ratings for appetite related factors like hunger rating, rating for abdominal fullness and satiety, fatigue and general energy levels, were carried out on a visual analogue scale (VAS) as higher is the rating on VAS scale, better is the improvement.
 - Rating for the performance of various activities directly or indirectly related to poor appetite, like academic performance and interest/ participation in extracurricular activities were recorded on a structured CRF.
- b) Secondary efficacy parameters: Following anthropometric evaluation for selected growth parameters were recorded on follow up visits on day 0, 15, 30 and 45.
- Body weight (up to 100 g least value)
 - Linear height (up to 1cm least value)
- b) Safety parameter: Following safety parameters were considered
- Recording of any undesirable experience since last visit
 - Physical examination during each visit
 - Following laboratory investigations on visit day 0 and 45 days – Liver function tests (LFT), Renal function tests (RFT), Complete blood counts (CBC), Stool examination
 - Serious Adverse events (if any) were graded and recorded according to their severity in clinical

Table 2 — Effect on various parameters (Mean ± SD of two groups over the time)

Variables	Groups	Visit 0 Baseline	Visit 2 15 days	Visit 2 30 days	Visit 3 45 days
Weight	Appetizer syrup	16.7±5.88	16.92±6.02	17.00±6.33	17.67±6.57
	Placebo syrup	14.08±1.89	14.90±2.62	14.50±2.39	14.6±1.64
Height	Appetizer syrup	113.56±19.70	113.56±19.70	113.57±19.69	113.69±19.65
	Placebo syrup	108.83±8.38	108.83±8.38	108.83±8.38	109±8.29
Hunger rating	Appetizer syrup	25.56±8.82	41.11±9.28	55.56±14.24	60±14.14
	Placebo syrup	18.33±7.53	33.33±5.16	40±12.65	58.33±14.72
Abdominal fullness	Appetizer syrup	17.78±8.33	34.44±18.10	51.11±12.69	45.56±14.24
	Placebo syrup	18.33±9.83	30±6.32	35±8.37	23.33±8.16
Satiety	Appetizer syrup	28.89±7.82	43.33±10.00	55.56±10.14	61.11±13.64
	Placebo syrup	28.33±13.29	36.67±5.16	38.33±11.69	48.33±11.69
General desire to eat	Appetizer syrup	26.67±10.00	44.44±11.30	57.78±15.63	64.44±17.40
	Placebo syrup	26.67±10.33	41.67±7.53	51.67±14.72	58.33±4.08
Quality of food intake	Appetizer syrup	24.44±7.26	44.44±10.14	53.33±15.00	64.44±19.44
	Placebo syrup	21.67±4.08	36.67±5.16	40±16.73	51.67±18.35
General Energy level	Appetizer syrup	56.67±21.21	65.56±20.07	75.56±13.33	77.78±14.81
	Placebo syrup	58.33±14.72	66.67±13.66	75±5.48	78.33±4.08

research form. The study was conducted in two parts. Part-1 of the study completed with the evaluation of the subjects after visit 4. This would give an idea regarding the appetite stimulating effects of the formulation. Part-2 was for evaluation of the benefits secondary to appetite stimulation, like effects on anthropometric measurements and academic performance; there shall be one more follow-up at the end of two months of treatment. Subjects were also followed up after visit 4 for assessment of sustenance of appetite stimulating effects. The benefits secondary to appetite stimulation, like effects on anthropometric measurements and academic performance, one more follow-up was done at the end of two months of treatment. All the observations were documented in the case record forms and data was incorporated for independent statistical analysis.

Results and discussion

The present study included 100 completed subjects falling in to the inclusion criteria. Both male and female children between 3-12 yrs of age formed subjects in the present study. They were randomized in to two groups' comprising 50 subjects each. The male vs female ratio in group I and II was 57:43 and 52:48, respectively. The mean average age of male children was 10.32 (± 1.62) and that of female children was 10.41 (±1.27) in group I while that in group II was 11.03 (±3.61) and 10.94 (±2.78), respectively. There was no significant variation in the observational

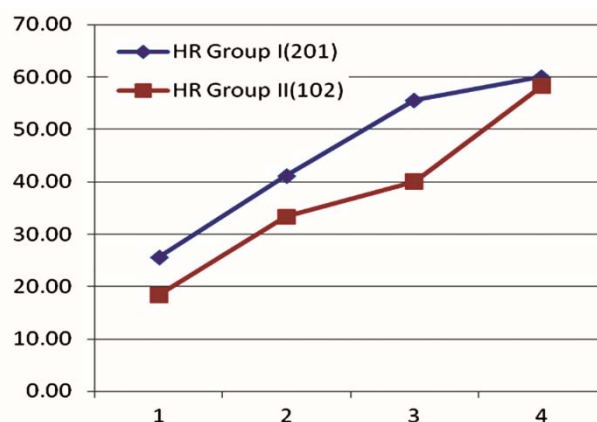


Fig. 1—Effect of the study drugs on hunger (HR)

parameters after 60 days of study. Therefore, the efficacy of the study drug was concluded on the basis of 45 days study period (Table 2). There was significant improvement in hunger in both the groups at all the visits when compared to baseline at the end of the study. In between group statistical analysis was not done as there was significant difference observed at baseline in between groups (Fig. 1). The abdominal fullness showed significant improvement at all the visits in group I and group II except at visit 3. Moreover, there was significant improvement observed in group I when compared to group II at visit 2&3 (Fig. 2). Significant improvement in satiety was observed at all the visits in group I&II when compared to baseline. In between group analysis showed significant improvement in group I, when compared to group II at all the visits (Fig. 3). General desire to eat

showed significant improvement in at all the visits in group I&II when compared to baseline. In between group analysis showed significant improvement in group I, when compared to group II at visit 2&3 (Fig. 4). There was significant change in food intake between visits 0 to visit 3 in both the groups from baseline. In between group statistical analysis was not done as there was significant difference was observed between the group I&II at baseline only (Fig. 5).

A significant improvement in general energy level was observed between visits 0 to 3 in both the groups from baseline. However, these scores were not significant when group I is compared to group II (Fig. 6).

No adverse events were reported during the study. Assessment of vitals like pulse, respiration and body temperature did not show any significant difference both within the group and between the groups. The study drug was found to be safe in the given dosage and well tolerated by the subjects.

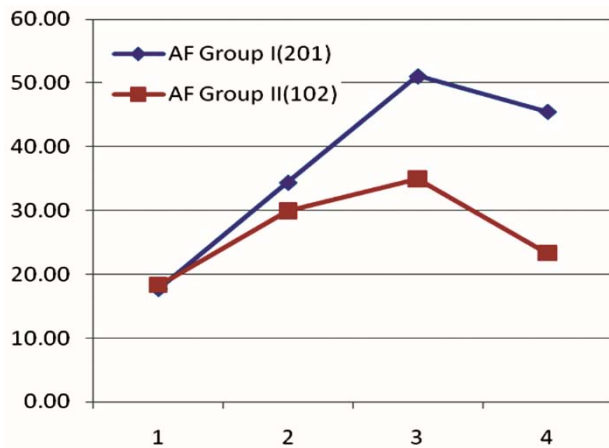


Fig. 2—Effect of the study drugs on abdominal fullness (AF)

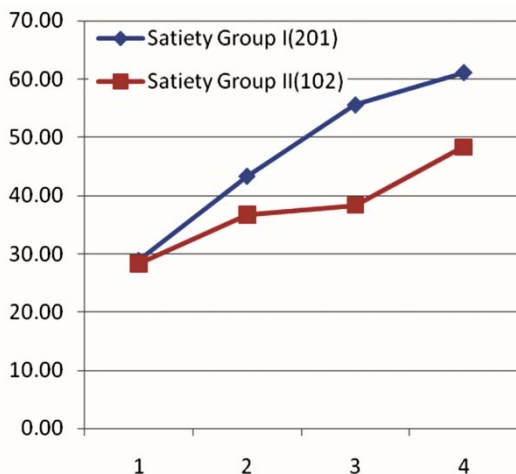


Fig. 3—Effect of the study drugs on satiety

Appetizer syrup is an *Ayurvedic* polyherbal formulation comprising ingredients such as *Kismis*

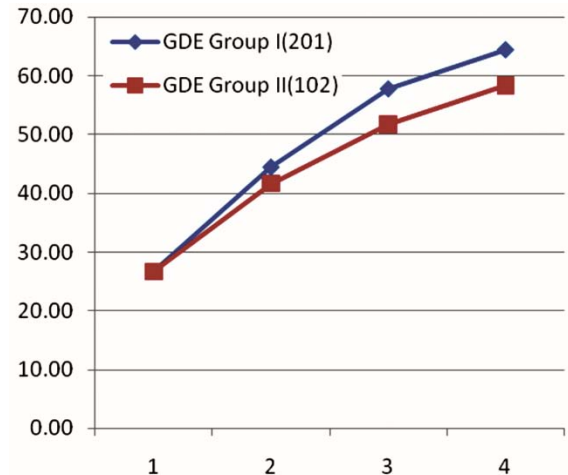


Fig. 4—Effect of the study drugs on general desire to eat (GDE)

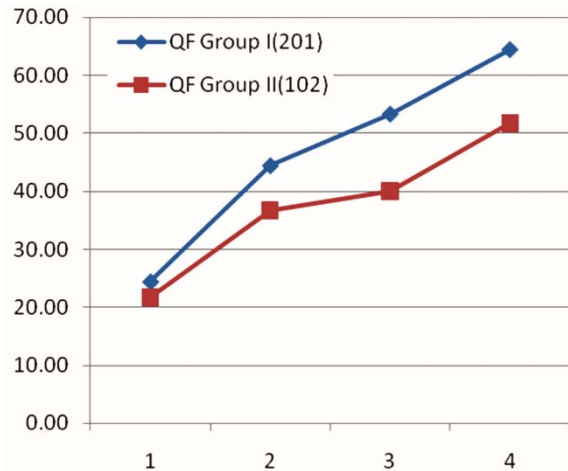


Fig. 5—Effect of the study drugs on quality of food intake (QF)

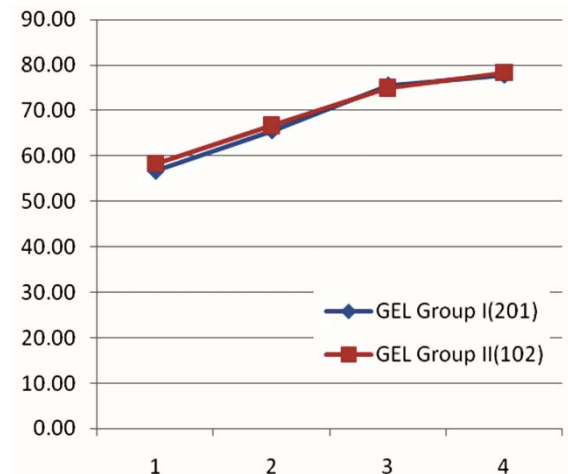


Fig. 6—Effect of the study drugs on general energy level (GEL)

(*Vitis vinifera* L.), *Pipalli* (*Piper longum* L.), *Anar* (*Punica granatum* L.), *Amla* (*Emblica officinalis* Gaertn.), etc., that are traditionally known to be useful in digestive impairment and are reported to possess appetite stimulant and strength promoting properties which may have contributed to its effects.

Conclusion

Regular consumption of appetizer syrup helped improve appetite, general energy levels, quality of food intake, abdominal fullness and satiety in children. Significant improvement was observed in abdominal fullness, the desire to eat and satiety with appetizer syrup when compared with placebo syrup. No adverse events were reported during the study and the product was found to be safe in the given dosage. It could be concluded that appetizer syrup could stimulate appetite in children with non-pathogenic anorexia and can be used safely.

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